A Phase 1/2 Study of the Highly-selective RET Inhibitor, BLU-667, in Patients with Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors

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To investigate how safe the new medicine pralsetinib is when it is administered to patients with non-resectable advanced solid tumor cancers including non-small cell lung cancer (NSCLC) and Thyroid cancers.

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

Summary

ID

NL-OMON56358

Source
ToetsingOnline

Brief title
ARROW

Condition

- Other condition
- Respiratory and mediastinal neoplasms benign (excl mesotheliomas)

Synonym
Lung Cancer and Other Advanced Solid Tumors, Thyroid Cancer

Health condition

Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors

Research involving
Human

Sponsors and support

Primary sponsor: F. Hoffmann La-Roche Ltd
Source(s) of monetary or material Support: F. Hoffmann La-Roche Ltd

Intervention

Keyword: Other Advanced Solid Tumors, Phase 1/2, RET Inhibitor, Thyroid Cancer

Outcome measures

Primary outcome

Phase 2, Dose Expansion Objectives

Primary Objectives

• To determine the overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (or Response Assessment in Neuro-Oncology [RANO], if appropriate for tumor type) according to patients* disease type, and/or RET-altered status if applicable, and/or prior treatment status if appropriate.

• To further define the safety and tolerability of pralsetinib

Secondary outcome

Secondary Objectives

• To assess additional measures of clinical benefit including DOR, CBR, DCR, PFS, and overall survival (OS) in all patients according to patients* disease type, and/or RET-altered status if applicable, and/or prior treatment status if appropriate.

• To assess baseline RET gene status in plasma and/or tumor tissue and correlate with measures of antineoplastic activity including, but not limited to ORR, CBR, DOR, and DCR.

• To characterize the pharmacokinetic (PK) profile of pralsetinib and correlate drug exposure with safety assessments, including changes in ECG intervals, and efficacy.

• To characterize the pharmacodynamics of pralsetinib, including, but not limited to, changes in blood calcitonin and carcinoembryonic antigen (CEA) in MTC patients only.

• To assess brain activity in patients with NSCLC.

Exploratory Objectives

• To identify potential new blood and tumor tissue biomarkers (eg, DNA, RNA, and/or protein markers) of pharmacodynamic activity, antineoplastic activity, and/or toxicity.

• To assess changes in quality of life (QoL) questionnaire

• To explore disease-related symptoms, as measured by bowel movement history (MTC patients only).

• To explore clinical benefit including ORR, CBR, DCR, PFS for patients previously treated with a selective RET tyrosine kinase inhibitor.

• To assess brain activity in patients with tumor types other than NSCLC.

Study description

Background summary

Pralsetinib was designed to treat patients with tumors that have changes in the RET (Rearranged during Transfection) gene that may make the tumors grow. Changes in RET are found commonly in Thyroid cancer (medullary thyroid cancer - MTC) and less commonly in other cancers such as NSCLC.

In Phase 2, all patients, except those with MTC, are required to have lab results from previous testing of their tumor, indicating a change in the RET gene before enrollment. All Phase 2 patients, including MTC, must also have tumor tissue from a previous biopsy or from a new biopsy available for testing that can be submitted for confirmatory testing and additional research tests.

Study objective

To investigate how safe the new medicine pralsetinib is when it is administered to patients with non-resectable advanced solid tumor cancers including non-small cell lung cancer (NSCLC) and Thyroid cancers.

Study design

This is a Phase 1/2, open-label, first-in-human (FIH) study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary antineoplastic activity of pralsetinib, a potent and selective RET inhibitor, administered orally in patients with medullary thyroid cancer, RET-altered NSCLC and other RET-altered solid tumors.
The study consists of 2 parts, a dose-escalation part (Phase 1) and an expansion part (Phase 2). The Netherlands will only take part in Phase 2 of the study. The study will enroll patients with advanced non-resectable NSCLC, advanced non-resectable thyroid cancer and other advanced non-resectable solid tumors that have progressed following standard systemic therapy, have not adequately responded to standard systemic therapy, or the patients must be intolerant to or the Investigator has determined that treatment with standard therapy is not appropriate, or there must be no accepted standard therapy for their disease.
In Phase 2, patients will enroll into 1 of 7 groups based on their tumor type and prior therapy status (if applicable), must have at least 1 target lesion evaluable by RECIST v1.1 (or RANO, if appropriate):
• Group 1: NSCLC with a RET fusion previously treated with a platinum-based chemotherapy (N ~80).
• Group 2: NSCLC with a RET fusion not previously treated with a platinum-based chemotherapy including those who have not had any systemic therapy. Prior platinum chemotherapy in the neoadjuvant and adjuvant setting is permitted if the last dose of platinum was 4 months or more before the first dose of study drug (N~200).
• Group 3: MTC previously treated with cabozantinib and/or vandetanib (N ~65).
• Group 4: MTC not previously treated with cabozantinib and/or vandetanib (N ~40)
• Group 5: Other solid tumors with a RET fusion not eligible for any of the other groups (N ~100). Patients should have previously received SOC appropriate for their tumor type, unless there is no accepted standard therapy for the tumor type or the Investigator has determined that treatment with standard therapy is not appropriate. As the intent of this cohort is to enroll a variety

