A Randomized Phase 3 Study of MRTX849 versus Docetaxel in Patients with Previously Treated Non-Small Cell Lung Cancer with KRAS G12C Mutation

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This study has been transitioned to CTIS with ID 2023-507263-19-00 check the CTIS register for the current data. To compare the efficacy of MRTX849 versus docetaxel in patients with NSCLC with KRAS G12C mutation and who have received prior treatment...

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

Summary

ID

NL-OMON56384

Source
ToetsingOnline

Brief title
Study of MRTX849 vs Docetaxel in Pts With Advanced NSCLC KRAS G12C Mut.

Condition

- Other condition
- Metastases

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

Health condition

NSCLC (Non-Small Cell Lung Cancer)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: KRAS G12C Mutation, Metastatic Cancer, Non-Small Cell Lung Cancer, NSCLC

Outcome measures

Primary outcome

• Progression-Free Survival (PFS)

Secondary outcome

• Secondary efficacy endpoints:

* Overall Survival (OS)

* Objective Response Rate (ORR),

* Duration of Response (DOR), and

* 1-Year Survival Rate.

Study description

Background summary

RAS proteins are part of the family of small GTPases and 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 molecules with severe consequences for the cell including 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. 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 (also known as KRAS (p.G12C), comprises approximately 14% of lung adenocarcinoma and defines a unique segment of lung cancer without a current targeted therapy option. Large genomics studies characterizing lung cancers have indicated that KRAS mutations, including G12C, are mutually exclusive with other known oncogenic driver mutations in non-small cell lung cancer (NSCLC) including EGFR, ALK, ROS1, RET, and BRAF indicating that KRAS mutations define a unique segment of lung cancer without a current targeted therapy option. Functional genomics studies have demonstrated that NSCLC cancer cells exhibiting KRAS mutations are highly dependent on KRAS function for cell growth and survival.

MRTX849 (also known as adagrasib) is a potent and orally available small molecule inhibitor of KRAS G12C. MRTX849 demonstrated 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. MRTX849 demonstrated broad-spectrum antitumor activity across several KRAS G12C-positive patient- or cell-derived tumor models implanted in mice, including complete tumor responses in a subset of models. Collectively, these results support the evaluation of MRTX849 in patients with malignancies having KRAS G12C mutations. Initial clinical trial observations with MRTX849 include demonstration of confirmed objective responses in NSCLC and colorectal cancer.

Study objective

This study has been transitioned to CTIS with ID 2023-507263-19-00 check the CTIS register for the current data.

To compare the efficacy of MRTX849 versus docetaxel in patients with NSCLC with KRAS G12C mutation and who have received prior treatment with a platinum-based regimen and immune checkpoint inhibitor therapy.

Study design

This Phase 3 study compares the efficacy of MRTX849 versus docetaxel in

patients with metastatic NSCLC with KRAS G12C mutation who have previously received treatment with a platinum-based chemotherapy regimen and an immune checkpoint inhibitor.

Intervention

Eligible patients will be randomized 2:1 to MRTX849 or docetaxel
Study treatment will be administered in 3-week cycles. Patients randomized to the investigational arm will receive MRTX849 administered orally (PO) at a starting dose of 600 mg twice daily (BID). Patients randomized to the comparator arm will receive treatment with docetaxel. Docetaxel will be administered by intravenous infusion at 75 mg/m2 over 1 hour or according to institutional practices every 3 weeks. Premedication with dexamethasone (or institutional equivalent) will be required in accordance with local standards.

Study burden and risks

Please check the protocol (English, V7.2 dated 21Apr2023) - Table 2 Schedule of assessments. Risks associated
with the study are described in the informed consent form, section 6

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 or cytologically confirmed diagnosis of NSCLC with KRAS G12C mutation.
Candidacy to receive treatment with docetaxel.

Crossover Inclusion Criteria
1. Evidence of RECIST 1.1 defined disease progressoin on docetaxel per BICR.
2. ECOG performance status 0 - 2.

Exclusion criteria

Prior treatment with an agent targeting KRAS G12C (e.g., AMG 510).
Active brain metastases.

Crossover Exclusion Criteria:
1. Receipt of any other systemic anti-cancer therapy after last administration of docetaxel on the study.

Study design

Design

Study phase:	3
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):	26-04-2023
Enrollment:	8
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Docetaxel Hikma 80 mg/4 ml
Generic name:	Docetaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Adagrasib

Ethics review

Approved WMO Date:	08-06-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-03-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2023
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-01-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	CTIS2023-507263-19-00
EudraCT	EUCTR2020-003645-11-NL
ClinicalTrials.gov	NCT04685135
CCMO	NL76496.029.21