A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with RET Activation (LIBRETTO-001)

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Primary objective:To determine the MTD/recommended dose for further study of oral LOXO-292 in patients with advanced solid tumors, including RET-fusion NSCLC, MTC, and other tumors with increased RET activity.Secondary objectives:* To determine the...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON48590

Source
ToetsingOnline

Brief title
LOXO-RET-17001

Condition

- Metastases
- Nervous system neoplasms malignant and unspecified NEC

Synonym
Advanced Solid Tumors, and Other Tumors with Increased RET Activity, Including RET-Fusion Non-Small Cell Lung Cancer, Medullary Thyroid Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Loxo Oncology, Inc.
Source(s) of monetary or material Support: Loxo Oncology Inc.

Intervention

Keyword: Carcinoma, Colonic Neoplasms, Lung Neoplasms, Non-Small-Cell Lung, Thyroid Diseases

Outcome measures

Primary outcome

Primary Endpoint:

* MTD/recommended dose for further study: incidence rate and category of DLTs

during the first 28-day cycle of LOXO-292 treatment.

Secondary outcome

Secondary Endpoints:

* Adverse drug reactions and serious adverse drug reactions, changes in

hematology and blood chemistry values, assessments of physical examinations,

vital signs, and ECGs.

* Plasma concentration of LOXO-292 and PK parameters including but not limited

to AUC0-24 (area under the curve from time 0 to 24 hours), Cmax (maximum drug

concentration), Tmax (time to maximum plasma concentration), T1/2 (terminal

elimination half-life), and degree of accumulation.

* ORR (CR+PR), DOR, proportion of patients that have any tumor regression as a

best response, CBR, PFS, OS.

Exploratory Endpoints:

* Changes in the serum tumor markers CEA and calcitonin (patients with MTC only).

* Identity of RET gene fusions and mutations and mutations in tumor biopsies and circulating tumor DNA.

* Identity of concurrently activated oncogenic pathways in fresh pre-treatment tumor biopsies.

* Identity of changes in tumor molecular status in fresh tumor biopsies and circulating tumor DNA obtained during treatment and after progression on LOXO-292.

Study description

Background summary

LOXO-292 is a highly potent and specific inhibitor of the RET RTK, with minimal inhibition of other kinase and non-kinase targets, and therefore may be of benefit to patients with tumors (such as NSCLC, MTC, PTC, and colon or breast carcinomas) that harbor RET alterations and/or depend on RET activity. This Phase 1 study of LOXO-292 is required to understand the PK, safety, and maximum tolerated dose (MTD) for LOXO-292 in patients, and to permit the preliminary assessment of efficacy.

Study objective

Primary objective:
To determine the MTD/recommended dose for further study of oral LOXO-292 in patients with advanced solid tumors, including RET-fusion NSCLC, MTC, and other tumors with increased RET activity.

Secondary objectives:
* To determine the safety profile and tolerability of LOXO-292, including both acute and chronic toxicities.
* To characterize the PK properties of LOXO-292.
* To assess, for each expansion cohort, the preliminary anti-tumor activity of

LOXO-292 when administered to patients with tumors harboring abnormalities in RET, by determining:
* Overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) or Response Assessment in Neuro-Oncology (RANO), as appropriate to tumor type;
* Duration of response (DOR) in patients with best overall response of complete response (CR) or partial response (PR);
* Best change in tumor size from baseline;
* Clinical benefit rate (CBR) based on the proportion of patients with best overall response of CR, PR or stable disease (SD) lasting 6 or more months following initiation of treatment with LOXO-292;
* Duration of PFS following initiation of LOXO-292
* Duration of overall survival (OS) following initiation of LOXO-292.