of RET-fusion tumor types, Blueprint will notify sites if/when sufficient data are available and accrual should cease for a particular tumor type.
• Group 6: Any Solid tumors with a RET alteration (fusion or mutation) previously treated with a selective RET tyrosine kinase inhibitor (TKI)
• Group 7: Other Solid tumors with a RET mutation previously treated with SOC appropriate for the tumor type (N ~20).

Determination of RET status as required for enrollment of all patients except those with MTC, is based on local assessment, or central assessment if local testing is not available. All patients enrolled in Phase 2 (all 7 groups) must submit tumor tissue (archived or new) for retrospective assessment of RET status and other pathway biomarkers. Patients enrolled into Group 6 (previously treated with a selective RET-inhibitor) are required to have a new tumor biopsy prior to enrollment.
All study visits are intended to be conducted on an outpatient basis, but may be conducted on an inpatient basis, as needed. After provision of written informed consent (within 8 weeks before study drug administration), patients will be evaluated for study eligibility during the Screening period within 28 days before study drug administration on Cycle 1, Day 1 (C1D1).
On C1D1, eligible patients will present to the study center approximately 2 hours before the first dose of study drug and will remain at the study center for at least 8 hours for serial PK sampling, pharmacodynamic sample collection, vital signs measurement, electrocardiogram (ECG) monitoring, safety laboratory tests, and safety monitoring. In Phase 2, patients will complete a QoL assessments (EORTC QLQ-C30). Additionally, in Phase 2 only, continuous ECG Holter monitoring will be performed approximately 1 hour before dosing until after collection of the 8-hour PK sample for approximately 20 evaluable patients at select study centers.

A treatment cycle is 28 days in duration. Initially, patients returned to the study center on C1D2 for PK sampling (24 hours after the C1D1 dose), C1D8 and C1D22 for safety monitoring, and on C1D15 and C1D16 for serial PK sampling and safety monitoring (including continuous Holter monitoring for 20 patients in Phase 2 at select study centers). Patients will also attend study center visits on C2D1 and C2D15, on Day 1 of C3 through C13, C15, C17, C21 and every 4 cycles thereafter for additional safety monitoring; PK and pharmacodynamic sampling; and disease response assessment by computed tomography (CT) or magnetic resonance imaging (MRI). In Phase 2 only, the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) will be administered on D1 of every cycle through C12. A tumor biopsy will be performed within 2 weeks (±) of C2D1 (Phase 1 only) and upon disease progression (both Parts), if the patient consents and the procedure is deemed to be safe and medically feasible by the Investigator.
All patients will attend an End-of-treatment (EOT) visit approximately 14 days (±7 days) after the last dose of study drug. A Follow-up telephone contact for resolution of any residual adverse event (AE) will be made on Day 30 (+7 days) after the last dose of study drug, or at the time the patient initiates another

antineoplastic therapy. All patients will be contacted every 3-4 months for PFS and every 3 months for overall survival.

Intervention

In Phase 2, all patients will receive the same dose of pralsetinib, being 400 mg once daily in 28-day cycles.
The dose should be taken in the morning and should be taken at approximately the same time each day. pralsetinib doses should be taken with a full glass of water on an empty stomach. Subject should not eat anything 2 hours before and until 1 hour after take the study drug.

Study burden and risks

Targeting oncogenic kinase mutants with selective inhibitors can provide dramatic therapeutic benefit in advanced solid tumours as observed with EGFR, ALK, and ROS1. However, there are no highly selective therapeutics currently available for targeting RET-altered cancers and limited anti-tumour activity as been demonstrated with multikinase inhibitors (MKIs). Additionally, MKIs are associated with significant toxicity that limit dose intensity and may prevent adequate suppression of RET-driven tumours. Therefore, RET-altered cancers remain a significant medical need.

