A Randomized, Open-Label, Phase 3 Study of Pralsetinib versus Standard of Care for First Line Treatment of RET fusion-positive, Metastatic Non-Small Cell Lung Cancer

Published: 15-04-2020
Last updated: 24-08-2024

This study has been transitioned to CTIS with ID 2023-505035-12-00 check the CTIS register for the current data

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

Summary

ID

NL-OMON49533

Source
ToetsingOnline

Brief title
AcceleRET Study of Pralsetinib for 1L RET fusion-positive Metastatic NSCLC

Condition

- Other condition

Synonym
Metastatic Non-Small Cell Lung Cancer

Health condition

Metastatic Non-Small Cell Lung Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Blueprint Medicines Corporation
Source(s) of monetary or material Support: Blueprint Medicines Corporation

Intervention

Keyword: Metastatic Non-Small Cell Lung Cancer, Phase 3, Pralsetinib, RET-fusion

Outcome measures

Primary outcome

Primary

* To assess whether pralsetinib improves progression-free survival (PFS) as compared to Investigator*s choice platinum-containing chemotherapy regimens for patients with RET fusion-positive metastatic NSCLC

Secondary outcome

Secondary

The key secondary objectives are:

* To evaluate objective response rate (ORR) determined by central radiology assessment according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1

* To evaluate overall survival (OS)

To control study-wide Type I error, the key secondary objectives will be tested in the order presented, as part of the sequential testing scheme for the study if the primary analysis is significant.

Additional secondary objectives are:

* To further characterize the safety and tolerability profile of pralsetinib

* To compare additional measures of anticancer activity, including duration of response (DOR), disease control rate (DCR), and clinical benefit rate (CBR)

* To assess central nervous system (CNS) activity as measured by time to intracranial progression (all patients) and intracranial response rate (for patients with measurable intracranial metastases at screening)

* To assess health-related quality-of-life (QoL) using the European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QLQ)-C30 scores

* To assess lung cancer symptoms using the EORTC-QLQ-LC13 scores

* To assess health status using the EuroQoL 5 Dimension (EQ-5D-5L) assessment to support future health economic analyses.

* To correlate steady state systemic exposure of pralsetinib with safety endpoints and antitumor activity

Exploratory:

Exploratory objectives are:

* To identify potential biomarkers of antineoplastic activity, and resistance.

Study description

Background summary

Pralsetinib (also known as BLU-667) is a potent and selective inhibitor of oncogenic rearranged during transfection (RET) alterations. RET receptor tyrosine kinase is expressed in several neural, neuroendocrine and genitourinary tissues types that normally requires ligand and co-receptor

binding for activation. Oncogenic RET rearrangements have been identified in 1-2% of non-small cell lung cancer (NSCLC) (Lin et al, 2015). These rearrangements typically produce chimeric transcripts that encode a fusion protein consisting of the RET kinase domain coupled to a protein with a dimerization domain (eg, KIF5B, CCDC6, NCOA4), resulting in a constitutively active kinase that promotes tumorigenesis.

Study objective

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Study design

This is an international, randomized, open-label, Phase 3 study designed to evaluate whether the potent and selective RET inhibitor, pralsetinib, improves outcome when compared to a platinum chemotherapy-based regimen chosen by the Investigator from a list of standard of care treatments, as measured primarily by PFS, for patients with RET fusion-positive metastatic NSCLC who have not previously received systemic anticancer therapy for metastatic disease.

All study visits are intended to be conducted on an outpatient basis, but may be conducted on an inpatient basis, as needed. Informed consent may be obtained up to 42 days (6 weeks) before study drug administration on C1D1. After informed consent, patients will be evaluated for study eligibility during the Screening Period, which is to be completed within 28 days or less before study drug administration. For study eligibility, RET fusion status may be determined locally or centrally. However, baseline tumor tissue samples for all patients must also be submitted for confirmation of RET status by central testing.

After the Screening assessments are performed, patients will be randomly assigned, in a 1:1 ratio, to 1 of 2 treatment arms: Arm A (pralsetinib) or Arm B (a platinum-containing chemotherapy regimen from an Investigator's choice list of standard of care regimens with or without pembrolizumab).