Exploratory objectives:
* To determine the relationship between PK and drug effects, including efficacy and safety.
* To evaluate the serum tumor markers carcinoembryonic antigen (CEA) and calcitonin before, during, and at the end of treatment with LOXO-292 (for patients with MTC only).
* To characterize RET gene fusions and mutations by molecular analysis, including next-generation sequencing (NGS) from tumor biopsies and circulating tumor DNA.
* To characterize concurrently activated oncogenic pathways in pre-treatment tumor biopsies with the aim of elucidating RET biology, and modifiers of response to LOXO-292.
* To assess changes in tumor molecular status in fresh tumor biopsies and circulating tumor DNA obtained during treatment and after progression on LOXO-292, with the aim of elucidating RET biology, modifiers of response, and mechanisms of acquired resistance to LOXO-292.

Study design

This is an open label, multi-center Phase 1 study in patients with advanced solid tumors, including RET-fusion NSCLC, MTC and other tumors with increased RET activity (e.g., fusions, mutations or other evidence of increased RET activity). This study includes two parts: dose escalation and dose expansion. Patients with RET alterations will be identified through molecular assays, as performed for clinical evaluation. The RET alteration result should be generated from a laboratory with certification by CLIA (Clinical Laboratory Improvement Amendments), ISO/IEC (International Organization for Standardization/ Independent Ethics Committee), CAP (College of American Pathologists), or other similar certification. The Sponsor should be contacted to discuss test results from labs where such certification is not clearly demonstrated to determine eligibility.

Intervention

Patients will begin dosing on C1D1 according to the assigned cohort. During dose escalation, the DLT period and cycle length will be 28 days; during dose expansion, cycle length will be 28 days. Individual patients will continue LOXO-292 dosing until PD, unacceptable toxicity, or other reason for treatment discontinuation. Patients with documented disease progression (PD) may be allowed to continue LOXO-292 if the patient is
tolerating treatment and, in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the Sponsor.

Study burden and risks

Risks: possible side effects of the study drug and study procedures
Burden: blood draws

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria for Dose Escalation:
1. Patients with a locally advanced or metastatic solid tumor that:
* Has progressed following standard therapy, or
* Has not adequately responded to standard therapy, or
* For which no standard therapy exists, or
* Patients who decline standard therapy, or
* In the opinion of the Investigator, are not candidates for, or would be unlikely to tolerate or derive
significant clinical benefit from standard therapy.
2. Any number of prior TKIs with anti-RET activity are allowed. Refer to Appendix A for examples of multikinase inhibitors (MKIs) with anti-RET activity. The specific agent(s), duration of treatment, clinical benefit and reason for discontinuation (e.g., PD, drug toxicity or intolerance) should be documented for all kinase inhibitors the patient has been exposed to.
3. Evidence of a RET gene alteration in tumor and/or blood (e.g., gene rearrangement and/or mutation, excluding synonymous, frameshift or nonsense mutations), as identified through molecular assays, as performed for clinical evaluation. The RET alteration result should be generated from a laboratory with certification by CLIA, ISO/EIC, CAP, or other similar certification. The Sponsor should be contacted to discuss test results from labs where such certification is not clearly demonstrated to determine eligibility.
Notes:
* During dose escalation, a RET gene alteration is not required initially. The Sponsor*s preclinical data indicates that a LOXO-292 plasma level of 70 ng/mL is equivalent to the 50% inhibitory concentration (IC50) for RET (corrected for human plasma protein binding). Therefore, once a dose level is achieved that: (1) is associated with a DLT rate of <33%; (2) is deemed safe by the SRC; and
(3) is associated with a minimum concentration (Cmin) of >70 ng/mL at steady state in *70% of
patients in the same dosing cohort (e.g., 3/3, 3/4, 4/5, 5/6 patients, etc.), enrollment to subsequent
dose levels during dose escalation will be restricted to patients with: (1) RET-fusion NSCLC; (2)
MTC; (3) an advanced solid tumor that harbors a RET gene alteration (e.g., gene rearrangement
and/or mutation, excluding synonymous, frameshift or nonsense mutations) or (4) with prior Sponsor
approval, an advanced solid tumor with other evidence of increased RET activity, e.g., increased RET expression in the absence of mutation, with strong preclinical/clinical evidence

