A Phase 2 Study of Poziotinib in Patients with Non-Small Cell Lung Cancer (NSCLC), Locally Advanced or Metastatic, with EGFR or HER2 Exon 20 Insertion Mutation (ZENITH20)

Published: 29-08-2018
Last updated: 12-04-2024

Objectives:To evaluate the following in NSCLC patients with EGFR or HER2 exon 20 insertion mutations (includingduplication mutations) who are treated with poziotinib:Primary Objective:Objective Response Rate (ORR)Secondary Objectives:• Disease...

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

Summary

ID

NL-OMON55568

Source
ToetsingOnline

Brief title
SPI-POZ-202

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
lung cancer, non-small-cell lung carcinoma, NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Spectrum Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Spectrum Pharmaceuticals;Inc.

Intervention

Keyword: EGFR or HER2 Exon 20 Insertion Mutation, Non-Small Cell Lung Cancer, Poziotinib

Outcome measures

Primary outcome

Primary Endpoint:

• Objective Response Rate (ORR, the rate of complete response and partial

response)

Secondary outcome

• Disease Control Rate (DCR, complete response+partial response+stable disease)

• Duration of Response (DoR)

• Safety and Tolerability Exploratory Endpoint:

• Progression-free Survival (PFS)

• Overal survival

• Quality of Life (QoL) (Cohorts 1 to 4 only)

Study description

Background summary

Poziotinib (HM781-36B) is a novel, oral, quinazoline-based pan-HER inhibitor that irreversibly blocks signaling through the EGFR family of tyrosine-kinase receptors, including human epidermal growth factor receptor (HER1/ErbB1/EGFR), HER2 (ErbB2), and HER4 (ErbB4), as well as HER receptor mutations. This, in

turn, leads to inhibition of the proliferation of tumor cells that overexpress these receptors. It is well established that several malignancies, including lung, breast, stomach, colorectal, head, and neck, and pancreatic carcinomas, are associated with a mutation in or overexpression of members of the EGFR receptor family.
To date, more than 200 patients have received poziotinib monotherapy in open-label clinical trials at doses ranging from 0.5 mg to 32 mg on an intermittent dosing schedule and from 12 mg to 24 mg on a continuous dosing schedule, or as combination therapy with trastuzumab and paclitaxel. Clinical activity was observed in patients on poziotinib monotherapy and in combination with other anti-cancer agents, as defined by objective responses or prolonged stabilization of disease. Clinical benefit has been observed in patients with several solid tumors.
Based on the promising clinical data and acceptable safety profile from studies in HER2-overexpressed tumors and the preclinical data suggesting activity against EGFR and HER2 exon 20 insertion mutations, a single-center Phase 2 Investigator Initiated Study (IIS) was started to evaluate poziotinib in the patients with NSCLC and EGFR or HER2 exon 20 insertion mutations. The design of this study is similar to the IIS and is intended for further evaluation of the efficacy and safety of poziotinib in this NSCLC patient population.

Study objective

Objectives:
To evaluate the following in NSCLC patients with EGFR or HER2 exon 20 insertion mutations (including
duplication mutations) who are treated with poziotinib:

Primary Objective:
Objective Response Rate (ORR)

Secondary Objectives:
• Disease Control Rate (DCR)
• Duration of Response (DoR)
• Safety and tolerability

Exploratory Objectives:
• Progression-free Survival (PFS)
• Quality of Life (QoL) (Cohorts 1 to 4 only)
• Evaluate alternate poziotinib starting doses and schedules
• Evaluate poziotinib in patients who progressed while on treatment with first-line osimertinib (Cohort 6 only)
• Evaluate poziotinib in patients with EGFR or HER2 activating mutations
• Evaluate overall survival
• Characterize the PK profile of poziotinib

Study design

This is a Phase 2, open-label, multicenter study to evaluate the efficacy and the safety/tolerability of poziotinib in up to 554 patients with previously treated and treatment-naïve NSCLC exon 20 insertion mutations.
Duration of Study: The study will run for approximately 5 years. The total duration of the study for each patient will be approximately 2 years. The duration of study participation for each patient includes the following segments:

• Screening Period: up to 30 days
• Treatment Period: 28 days per cycle until disease progression or a maximum of 24 months after the initiation of the study treatment, whichever comes first
• Safety Follow-up Visit: 35 (±5) days after the last dose of poziotinib
• Long-Term Follow-up: After study drug discontinuation, patients who have consented will be contacted every 3 months, for up to 2 years after patient*s first dose of poziotinib, for survival assessment

Intervention

The Screening period (Day -30 to Day -1) lasts up to approximately 30 days prior to Cycle 1, Day 1. Patients must meet all Inclusion/Exclusion Criteria to participate in the study. Eligible patients will provide written Informed Consent prior to undergoing any study procedures.
Each treatment cycle is 28 calendar days in duration. There will be four cohorts and eligible patients will be enrolled into each cohort based on EGFR or HER2 exon 20 mutation status and prior treatment status:

• Cohort 1 (ZENITH20-1): Previously treated patients with EGFR exon 20 insertion mutation positive NSCLC
• Cohort 2 (ZENITH20-2): Previously treated patients with HER2 exon 20 insertion mutation positive NSCLC
• Cohort 3 (ZENITH20-3): Treatment naïve patients with EGFR exon 20 insertion mutation positive NSCLC
• Cohort 4 (ZENITH20-4): Treatment naïve patients with HER2 exon 20 insertion mutation positive NSCLC
• Cohort 5 (ZENITH20-5): Patients who meet the criteria for enrollment in Cohort 1 to 4, but the enrollment in the respective cohort has been closed
• Cohort 6 (ZENITH20-6): Patients with acquired EGFR mutation who progressed while on treatment with first-line osimertinib
• Cohort 7 (ZENITH20-7): Patients with EGFR or HER2 activating mutations

Toxicity will be assessed based on the grade of the adverse events using CTCAE version 4.03.
All treatments will be taken orally, once daily (QD) at approximately the same time each morning. On Day 1 of each 28-day cycle, the patient*s absolute

neutrophil count (ANC) must be >=1.5×109/L and platelet count must be >=100×109/L before administering poziotinib. All patients will be treated until disease progression, death, intolerable adverse events, or up to a maximum of 24 months, whichever comes first.
Taking of poziotinib is once a day (QD). Poziotinib is supplied as 8-mg tablets and 2-mg tablets and will be administered on an outpatient basis orally once daily with breakfast at approximately the same time each morning. If the morning dose is missed, this dose may be administered any time during the day preferably with food, but at least 8 hours prior to the next scheduled dose. On Cycle 2 Day 1, the daily dose will be taken at the clinic after the ECG is performed.

(text deleted)
Additional blood samples will be collected (an additional 4 teaspoons) to test for pharmacogenomics.
During the study, blood plasma will be taken (an additional 4 teaspoons) and sent to a central laboratory for biomarker testing at each imaging session (beginning at Cycle 3).

The PK profile of poziotinib and its metabolites (M1 and M2) will be characterized. All patients will have blood samples drawn pre-dose and at 1 hour and 2 hours (±15 min) post-dose on Cycle 1, Day 1 and Cycle 2, Day 1 for sparse PK and time-matched concentration-ECG analysis. At select study centers, patients (a minimum of 6 patients per dosing schedule) will be specifically consented for intensive PK in the 8 mg BID groups in Cohort 5. Intensive PK blood sampling will replace sparse PK blood sampling in Cycle 1 and sparse sampling on Cycle 2, Day 1 is not required in these patients. The schedule for intensive PK blood sampling will be pre-dose and 1, 2, 4, 8, 12, and 24 hours post-dose on Cycle 1, Day 1 and Cycle 1, Day 8 (±2 days). The 12-hour PK sample must be collected prior to the second daily dose (12-hour dose). Patient must be on drug at the time of blood sampling.

