A Phase 2 Trial of Adagrasib Monotherapy and in Combination with Pembrolizumab and a Phase 3 Trial of Adagrasib in Combination with Pembrolizumab versus Pembrolizumab plus Chemotherapy in Patients with Advanced Non-Small Cell Lung Cancer with KRAS G12C Mutation

Published: 11-01-2021
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2023-508922-83-00 check the CTIS register for the current data. Primary Objective:To evaluate the efficacy of adagrasib monotherapy and in combination with pembrolizumab administered in the first-line...

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

Summary

ID

NL-OMON54311

Source
ToetsingOnline

Brief title
KRYSTAL-7

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Advanced Pulmonary Non-Small Cell Cancer, Metastatic Non-Small Cell Lung Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Mirati Therapeutics, Inc.
Source(s) of monetary or material Support: Mirati Therapeutics (the sponsor)

Intervention

Keyword: KRAS G12C, Metastatic Cancer, Non-small cell lung cancer, NSCLC

Outcome measures

Primary outcome

Objective Response Rate (ORR) as defined by Response Evaluation Criteria in

Solid tumors version 1.1 (RECIST 1.1) by Investigator

Secondary outcome

- Safety characterized by type, incidence, severity, timing, seriousness and

relationship to study treatment of AE's and laboratory abnormailities

- Plasma MRTX849 and potential metabolite concentrations

- Duration of Response (DOR) by Investigator

- Progression-Free Survival (PFS) by Investigator

- 1-Year Survival Rate

- Overall Survival (OS)

Study description

Background summary

RAS proteins are part of the family of small GTPases that are activated in

response to growth factor stimulation and various other extracellular stimuli to regulate intracellular signaling pathways responsible for growth, migration, survival and differentiation of cells. The activation of RAS proteins at the cell membrane by growth factors results in the binding of key effector molecules, formation of signaling complexes, and the initiation of a cascade of intracellular signaling pathways within the cell including the RAF and PI3 kinase pathways. RAS proteins normally alternate between GTP- and GDP-bound conformations, where the GTP-bound conformation represents the *On* and GDP-bound the *Off* state. Dependence of RAS and other GTPases on guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) to switch them on and off allows both processes to be highly regulated and responsive to multiple signal inputs. In contrast, oncogenic mutants of RAS generally function by preventing hydrolysis of GTP, thereby generating constitutively active, GTP-bound RAS leading to uncontrolled cellular growth and malignant transformation.

KRAS is the most frequently mutated gene of the RAS family, and KRAS mutations occur in approximately 30% of lung adenocarcinomas, 50% of colorectal cancers, and 90% of pancreatic ductal adenocarcinomas. The mutation of the glycine at residue 12 produces a steric block that prevents GAP proteins from accessing KRAS, thereby inhibiting GTP hydrolysis resulting in a highly activated GTP-bound form of RAS. Mutation of that amino acid residue to cysteine, noted as KRAS G12C, comprise approximately 14% of lung adenocarcinoma and defines a unique segment of lung cancer without a current targeted therapy option.

Adagrasib is a potent and orally available small molecule inhibitor of KRAS G12C. Adagrasib demonstrates potent inhibition of KRAS-dependent signal transduction and cancer cell viability with selectivity for KRAS G12C of over 1000-fold compared to KRAS wild-type. Adagrasib demonstrated broad-spectrum antitumor activity across several KRAS G12C-positive patient- or cell-derived tumor models implanted in mice at well-tolerated dose levels, including complete tumor responses in a subset of models. Collectively, these results support the evaluation of Adagrasib in patients with malignancies having KRAS G12C mutations.

Pembrolizumab is a monoclonal antibody (mAb) directed against programmed cell death 1 (PD-1) and blocks the interaction between PD-1 and its ligands, thereby releasing PD-1-mediated inhibition of T-cell proliferation (including cytotoxic CD8+ T-cells) and cytokine production.

The rationale for the combination of adagrasib with pembrolizumab stems from various lines of work. First, large-scale functional genomics studies have demonstrated that NSCLC cells exhibiting KRAS mutations are highly dependent on KRAS function for cell growth and survival, supporting the potential role of adagrasib in KRAS G12C mutated NSCLC. Second, clinical observations of patients with KRAS mutant NSCLC suggest that these tumors have higher tumor

mutational burden, which putatively results in an increase in tumor neoantigens and increased responsiveness to PD 1/PD-L1-directed immunotherapy. Studies in mutant KRAS G12C tumor models show that adagrasib enhances the potential for tumor cells to present antigens and reconditions the tumor microenvironment through changes in the proportions of key cell populations, both of which are predicted to augment susceptibility to immune checkpoint inhibition. Thus, not only has activity been observed with each agent individually, but these observations also suggest potential synergistic activity of the combination of adagrasib with pembrolizumab to translate into significant antitumor activity.