for RET dependence.
* A positive germline test for a RET mutation is acceptable for patients with MTC.
* Local testing in a CLIA, ISO/IEC, CAP, or other similar certified laboratory is sufficient.
* In all cases, an anonymized/redacted Molecular Pathology Report, or other report(s) describing tumor RET (and other) mutation analysis should be submitted to the Sponsor or designee during Screening.
4. Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumor type.
5. At least 18 years of age.
* For countries and sites where approved, patients as young as 12 years of age may be enrolled.
6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 with no sudden deterioration 2 weeks prior to the first dose of study treatment.
7. Life expectancy of at least 3 months.
8. Archived tumor tissue sample available.
Notes:
* Patients who do not have adequate archival tumor tissue available (see specific archival tissue
requirements in Section 7.8.4.1) should undergo a fresh tumor biopsy, if it is considered safe to
perform, prior to treatment.
* If adequate archived tumor tissue (see specific archival tissue requirements in Section 7.8.4.1) is not available and a fresh biopsy cannot be safely performed, the patient may still be eligible with prior Sponsor approval.
* If archived tumor tissue was obtained prior to progression on the last TKI with anti-RET activity, the
patient may undergo a fresh tumor biopsy, if it is considered safe to perform, prior to treatment.
9. Adequate hematologic status, defined as:
* Absolute neutrophil count (ANC) *1.0× 109/L not requiring growth factor support for at least 7 days
prior to treatment, and
* Platelet count *75 × 109/L not requiring transfusion support for at least 7 days prior to treatment, and
* Hemoglobin (Hb) *9 mg/dL not requiring transfusion support or erythropoietin for at least 7 days
prior to treatment.
10. Adequate hepatic function, defined as:
* ALT or AST *2.5 × the upper limit of normal (ULN) or *5 × ULN with documented liver involvement (such as liver metastasis or a primary biliary tumor) and
* Total bilirubin *1.5 × ULN or *3 × ULN with documented liver involvement (patients with Gilbert*s
Disease may be enrolled with prior Sponsor approval).
11. Adequate renal function, with estimated glomerular filtration rate *30 mL/minute.
12. Ability to swallow capsules and comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
13. Willingness of men and women of reproductive potential to observe conventional and

effective birth control for the duration of treatment and for 3 months following the last dose of study treatment; this may include barrier methods such as condom or diaphragm with spermicidal gel.
Notes:
* A postmenopausal woman will be defined as having no menses for 12 months without an alternative medical cause. Male sterility will be defined as only men sterilized surgically. For male patients with a pregnant partner, a condom should be used for contraception. For male patients with a non-pregnant female partner of child-bearing potential and woman of child-bearing potential one of the following birth control methods with a failure rate of less than 1% per year when used consistently and correctly are recommended:
a. Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally
b. Progestogen-only hormonal contraception associated with inhibition of ovulation given orally,
by injection, or by implant
c. Intrauterine device (IUD)
d. Intrauterine hormone-releasing system (IUS)
e. Bilateral tubal occlusion
f. Vasectomized partner
g. Sexual abstinence
* Birth control methods unacceptable for this clinical trial are:
a. Periodic abstinence (calendar, symptothermal, or post-ovulation methods)
b. Withdrawal (coitus interruptus)
c. Spermicide only
d. Lactational amenorrhea method;Inclusion Criteria for Dose Expansion:
1. Patients with a locally advanced or metastatic solid tumor that:
* Has progressed following standard therapy, or
* Has not adequately responded to standard therapy, or
* For which no standard therapy exists, or
* Patients who decline standard therapy, or
* In the opinion of the Investigator, are not candidates for, or would be unlikely to tolerate or derive
significant clinical benefit from standard therapy.
2. Patients with a locally advanced or metastatic solid tumor with evidence of a RET gene alteration in tumor and/or blood (e.g., gene rearrangement and/or mutation, excluding synonymous, frameshift and nonsense mutations), as determined through molecular assays, as performed for clinical evaluation. The RET alteration result should be generated from a laboratory with certification by CLIA, ISO/IEC, CAP, or other similar certification. The Sponsor should be contacted to discuss test results from labs where such certification is not clearly demonstrated to determine eligibility.
Notes:
* Enrollment to Cohorts 1, 2, 3 and 4 will be restricted to patients with evidence of a RET gene alteration in tumor (i.e., not just blood) as defined in Table 2 (Table 3-3 in main protocol) However, a positive germline DNA test for a RET gene mutation as defined in Table 2 (Table 3-3 in main protocol) is acceptable in the absence of tumor tissue testing for patients with MTC.
* Patients with a tumor that harbors a RET gene alteration not defined in Table 2 (Table 3-3 in

