A PHASE Ib/II, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY, ACTIVITY, AND PHARMACOKINETICS OF GDC-6036 IN COMBINATION WITH OTHER ANTI-CANCER THERAPIES IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER WITH A KRAS G12C MUTATION

Published: 03-05-2023
Last updated: 05-10-2024

This study has been transitioned to CTIS with ID 2023-507171-22-00 check the CTIS register for the current data. The purpose of this study is to evaluate the safety, pharmacokinetics, and activity of GDC-6036 combined with other anti-cancer...

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

Summary

ID

NL-OMON53747

Source
ToetsingOnline

Brief title
BO44426 - GDC-6036- NSCLC KRAS

Condition

- Other condition

Synonym
NON-SMALL CELL LUNG CANCER WITH A KRAS G12C MUTATION

Health condition

NON-SMALL CELL LUNG CANCER MET EEN KRAS G12C MUTATION

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Roche

Intervention

Keyword: GDC-6036, KRAS G12c mutation, NSCLC, untreated advanced or metastatic

Outcome measures

Primary outcome

1. Occurrence of adverse events

2. Change from baseline at each visit in targeted safety parameters

Secondary outcome

1. Objective response rate

2. Duration of response

3. Progression free survival

4. Presence, frequency of occurrence, severity, and/or degree of interference

with daily function of symptomatic side effects as assessed

through use of the Patient-Reported Outcomes Common Terminology Criteria for

Adverse Events (PRO*CTCAE)

5. Change from baseline in symptomatic side effects, as assessed through use of the PRO-CTCAE

6. Proportion of participants reporting "frequent" or "almost constant" diarrhea during the first three cycles of treatment according to the PRO CTCAE-criteria

7. Proportion of participants reporting "severe" or "very severe" nausea or vomiting during the first three cycles of treatment according to the PRO-CTCAE

8. Frequency of participant's response of the degree they are troubled with treatment symptoms, as assessed through use of the single-item European Organisation for Research and Treatment of Cancer (EORTC) Item List 46 (IL46)

9. Plasma concentration of GDC-6036 at specified timepoints

10. Identification of GDC-6036 recommended dose in combination with pembrolizumab based on the totality of safety, activity, and PK data

Study description

Background summary

Lung cancer remains the leading cause of cancer deaths worldwide and is one of the most common cancers in both men and women. NSCLC is the predominant subtype of lung cancer, accounting for approximately 85% of all cases. The overall 5-year survival rate for advanced disease is 2%-4%, depending on geographic location. NSCLC is a heterogeneous disease, and it has become increasingly important to perform broad predictive molecular biomarker analyses when determining a treatment approach for patients with advanced or metastatic disease. The recommendation to test for KRAS mutations is relatively recent. PD-L1 expression is considered the best available predictive biomarker for immunotherapy and is also recommended to be tested in all patients with

advanced or metastatic NSCLC. Despite improvements and benefits with PD-L1/PD-1 targeting agents, nearly all patients experience disease progression. Consequently, new treatments and treatment regimens, including CPI/targeted therapy combinations, are needed to address this unmet medical need. GDC-6036 is an oral, covalent, anti-cancer therapeutic agent that selectively inhibits KRAS G12C.

Study objective

This study has been transitioned to CTIS with ID 2023-507171-22-00 check the CTIS register for the current data.

The purpose of this study is to evaluate the safety, pharmacokinetics, and activity of GDC-6036 combined with other anti-cancer therapies in patients with previously untreated, advanced or metastatic non-small cell lung cancer (NSCLC) that harbors a Kirsten rat sarcoma viral oncogene homolog (KRAS) glycine 12 to cysteine (G12C) mutation (KRAS G12C*). First-line treatment options for patients with KRAS G12C* NSCLC include immunotherapy as a single agent or in combination with chemotherapy. Although a minority of patients achieve long-term disease control with programmed death*1 (PD-1)/programmed death*ligand 1 (PD-L1) inhibitor treatment, in general, advanced stage or metastatic NSCLC remains an incurable disease with limited benefit from the available standard of care treatments, thus demonstrating an unmet medical need in this patient population. Novel combinations using a more targeted, biomarker directed approach may further improve outcomes. The first combination to be evaluated in the study will be GDC-6036 in combination with pembrolizumab but other combinations with GDC 6036 may be added to the study through protocol amendments in line with the overall study rationale. Anticipated future combinations with GDC-6036 may for example include immunotherapy combined with another immunotherapy or immunotherapy combined with chemotherapy.