Given the strong genetic and preclinical evidence tht activated RET is an oncogenic disease driver, the lack of selective RET inhibitors available, and the poor prognosis of many patients with RET-driven tumours, the use of a selective, targeted agent against this tumour alteration may be beneficial.

BLU-667 potently and selectively targets RET and RET-activated mutants such as M918T and V804L/M, shows potent anti-tumour activity in RET-driven tumour models, and demonstrates tolerability at pharmacologically active doses in preclinical toxicology species. Results of preclinical pharmacology studies and GLP toxicology studies with BLU-667 suggest that a manageable safety and tolerability profile can be achieved in humans. Currently, patients with advanced, RET-altered cancer have limited therapeutic options and poor prognosis. BLU-667 may provide the potential for significant therapeutic benefit in patients with RET-altered cancers as well as an acceptable risk profile. Therefore, further development of pralsetinib is warranted in a well-controlled, clinical trial setting.

(for the most updated data please refer to the Protocol summary and protocol section 1.5).

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

1. Patient is >= 18 years of age.
2. Diagnosis during dose escalation (Phase 1) - Pathologically documented, definitively diagnosed non-resectable advanced solid tumor.
• All patients treated at doses > 120 mg per day must have MTC, or a RET-altered solid tumor per local assessment of tumor tissue and/or blood.
• Phase 1 enrichment patients must have MTC or a RET-altered solid tumor per local assessment of tumor tissue and/or blood.
3. Diagnosis during dose expansion (Phase 2) - All patients (with the exception of patients with MTC enrolled in Groups 3 and 4) must have an oncogenic RET fusion or

mutation (excluding synonymous, frameshift, and nonsense mutations) solid tumor, as determined by local testing of tumor or circulating tumor nucleic acid in blood; as detailed below.
• Group 1 - patients must have pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a RET fusion previously treated with a platinum-based chemotherapy.
• Group 2 - patients must have pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a RET fusion not previously treated with a platinum-based chemotherapy, including those who have not had any systemic therapy. Prior platinum chemotherapy in the neoadjuvant and adjuvant setting is permitted if the last dose of platinum was 4 months or more before the first dose of study drug.
• Group 3 - patients must have pathologically documented, definitively diagnosed advanced MTC that has progressed within 14 months prior to the Screening Visit and was previously treated with cabozantinib and/or vandetanib.
• Group 4 - patients must have pathologically documented, definitively diagnosed advanced MTC that has progressed within 14 months prior to the Screening Visit and was not previously treated with cabozantinib or vandetanib.
• Group 5 - patients must have a pathologically documented, definitively diagnosed advanced solid tumor with an oncogenic RET fusion, have previously received SOC appropriate for their tumor type (unless there is no accepted standard therapy for the tumor type or the investigator has determined that treatment with standard therapy is not appropriate), and must not eligible for any of the other groups.
• Group 6 - patients must have a pathologically documented, definitively diagnosed advanced solid tumor with an oncogenic RET fusion or mutation, previously treated with a selective TKI that inhibits RET, such as LOXO-292.
• Group 7: patients must have a pathologically documented, definitively diagnosed advanced solid tumor with an oncogenic RET mutation previously treated with SOC appropriate for the tumor type and not eligible for any of the other groups.
4. Patients must have non-resectable disease. Prior to protocol amendment 9, patients
must have progressed following standard therapy or have not adequately responded to standard therapy, or the patient must be intolerant to, or the Investigator has determined that treatment with standard therapy is not appropriate, or there must be no accepted standard therapy for their disease.
5. Dose expansion (Phase 2) patients in all groups (except group 7) must have measurable disease per RECIST v1.1 (or RANO, if appropriate for tumor type).
6. Patient agrees to provide tumor tissue (archived, if available or a fresh biopsy) for RET status confirmation and is willing to consider an on-treatment tumor biopsy, if considered safe and medically feasible by

the treating Investigator. For Phase 2, Group 6, patients are required to undergo a pretreatment biopsy to define baseline RET status in tumor tissue.
7. Patient has Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1.
8. Patient or legal guardian provides informed consent to participate in the study.