The Phase 2 portion of the study evaluates the efficacy and safety of adagrasib monotherapy and in combination with pembrolizumab in cohorts of patients with advanced NSCLC with KRAS G12C mutation and any PD-L1 TPS and who are candidates for first-line treatment.

Study objective

This study has been transitioned to CTIS with ID 2023-508922-83-00 check the CTIS register for the current data.

Primary Objective:

To evaluate the efficacy of adagrasib monotherapy and in combination with pembrolizumab administered in the first-line treatment setting to patients having NSCLC with KRAS G12C mutation.

Secondary Objectives:

• To characterize the safety and tolerability of the monotherapy and the combination regimen in the selected population.
• To evaluate secondary efficacy endpoints using monotherapy and the combination regimen in the selected population.
• To evaluate the pharmacokinetics (PK) of adagrasib administered as monotherapy and in combination with pembrolizumab.

Study design

Study 849-007 is an open-label clinical trial evaluating the efficacy of MRTX849 administered as monotherapy and in combination with pembrolizumab in the first-line treatment setting to patients with NSCLC with KRAS G12C mutation. Secondary and exploratory objectives include evaluation of safety, adagrasib PK, pharmacodynamic for the combination regimen in the study population.

Arms:

PD-L1 TPS < 1% - 1:1 randimized:
o Cohort 1a, adagrasib 400mg twice daily (BID) in combination with pembrolizumab or
O Cohort 1b, adagrasib 600mg twice daily monotherapy

PD-L1 TPS >= 1% - assign to:
o Cohort 2, adagrasib 400mg twice daily in combination with pembrolizumab

Genetic eligibility may be established using tumor tissue samples or ctDNA. Submission of tumor tissue samples for all enrolled patients is required for central laboratory testing for retrospective confirmation of KRAS mutation status, PD-L1 TPS status and identification of concurrent gene alterations. Samples for the central laboratory must be submitted in a timely manner (e.g., within 90 days after initiation of study treatment).

The presence of tumor KRAS G12C mutation for the purpose of patient eligibility and the PD-L1 TPS status used to stratify patients in cohorts must be established using Sponsor pre-approved methods and laboratories.

Study treatment will be expressed in 3-week cycles.
Adagrasib is to be administered orally on a continuous basis until disease progression, or protocol defined reason for discontinuation.
Pembrolizumab will be administered by intravenous (IV) infusion, 200 mg over approximately 30 minutes every 3 weeks (Q3W).

Patients will receive study treatment until disease progression, unacceptable adverse events, receipt of maximal number of cycles per local standard-of-care, investigator decision, patient refusal or death. Patients experiencing clinical benefit in the judgment of the Investigator may continue study treatment beyond disease progression as defined by RECIST 1.1. In the event a patient discontinues study treatment for a reason other than objective disease progression, disease assessments post-treatment should continue until objective disease progression is documented by the Investigator or start of subsequent anti-cancer therapy, whichever is sooner.

Intervention

Adagrasib Monotherapy and in combination with pembrolizumab

Study burden and risks

Please check the protocol - Schedule of assessments in the Section "Study Summary".

Risks associated with the study are described in the informed consent form,

section 6.

Contacts

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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

Histologically confirmed diagnosis of unresectable or metastatic NSCLC with KRAS G12C mutation and any PD-L1 TPS.

Exclusion criteria

1. Prior systemic treatment for locally advanced or metastatic NSCLC including chemotherapy, immune checkpoint inhibitor therapy, or a therapy targeting KRAS

G12C mutation (e.g., AMG 510).
2. Active brain metastases.

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):	29-07-2021
Enrollment:	35
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	-
Generic name:	-
Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	11-01-2021

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-06-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	16-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-09-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-11-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-03-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-03-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-04-2024

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2024
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	CTIS2023-508922-83-00
EudraCT	EUCTR2020-003101-58-NL
ClinicalTrials.gov	NCT04613596
CCMO	NL75584.031.20