Main Treatment Period:
During the Main Treatment Period, patients randomized to Arm A will receive pralsetinib by daily oral (PO) administration at a dose of 400 mg in continuous 21-day treatment cycles. Patients may continue to receive pralsetinib until precluded by toxicity, centrally confirmed disease progression, noncompliance, withdrawal of consent, death, or closure of the study by the Sponsor.
Patients randomized to Arm B will receive 1 of the following platinum-based chemotherapy treatment regimens based on standard of care treatment cycles as determined by the treating Investigator.
Nonsquamous histology
* Carboplatin or cisplatin / pemetrexed (with vitamin supplementation)

* Pembrolizumab / carboplatin or cisplatin / pemetrexed (with vitamin supplementation)

Squamous histology:
Carboplatin or cisplatin / gemcitabine Investigator choice platinum-based chemotherapy regimen may continue in accordance with standard of care (four 3-week treatment cycles). Patients with nonsquamous histology receiving carboplatin- or cisplatin-containing regimens may optimally receive subsequent maintenance pemetrexed (and pembrolizumab, if selected) for up to 2 years unless stopped earlier for toxicity, confirmed disease progression, noncompliance, withdrawal of consent, death, or closure of the study by the Sponsor.

All patients will present to the study center on C1D1 for the first dose of study drug; safety monitoring (including ECOG PS assessment, physical examination, vital signs, electrocardiogram (ECG), safety laboratory tests, AE and concomitant medication recording, etc.); QoL questionnaires; biomarker sample collection; and PK assessments. Additional study visits for assessments of safety and PK will be conducted periodically throughout study treatment in accordance with the schedule of assessments (SoA). Disease assessments will be performed at 6 weeks and 12 weeks, then every 9 weeks for the first 48 weeks, and every 12 weeks thereafter, until confirmation of progressive disease by central radiographic review. Tumor response and progression will be assessed in accordance with RECIST 1.1. At any point in time between treatment cycles, patients should attend or contact the study center for AE reporting, evaluation, and medical intervention.

Patients who discontinue study treatment without documented progressive disease will continue to undergo disease assessments until documentation of progressive disease, initiation of another antineoplastic therapy, death, or closure of the study by the Sponsor.

Crossover Treatment Period:
Patients randomized to Arm B who experience disease progression, as confirmed by central radiology review, on Investigator*s choice platinum-based chemotherapy regimen may be offered the opportunity to cross over to the pralsetinib treatment arm (Arm A) after a confirmation of their disease progression by central radiology review. Patients must separately consent to cross over to pralsetinib treatment after disease progression and meet minimal criteria for crossover.

Upon entering the Crossover Treatment period on Crossover Cycle 1 Day 1 (CC1D1), patients will have the following assessments performed: ECOG PS assessment, physical examination, vital signs, ECG, safety laboratory tests, AE and concomitant medication recording, QoL questionnaires, PK and biomarker sample collections. Patients will also present to the study center on Day 1 of every subsequent cycle to repeat the applicable procedures as indicated in the

SoA. At any point in time between treatment cycles patients should attend or contact the study center for AE reporting, evaluation, and medical intervention. Disease assessments will be performed at 6 weeks and 12 weeks, then every 9 weeks for the first 48 weeks, and every 12 weeks thereafter until new disease progression, initiation of new antineoplastic therapy, death, patient withdrawal of consent, or closure of the study by the Sponsor.

End of Treatment Period:
All patients will attend an End of Treatment (EOT) Visit 14 days (±7 days) after the permanent discontinuation of study drug (ie, last dose) or before a patient starts another antineoplastic therapy. A follow-up telephone contact for a safety assessment to confirm resolution of any AEs will be made 30 days (±7 days) after the last dose of study drug or at the time the patient initiates another antineoplastic therapy.

Follow-up Period:
After discontinuation of study drug, patients without confirmed progressive disease will be followed for PFS until confirmation of progressive disease by central radiology review, withdrawal of consent, initiation of another antineoplastic therapy, or death. All patients will be followed for overall survival by telephone contact approximately every 3 months from the EOT visit until death, withdrawal of consent, or closure of the study by the Sponsor.

Intervention

It is anticipated that patients will receive at least 1 cycle of study treatment (pralsetinib if randomized to Arm A and a platinum-containing chemotherapy regimen from an Investigator's choice list of standard of care regimens if randomized to Arm B). After Cycle 1, patients randomized to Arm B will receive study treatment in accordance with standard of care, patients randomized to Arm A may continue to receive study treatment until precluded by toxicity, noncompliance, pregnancy, progressive disease, withdrawal of consent, death, or closure of the study by the Sponsor.