Exclusion criteria

1. Patient's cancer has a known primary driver alteration other than RET. Investigators should discuss enrollment with Sponsor regarding comutations
2. Patient has any of the following within 14 d prior to the first dose of IMP:
a. Platelet count < 75 × 109/L
b. Absolute neutrophil count < 1.0 × 109/L
c. Hemoglobin < 9.0 g/dL red blood cell transfusion and erythropoietin may be used to reach at least 9.0 g/dL, but must have been administered at least 2 weeks prior to 1st IMP dose
d. AST or ALT > 3 × ULN if no hepatic metastases are present; > 5 × ULN if hepatic metastases are present
e. Total bilirubin > 1.5 × ULN; > 3 × ULN with direct bilirubin > 1.5 × ULN in presence of Gilbert's disease
f. Estimated (Cockroft-Gault formula) or measured creatinine clearance < 40 mL/min
g. Total serum phosphorous > 5.5 mg/dL
3. Patient has a QTcF > 470 msec. Patient has a history of prolonged QT syndrome or Torsades de pointes. Patient has a familial history of prolonged QT syndrome
4. Patient has clinically significant, uncontrolled, cardiovascular disease including congestive heart failure Grade III or IV according to the New York Heart Association classification; myocardial infarction or unstable angina within the previous 6 months, uncontrolled hypertension, or clinically significant, uncontrolled arrhythmias, including bradyarrhythmias that may cause QT prolongation
5. Patient has CNS metastases or a primary CNS tumor 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 preceding C1D1
6. Presence of clinically symptomatic interstitial lung disease or interstitial pneumonitis, including radiation pneumonitis
7. Patient received the following anti-cancer therapy:
a. Any systemic anticancer therapy (except for immunotherapy or other antibody therapies) and all forms of radiotherapy within 14 d or 5 halflives

prior to first IMP dose. IMP may be started within these washout periods if considered by the Investigator to be safe and within the best interest of the patient prior Sponsor approval
b. Any immunotherapy or other antibody therapy within 28 d prior to the 1st dose of IMP (immune related toxicities must have resolved to < Grade 2 prior to starting IMP)
8. Dose expansion patients in Groups 1-5 and 7 (Phase 2): patient has previously received treatment with a selective RET inhibitor such as selpercatinib
9. Patient received neutrophil growth factor support within 14 d of 1st IMP dose
10. Patient requires treatment with a prohibited medication or herbal remedy that cannot be discontinued at least 2 weeks before start of IMP administration. IMP may be started within 14 d or 5 half-lives of prior therapy if considered by the Investigator to be safe and within the best interest of the patient, with prior Sponsor approval
11. Patient has had a major surgical procedure within 14 d of the first IMP dose
12. Patient has a history of another primary malignancy that has been diagnosed or required therapy (except maintenance anti-hormonal therapy) within the past year. The following prior malignancies are not Not exclusionary are: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, curatively treated localized thyroid cancer, and completely resected carcinoma in situ of any site
13. Patient is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, or other study procedures and study restrictions
14. Women who are unwilling, if not postmenopausal or surgically sterile, to abstain from sexual intercourse or employ highly effective contraception during IMP administration period and for at least 14 days after the last IMP dose. Men who are unwilling, if not surgically sterile, to abstain from sexual intercourse or employ highly effective contraception during the IMP administration period and for at least 7 days after the last IMP dose
15. Pregnant females, as documented by a serum β-hCG pregnancy test consistent with pregnancy, obtained within 7 days prior to the first dose of study drug. Females with β-hCG values that are within the range for pregnancy but are not pregnant (false-positives) may be enrolled with written consent of the Sponsor, after pregnancy has been ruled out. Females of non-childbearing potential (postmenopausal for more than 1 year; bilateral tubal ligation; bilateral oophorectomy; hysterectomy) do not require a serum β-hCG test
16. If female, patient is breastfeeding
17. Patient has prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the Investigator's or Sponsor's opinion, could affect the safety of

the patient;
alter the absorption, distribution, metabolism, or excretion of the study drug; or impair the assessment of study results

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-03-2017
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	pralsetinib
Generic name:	RO7499790

Ethics review

Approved WMO Date:	01-10-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-12-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-06-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-09-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	06-07-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-05-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-05-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-07-2022
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Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-01-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	02-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-08-2023
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
EudraCT	EUCTR2016-004390-41-NL
ClinicalTrials.gov	NCT03037385
CCMO	NL67119.042.18