KontRASt-06: An open-label phase II trial evaluating the activity and safety of JDQ443 single-agent as first-line treatment for patients with locally advanced or metastatic KRAS G12C-mutated non-small cell lung cancer with a PD-L1 expression < 1% or a PD-L1 expression >= 1% and an STK11 co-mutation.

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This study has been transitioned to CTIS with ID 2024-511708-18-00 check the CTIS register for the current data. the Sponsor aims to investigate if JDQ443 will stop abnormal cell growth related to the marker KRAS G12C mutation in patients with NSCLC...

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

Summary

ID

NL-OMON53674

Source
ToetsingOnline

Brief title
CJDQ443B12201

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
lung cancer; non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: JDQ443, KRASG12C, NSCLC

Outcome measures

Primary outcome

Overall response rate (ORR), defined as the proportion of participants with a confirmed complete response (CR) or partial response (PR) as best overall response (BOR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by blinded independent review committee (BIRC).

Het primaire eindpunt van het onderzoek is ORR, gedefinieerd als de proportie van deelnemers met een bevestigde CR/PR als BOR. BOR is gedefinieerd als de beste respons geregistreerd vanaf het begin van de behandeling tot aan de ziekte progressie per RECIST 1.1 door BIRC. CR en PR moeten worden bevestigd door: herhaal beoordelingen die niet minder dan 4 weken moeten worden uitgevoerd nadat voor het eerst aan de criteria voor respons was voldaan.

Gedocumenteerde reacties na het gebruik van een nieuwe antineoplastische

therapie zal worden beschouwd als:

non-respons.

Secondary outcome

• ORR per RECIST 1.1 by BIRC.

• DOR, defined as the time from the first occurrence of a PR or a CR per RECIST 1.1 by BIRC to the occurrence of disease progression or death due to any cause.

• PFS, defined as the time from the date of enrollment to the date of the first documented disease progression per RECIST 1.1 by BIRC or date of death due to any cause.

• OS, defined as the time from the date of enrollment to the date of death due to any cause.

• Disease control rate (DCR), defined as the proportion of participants with a BOR of confirmed CR, PR and stable disease (SD) per RECIST 1.1 by BIRC.

• Time to response (TTR), defined as the time from the date of enrollment to the first documented response of either CR or PR per RECIST 1.1 by BIRC.

• ORR, DOR, DCR, TTR and PFS per RECIST 1.1 by local radiology assessment.

• ORR, DOR, DCR and TTR per RECIST 1.1 by BIRC and by local radiology assessment.

• PFS and OS

• Type, frequency and severity of adverse events, changes in laboratory values, vital signs, electrocardiograms (ECGs).

• Concentration of JDQ443 in plasma and derived PK parameters, as appropriate.

• Time to definitive deterioration (TTD) in the NSCLC-SAQ total score, and TTD in the physical functioning (PF) scale of the EORTC QLQ-C30

• Change from baseline to each treatment visit and EOT for NSCLC-SAQ total score, pain, cough, dyspnea and items.

• Change from baseline to each treatment visit and EOT for all EORTCQLQ C30 domains, subscales and items

• Change from baseline to each treatment visit and to EOT for the FACT GP5

For the key secondary endpoint, ORR per RECIST 1.1 by BIRC in cohort B, the same definition as in the Protocol, Section 9.3.1 applies.

Treatment with JDQ443 will be considered to have clinically relevant efficacy in cohort B if an ORR of >= 40% is observed with the lower bound of the 95% confidence interval >= 20%.

Study description

Background summary

This study investigates JDQ443 in patients with NSCLC who have a specific change (*mutation*) in the DNA of the tumor cells. This mutation is called the KRAS G12C mutation. The mutation is present in approximately 13% of all patients with NSCLC and causes the tumor to grow faster. JDQ443 is a targeted treatment that blocks the effects of the KRAS G12C mutation. This can cause the growth of the tumor to be inhibited or come to a standstill.
Due to the targeted action of JDQ443 on the KRAS G12C mutation, only patients with NSCLC and this mutation can participate in the study. During the pre-selection it was determined that your tumor cells have this mutation.
In order to participate, one of the following must also be present: a small amount (less than 1%) of the protein PD-L1 or an STK11 mutation. If either of these properties is present, patients with NSCLC will benefit less from immunotherapy. Immunotherapy is one of the commonly used treatments (*standard treatments*) for NSCLC. During the pre-selection it was determined that your

tumor has one of the two characteristics.
JDQ443 has not yet been approved (*registered*) as a medicine by the Dutch government. Doctors are not allowed to prescribe the drug to patients. JDQ443 can only be administered during a medical scientific examination. For registration, research in patients is required. That is why your cooperation in this research is requested.
Since August 2021, approximately 25 subjects with various cancers with a KRAS G12C mutation have been treated with JDQ443. We don't know if the drug will work for you. Your health may improve, deteriorate or not change during the examination.

Study objective

This study has been transitioned to CTIS with ID 2024-511708-18-00 check the CTIS register for the current data.

the Sponsor aims to investigate if JDQ443 will stop abnormal cell growth related to the marker KRAS G12C mutation in patients with NSCLC whose tumors have specific characteristics, such as the presence of a KRAS G12C mutation, as well as the presence of low levels of PD-L1 expression (cohort A) or an STK11 mutation (cohort B). The purpose of this study is to investigate if treatment with JDQ443 will be efficacious and safe to control the growth of NSCLC in study participants.