Study burden and risks

Patients will be required to: take poziotinib by mouth twice a day starting with with breakfast at approximately the same time each morning during each 28-day treatment cycle; come to the hospital for study drug visits, tests and procedures, use an effective form of birth control while on study drug and for a minimum of 30 days after the last dose of the study drug; take a preganncy test at screening; complete diaries and questionnaires.
The most commonly reported risks of poziotinib are: loose stools or diarrhea, which could lead to dehydration, rash, mouth sores and lesions, decreased appetite, dry skin and itchiness, upset stomach and abdominal pain, nausea, vomiting, fatigue, runny nose, infection of the hand or foot including nail infection, hand-foot syndrome (redness, swelling and numbness of hands and feet).

Contacts

Public
Spectrum Pharmaceuticals, Inc.

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Scientific
Spectrum Pharmaceuticals, Inc.

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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

1. Patient is at least 18 years of age
2. Patient must be willing and capable of giving written Informed Consent, adhering to dosing and visit schedules, and meeting all study requirements
3. Patient has histologically or cytologically confirmed locally advanced or metastatic non-small cell lung cancer (NSCLC) that is not amenable to treatment with curative intent
4. Prior treatment status:
• Cohorts 1 and 2: Patient has had at least one prior systemic treatment for locally advanced or metastatic NSCLC
• Cohorts 3 and 4: Patient is treatment-naïve for locally advanced or metastatic NSCLC and eligible to receive first-line treatment with poziotinib

as determined by the Investigator. Adjuvant/neo-adjuvant therapies (chemotherapy, radiotherapy, or investigational agents) are permissible as long as they end at least 15 days prior to study entry.
• Cohort 5: Patients who meet the criteria for enrollment in Cohort 1 to 4, but the enrollment in the respective cohort has been closed • Cohort 6: Patients with EGFR mutation-positive NSCLC who progressed while on treatment with first-line osimertinib. • Cohort 7: Patient has had at least one prior systemic treatment for locally advanced or metastatic NSCLC
5. Tissue and plasma samples for mutation confirmation: • Cohorts 1 to 5: Patient has adequate tumor tissue obtained from a biopsy or surgical procedure to enable molecular profiling for retrospective central laboratory confirmation of the mutation. If tissue is not available, the patient must have biopsy accessible disease and must be willing to undergo a biopsy to provide an appropriate tissue sample prior to receiving treatment in the study. • Cohort 6: Either tissue or plasma samples after osimertinib progression. • Cohort 7: Either tissue or plasma samples.
6. Patient is positive for EGFR or HER2 exon 20 mutations based on tissue testing:
• Cohorts 1 and 3: Documented EGFR exon 20 insertion mutation (including duplication mutations) using a next generation sequencing diagnostic test, such as OncoMine Comprehensive Assay (OCA) or FoundationOne Assay, or by an FDA approved test (eg, cobas® EGFR mutation test v2 or therascreen EGFR RGQ PCR kit) performed by a US CLIA certified and locally licensed clinical laboratory or similarly accredited lab for ex-US sites using tissue samples
• Cohorts 2 and 4: Documented HER2 exon 20 insertion mutation (including duplication mutations) using a next generation sequencing diagnostic test, such as OncoMine Comprehensive Assay (OCA) or FoundationOne Assay, performed by a US CLIA certified and locally licensed clinical laboratory or similarly accredited lab for ex-US sites using tissue samples
• Cohort 6: Documented acquired EGFR mutation (tested after osimertinib progression) who have progressed while on first-line osimertinib treatment using tissue or plasma tested with a next generation sequencing assay. • Cohort 7: Documented EGFR or HER2 activating mutations using tissue or plasma tested with a next-generation sequencing assay.
7. Patient has measurable NSCLC disease, as per the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). (Text removed).
8. Brain metastases may be allowed if patient's condition is stable, defined as clinically asymptomatic, no requirement for high dose or increasing dose of systemic corticosteroids, and no need for any anticonvulsant therapy for metastatic brain disease. For the patient who has had radiation therapy, sequential post-treatment MRI tests, at least
4-6 weeks apart, should show no increases in brain lesion size/volume within 4 weeks prior to the study.
9. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and has a life-expectancy of more than 6 months
10. Patient has recovered from prior systemic therapy for metastatic disease to Grade <=1 for non-hematologic toxicities (except for Grade <=2 peripheral