Study burden and risks

Drug side effects
Patients may experience side effects from the drugs used in this study. Side effects can vary from mild to very serious and may vary from person to person. Every patient taking part in the study will be watched carefully for any side effects. However, not all of the side effects that could occur are known. Patients will be given medications to help lessen some of the side effects. Many side effects go away soon after the causative factor is removed. However, in some cases, side effects can be serious and may be long lasting or may never go away. There also is a rare risk of death. Patients will be encouraged to talk to the study doctor about any side effects they experience while taking

part in the study. They will also be given a patient identification card to carry with them at all times in case they cannot make it to the study site and have to go for treatment elsewhere so the medical professional treating the patient can contact the study doctor and obtain information about the study, study drugs and their possible side effects. If patients develop serious side effects their treatment with study medication will be stopped. They will be treated or monitored until resolution or stabilisation of the side effect. Patients who experience less serious side effects will have their treatment interrupted until the side effect subsides after which they may resume their treatment, however, the dose may be reduced.

Less effective experimental therapy
Although there is some data on the use of pralsetinib in NSCLC patients, the drug may be less effective than the standard treatment. For some patients the experimental treatment or the standard treatment they are assigned to receive may not work and their health may not improve as a result of participation in the study. Patients whose NSCLC worsens while they are receiving study treatment will be taken off the study drugs. They will then be able to receive standard of care treatment appropriate for their health condition at the time. They will also be followed for survival as part of their participation in this study.

Dietary and medication restrictions
Patients taking pralsetinib as part of the study will not be allowed to consume grapefruit, grapefruit juice or take St. John*s Wort. This is to limit their effect on the metabolism of pralsetinib. There is also a number of prescription medications that patients will not be allowed to take. There are some drugs that will have to be used with caution. All medications that patients are taking will be reviewed by their study doctor and patients will be advised which medications will have to be stopped, replaced or restricted.

Risks associated with study procedures
Risks with biopsies
Patients who do not have their tumour tissue stored at the hospital will have to undergo biopsy at screening to confirm RET fusion status. The exact procedure depends on the location of the tumour.
General risks of biopsies include minor local bleeding, pain at the needle insertion site* swelling under the skin that contains blood* sleepiness, if patients receive a pain killer and/or a medicine to make them relax. Rarely, infection and shortness of breath can occur. If patients receive a pain killer and/or medicine to make them relax, in some cases they may experience slow heart rate and low blood pressure.

Risks with Infusions
All standard of care drugs will be given by infusion into a vein over up to an hour. Administration of cisplatin will have to include pre-and post-administration hydration procedures which may take many hours and involve

IV infusions. In order to do the infusion, the study staff may insert a catheter (a small hollow tube) into a vein in patient*s arm by a needle. The needle is removed, but the tube temporarily remains in patient*s vein. The catheter will be flushed or cleaned out with a small amount of salt water before and after it is used.

There could be discomfort or pain when the catheter and needle are inserted. There is a risk of feeling faint or passing out. There is also a risk of infection, bleeding, soreness, blood clots, tenderness, or bruising at the puncture site. A swelling at the infusion site can develop if fluid accidentally enters the tissue rather than the vein.

Blood sampling
During this study, small amounts of blood will be drawn from a vein and used for tests. Drawing blood may cause pain where the needle is inserted, and there is a small risk of bleeding, bruising or infection. Rarely, some people experience dizziness, upset stomach, or fainting when their blood is drawn.

Electrocardiogram (ECG)
Patients will have small, soft pads, placed temporarily on different parts of their body. There is no pain or discomfort during an ECG* however, the area of skin in which the ECG pads will be stuck may need to be shaved, and the pads may cause a skin reaction such as redness or itching. Taking the pads off may cause localised irritation to the skin and/or hair loss, similar to having a bandage taken off.