Study design

Open-label phase II study investigating the activity and safety of JDQ443 as a sole drug for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer with a KRAS G12C mutation, with an expression of PD-L1 less than 1% or a PD-L1 expression of 1% or more and a STK11 co-mutation. This study will require approximately 120 subjects with NSCLC from 24 different countries.

Intervention

treatment with JDQ443

Study burden and risks

Very common side effects (affecting more than 1 in 10 users) were: tiredness; diarrhea, shortage of red blood cells (these cells transport oxygen through the body, which can cause complaints such as fatigue (anemia)); fluid retention in the extremities (arms and legs) (swelling); nausea; yield; pain in the joints (arthralgia), increased levels of liver proteins in the blood (this may be a sign of liver damage); pain in the muscles (myalgia); itch; reduced number of a type of white blood cells called neutrophils (neutropenia); pain in the limbs;

lack of energy, physical weakness (asthenia).
Common side effects (affects less than 1 in 10 people): rash, signs of possible damage to the pancreas/increased pancreatic values, increased skin reaction to light (photosensitivity reaction), rash with both raised and flat skin lesions (maculo-papular skin rash), signs of possible damage to the liver/increased liver enzyme levels, skin condition with the presence of large and small blisters filled with clear fluid (bullous dermatitis), swelling (edema).

Other potential side effects listed below are based on information collected from laboratory and animal studies, as well as from clinical study data with drugs that have a similar mechanism of action as JDQ443:
• Animal experiments have shown that JDQ443 can cause skin sensitization to sunlight, therefore you may get sunburned more easily. It is important that you avoid exposure to sunlight by limiting outdoor activities in sunlight, wearing appropriate clothing and applying sunscreen [sunscreen that at least has a protection factor of 15, includes ultraviolet A (UVA) and ultraviolet B (UVB) protection, and is PABA free (PABA stands for para-aminobenzoic acid)]. It is also advised to avoid use of sun lamp therapy and tanning bed (to avoid artificial UV exposure).
• Changes in kidney function.
• Changes in adrenal gland function, including adrenal insufficiency with symptoms such as tiredness (fatigue), muscle weakness, loss of appetite, upper body obesity, high blood sugars, swelling of legs, skin problems (acne), changes in blood pressure
• Side effects related to progesterone receptor inhibition, including menstrual disorder, hemorrhage, and uterus pain.
• Side effects related to the heart and blood vessels (cardiovascular side effects), such as abnormal heart rate and blood pressure.
• Side effects affecting your lungs, such as increased inflammation in your lungs which could lead to cough and shortness of breath.
• Side effects affecting the female and male reproductive systems including the ovaries, testes, epididymis and prostate gland, which could cause changes in hormone levels or effects on fertility
Some side effects related to the eye and lung have been observed with drugs that work similarly to JDQ443. Side effects related to the eye may include retinal vein occlusion (RVO) where there is a blockage of the small veins that carry blood away from the retina (the layer of tissue at the back of the inner eye that converts light images to nerve signals and sends them to the brain), reversible disease of the retina that results in vision changes and general changes in vision.
Side effects related to lung includes interstitial lung disease (a type of inflammation of lung tissue also called pneumonitis). It is important that you alert your doctor of any signs of breathing difficulties (e.g., shortness of breath, cough, fever) or new onset of cough while taking the study medication..
Problems or side effects that are not currently known could also occur, including serious/severe side effects.

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

• Histologically confirmed locally advanced (stage IIIb/IIIc not eligible for definitive chemoradiation or surgical resection with curative intent) or metastatic (stage IV) NSCLC without previous systemic treatment for metastatic disease. Prior (neo)adjuvant treatment with chemotherapy and/or immunotherapy, or prior radiotherapy administered sequentially or concomitantly with chemotherapy and/or immunotherapy for localized or locally advanced disease are accepted if the time between therapy completion and enrollment is > 12 months.
• Presence of a KRAS G12C mutation (all participants) and:
• Cohort A: PD-L1 expression < 1%, regardless of STK11 mutation status
• Cohort B: PD-L1 expression >= 1% and an STK11 co-mutation
• At least one measurable lesion per RECIST 1.1.
• ECOG performance status <= 1.

• Participants capable of swallowing study medication.

Exclusion criteria

• Participants whose tumors harbor an EGFR-sensitizing mutation and/or ALK rearrangement by local laboratory testing. Participants with other known druggable alterations will be excluded, if required by local guidelines
• Previous use of a KRAS G12C inhibitor or previous systemic treatment for metastatic NSCLC.
• A medical condition that results in increased photosensitivity (i.e. solar urticaria, lupus erythematosus, etc).
• Known active central nervous system (CNS) metastases and/or carcinomatous meningitis
• Participants who are taking a prohibited medication (strong CYP3A inducers) that cannot be discontinued at least seven days prior to the first dose of study treatment and for the duration of the study

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):	24-07-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.v.t.

Generic name:	opnurasib

Ethics review

Approved WMO Date:	03-10-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-12-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-05-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	22-03-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-04-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	CTIS2024-511708-18-00
EudraCT	EUCTR2022-001088-29-NL
ClinicalTrials.gov	NCT05445843
CCMO	NL82042.028.22