neuropathy) and has adequate hematologic, hepatic, and renal function at Baseline, as defined by:
• Leukocytes >=3.0×10 9/L
• Absolute neutrophil count (ANC) must be >=1.5×10 9/L
• Platelet count >=100×10 9/L
• Hemoglobin >=9.0 g/dL
• Total bilirubin <=2 mg/dL; if hepatic metastases are present, <=2.5×ULN
• SGOT (AST) and SGPT (ALT) <=2.5×ULN with the following exception; Patients with liver metastases AST, ALT <=5×ULN
• Creatinine clearance >=50 mL/min
11. Patient is willing to practice 2 forms of contraception, one of which must be a barrier method, from study entry until at least 30 days after the last dose of poziotinib
12. Females of childbearing potential must have a negative pregnancy test within 7 days prior to Day 1. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) or who are surgically sterilized do not require this test.

Exclusion criteria

1. Patient has:
• All Cohorts: EGFR T790M
• Cohorts 1 to 5: EGFR exon 20 point mutation
• Cohort 7: EGFR Exon 19 deletion and L858R or HER2 T798I mutations, EGFR and HER2 Exon 20 insertion mutation
2. Patient has had previous treatment with poziotinib or any other EGFR or HER2 exon 20 insertion mutation-selective tyrosine kinase inhibitor (TKI) prior to study participation. The currently approved TKIs (ie, erlotinib, gefitinib, afatinib, osimertinib) are not considered to be exon 20 insertion-selective and are permissible (Cohorts 1 and 2).
3. Patient is concurrently receiving chemotherapy, biologics, immunotherapy for cancer treatment; systemic anti-cancer treatment or investigational treatment should not be used within 2 weeks or 5 halflives, whichever is longer; local radiation therapy for bone pain may be allowed.
4. Patient has a history of congestive heart failure (CHF) Class III/IV according to the New York Heart Association (NYHA) Functional Classification or serious cardiac arrhythmias requiring treatment
5. Patient has a high risk of cardiac disease, as determined by the Investigator, may undergo either echocardiogram (ECHO) or multi-gated acquisition (MUGA) during Screening and has a cardiac ejection fraction <50%.
6. Patient has had other malignancies within the past 3 years, except for stable non-melanoma skin cancer, fully treated and stable early stage prostate cancer or carcinoma in situ of the cervix or breast without need of treatment
7. Patient is confirmed to have clinically significant or recent acute gastrointestinal disease presenting as diarrhea and/or coloenteritis as a main

symptom (ie, acute enteritis, malabsorption, or Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) Grade 2 or above diarrhea due to other etiologies)
8. Patient has an active Grade >=2 skin disorder, rash, mucositis, or skin infection that needs medication or therapy or existing Grade >=2 skin toxicity from previous therapies; Grade >=2 neuropathy, Grade >=2 pneumonitis.
9. Patient is unable to take drugs orally due to disorders or diseases that may affect gastrointestinal function, such as inflammatory bowel diseases (eg, Crohn's disease, ulcerative colitis) or malabsorption syndrome, or procedures that may affect gastrointestinal function, such
as gastrectomy, enterectomy, or colectomy
10. Patient has an active liver disease or biliary tract disease (except for Gilbert's disease, asymptomatic biliary stones, liver metastasis, or stabilized chronic liver diseases)
11. Patient has known hypersensitivity to poziotinib or has a history of allergic reactions attributed to chemically similar compounds or other tyrosine kinase inhibitors (TKIs)
12. Patient has an active uncontrolled infection, underlying medical condition, or other serious illness that would not be appropriate for this study
13. Patient has unstable, uncontrolled, active bleeding disorders that the investigator considers that the patient could be at increased risk or not be suitable for treatment in this study
14. Patient is pregnant or breast-feeding.
15. Cohort 5 only: Patient is eligible for treatment in an open cohort (Cohorts 1 to 4).

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-01-2019

Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Poziotinib Hydrochloride
Generic name:	Poziotinib

Ethics review

Approved WMO Date:	29-08-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-10-2019

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-11-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-03-2022
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2018-001868-36-NL
ClinicalTrials.gov	NCT03318939
CCMO	NL66741.078.18