Risks with imaging procedures
Patients* response to treatment will be assessed with the use of imaging procedures which include CT and MRI scans. Each CT scan that patients will receive on the study provides the dose of radiation equivalent to 5-8 years* natural background radiation. A contrast dye may be injected into the vein or administered orally before the CT scan. This may cause a slight discomfort, bruising, swelling and sometimes an allergic reaction. Severe allergic reactions (for example, a drop in blood pressure, difficulty in breathing, or kidney problems) are very rare. Patients will have a kidney function test to determine if the contrast can be given safely. Some patients may find the CT scanner mildly claustrophobic.
Patients who are unable to undergo CT scans may be asked to have an MRI scan instead. Unlike CT, an MRI scan does not provide a dose of harmful X-ray radiation. For most patients, the risks or side effects associated with undergoing MRI are minimal. However, patients cannot have any metal implants to have an MRI scan. Patients will be asked questions to make sure they can safely have an MRI scan. There may be some anxiety and claustrophobia associated with the MRI scanner. Patients will be asked to lie still for around 30 minutes during each scan. As part of the MRI scan, a contrast agent may be injected into the vein. The risks associated with the contrast agent include mild nausea, headache, hives and temporary low blood pressure, although such

reactions are very rare. Patients will have kidney function tests to ensure the contrast agent can be given safely. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed.

It may also be necessary to perform any biopsy procedures using CT guidance to help the doctors accurately locate the tumour. The dose from the procedure will vary depending on its complexity, but may be equivalent to up to eight years* natural background radiation.

The ionising radiation from CT, and CT-guided biopsy procedures can cause cell damage that may, after many years or decades, turn cancerous. The theoretical chance of this happening to a patient who stays on the study for 2 years is around 1.7 %. Each additional year of participation would further increase the theoretical risk by around 0.5%.

However, the real risk is considered to be much smaller due to the short life expectancy of the participants in the study.

Reproductive risks
To avoid exposing a developing baby or breastfed infant to harmful effects of the study drugs and exposing the foetus to ionising radiation from some imaging procedures, pregnant or breastfeeding women will not be allowed to participate in the study.

Women who can have children and men with female partners who can have children will also be required to use effective contraception during treatm

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

Main inclusion criteria:
* Patient is *18 years of age
* Patient has pathologically confirmed, definitively diagnosed, advanced (not able to be treated with surgery or radiotherapy) or metastatic NSCLC and has not been treated with systemic anticancer therapy for metastatic disease.
* Patient must meet 1 of the following 2 criteria:
* Have a documented RET fusion using either tissue or plasma as determined by a local test. Refer to laboratory manual for details on acceptable local RET fusion testing methods and tissue requirements. Patient agrees to provide adequate tumor tissue (archived, if available, or a fresh biopsy) for central confirmation of RET fusion using a next generation sequencing (NGS) based assay. If no adequate tumor tissue is available and a new biopsy is not feasible, the patient will not be eligible for enrollment.
* Have documentation of a RET fusion by a positive result from tumor tissue testing performed at a Sponsor designated central laboratory using an NGS-based assay.
* Patient has measurable disease based on RECIST 1.1 as determined by the local site Investigator/radiology assessment.
* Patient has an ECOG PS of 0-1.
* Patient should not have received any prior anticancer therapy for metastatic disease.
* Patients can have received previous anticancer therapy (except a selective RET inhibitor) in the neoadjuvant or adjuvant setting but must have experienced an interval of at least * 6 months from completion of therapy to recurrence.
* Patients that received previous immune checkpoint inhibitors in the adjuvant or consolidation following chemoradiation are not allowed to receive pembrolizumab if randomized in Arm B
* Patient is an appropriate candidate for and agrees to receive 1 of the Investigator choice platinum-based chemotherapy regimens if randomized to Arm B.

* Patient provides signed informed consent to participate in the study.

Exclusion criteria

* Patient's tumor has any additional known primary driver alterations other than RET, such as targetable mutations of EGFR, ALK, ROS1, MET, and BRAF. Investigators should discuss enrollment with Sponsor designee regarding co-mutations.
* Patient previously received treatment with a selective RET inhibitor.
* Patient received radiotherapy or radiosurgery to any site within 14 days before randomization or more than 30 Gy of radiotherapy to the lung in the 6 months before randomization.
* Patient has a presence of Grade 2 or worse interstitial lung disease or interstitial pneumonitis, including radiation pneumonitis within 28 days before randomization.
* 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 before C1D1.

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):	22-04-2021
Enrollment:	10

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ALIMTA®
Generic name:	Pemetrexed
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	BLU-667
Generic name:	Pralsetinib
Product type:	Medicine
Brand name:	Keytruda®
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	n/a - differs per hospital
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	n/a - differs per hospital
Generic name:	Cisplatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-04-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-05-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved	
Date:	27-05-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	
Date:	14-09-2021
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
	CTIS2023-505035-12-00
EudraCT	EUCTR2019-002463-10-NL
ClinicalTrials.gov	NCT04222972
CCMO	NL72162.042.20