Study design

This is an open-label, multicenter Phase Ib/II study designed to evaluate the safety, pharmacokinetics, and activity of GDC-6036 in combination with other anti-cancer therapies in patients with untreated advanced or metastatic NSCLC that harbors a KRAS G12C mutation. This study is designed with the intention to include new, additional treatment arms during study conduct and in line with the overall study rationale (via substantial protocol amendments) to explore combinations for GDC-6036 with other anti-cancer therapies based on emerging nonclinical and clinical data with GDC-6036 and other KRAS G12C inhibitors. Initially, a cohort of GDC 6036 in combination with pembrolizumab (Cohort A) will be evaluated. Anticipated future combinations with GDC 6036 may for example include immunotherapy combined with another immunotherapy or immunotherapy combined with chemotherapy.

Intervention

• GDC-6036: 200 mg or 400 mg orally, once a day, on Days 1-21 of each 21-day cycle.
The dose of GDC-6036 can be reduced up to two times for management of drug related toxicities.
• Pembrolizumab: 200 mg IV, every 3 weeks, on Day 1 of each 21-day cycle.

Modification of the pembrolizumab dose, including dose reductions, is not permitted.

Study burden and risks

The purpose of this study is to assess the safety, pharmacokinetics, and activity of GDC 6036 in combination with other anti-cancer therapies to address a significant unmet medical need in patients with previously untreated, advanced or metastatic NSCLC harboring a KRAS G12C mutation, and who are not eligible for curative surgery and/or definitive chemoradiotherapy.
It has recently become a recommendation to test for KRAS G12C mutations based on the emergence of specific targeted treatment options. While there have been several advances in the treatment of advanced or metastatic NSCLC with targeted therapies that inhibit specific actionable driver mutations such as EGFR, ALK, ROS1, and BRAF as an example, mutant KRAS has historically been considered "undruggable" due to its high affinity for GTP, lack of accessible binding pockets, and the toxicity associated with non*mutant-specific targeting approaches.
With the landmark discovery of the switch II pocket, covalent small molecule inhibitors aimed at targeting KRAS, and specifically the KRAS G12C mutation, are being evaluated in clinical development. A brief summary of available clinical data for other KRAS G12C inhibitors in development is provided in paragraph 2.3 of the protocol, followed by a detailed description of GDC 6036, the KRAS G12C inhibitor that will be administered in this study.
Based on the considerations described in paragraph 2.3 of the Protocol, and the planned safety monitoring and management guidance, the proposed treatments are considered to have an appropriate benefit-risk profile for the population included in this cohort.

Contacts

Public
Roche Nederland B.V.

Beneluxlaan 2A
Woerden 3446AA

NL
Scientific
Roche Nederland B.V.

Beneluxlaan 2A
Woerden 3446AA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histologically or cytologically documented locally advanced unresectable or metastatic NSCLC that is not eligible for curative surgery and/or definitive chemoradiotherapy
- No prior systemic treatment for advanced unresectable or metastatic NSCLC
- Confirmation of Biomarker eligibility:
.. Documented history of the KRAS G12C mutation
.. Documented history of PD-L1 tumor cell expression >=1%
- Pre-treatment tumor tissue along with an associated pathology report is required for all participants enrolled on study. Representative tumor specimens must be in formalin*fixed, paraffin embedded (FFPE) blocks (preferred) or 15 unstained, freshly cut, serial slides. Although 15 slides are required, if only 10 slides are available, the participant may be eligible for the study following consultation with the Sponsor
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
- Measurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Exclusion criteria

- Known concomitant second oncogenic driver with available targeted treatment
- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases
- Prior treatment with a KRAS G12C inhibitor
- Known hypersensitivity to any of the components of GDC-6036 or pembrolizumab
- History of malignancy other than NSCLC within 5 years prior to initiation of study treatment, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate more >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal breast carcinoma in situ, or Stage I uterine cancer
- Uncontrolled tumor related pain, pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures, uncontrolled or symptomatic hypercalcemia
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis, active tuberculosis, significant cardiovascular disease within 3 months prior to initiation of study treatment

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-09-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	nvt
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatin
Generic name:	nvt
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	GDC-6036
Generic name:	Niet van toepassing
Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Pemetrexed
Generic name:	nvt
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-05-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-06-2023
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	03-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-02-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-03-2024
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	CTIS2023-507171-22-00
EudraCT	EUCTR2022-003048-28-NL
Other	IND: 147339, NCT05789082
CCMO	NL83211.041.23