main
protocol) (excluding synonymous, frameshift or nonsense mutations) may be enrolled to Cohort 5.
* Patients with other evidence of increased RET activity, e.g., increased RET expression in the absence of mutation, with strong preclinical/clinical evidence for RET dependence, may be enrolled to Cohort 5 with prior Sponsor approval.
* cfDNA-positive patients (i.e., for a RET gene alteration) with tumor tissue negative or discordant and not further evaluable may be enrolled to Cohort 5.
* During dose expansion, since available genotyping assays for RET may not include all of the exons in which clinically relevant activating mutations have been previously identified, MTC patients with a tumor that tests negative for a RET gene mutation may be enrolled to Cohort 5 with prior Sponsor approval.
* Local testing in a CLIA, ISO/IEC, CAP, or other similar certified laboratory is sufficient.
* In all cases, an anonymized/redacted Molecular Pathology Report, or other report(s) describing tumor RET (and other) mutation analysis should be submitted to the Sponsor or designee during /prior to eligibility.
3. For MTC patients: Radiographic PD within the previous 14 months.
Note: Patients without radiographic PD within the previous 14 months may be enrolled with prior Sponsor approval.
4. Any number of prior TKIs with anti-RET activity are allowed. Refer to Appendix A for examples of MKIs with anti-RET activity. The specific agent(s), duration of treatment, clinical benefit and reason for discontinuation (e.g., PD, drug toxicity or intolerance) should be documented for all kinase inhibitors the patient has been exposed to.
Note: Patients with prior exposure to TKI(s) with RET-fusion NSCLC or RET-mutant MTC will be enrolled to Cohorts 1 or 3, respectively. TKI-naïve patients with RET-fusion NSCLC or RET-mutant
MTC will be enrolled to Cohorts 2 or 4, respectively.
5. At least one measurable lesion as defined by RECIST 1.1 or RANO, as appropriate to tumor type, not previously irradiated. Patients without RECIST 1.1 or RANO measurable disease will be eligible for enrollment to Cohort 5.
6. At least 18 years of age.
* For countries and sites where approved, patients as young as 12 years of age may be enrolled.
7. ECOG performance status score of 0, 1, or 2 with no sudden deterioration 2 weeks prior to the first dose of study treatment.
8. Life expectancy of at least 3 months.
9. Archived tumor tissue sample available.
Notes:
* Patients who do not have adequate archival tumor tissue available (see specific archival tissue requirements in Section 7.8.4.1) should undergo a fresh tumor biopsy, if it is considered safe
to perform, prior to treatment.
* If adequate archived tumor tissue (see specific archival tissue requirements in Section 7.8.4.1) is not available and a fresh biopsy cannot be safely performed, the patient may still be eligible for Cohort 5 with prior Sponsor approval.
* If archived tumor tissue was obtained prior to progression on the last TKI with anti-RET activity, the

patient may undergo a fresh tumor biopsy, if it is considered safe to perform, prior to treatment.
10. Adequate hematologic status, defined as:
* ANC *1.0× 109/L not requiring growth factor support for at least 7 days prior to treatment, and
* Platelet count *75 × 109/L not requiring transfusion support for at least 7 days prior to treatment, and
* Hb *9 mg/dL not requiring transfusion support or erythropoietin for at least 7 days prior to treatment.
11. Adequate hepatic function, defined as:
* ALT and AST *2.5 × ULN or *5 × ULN with documented liver involvement (such as liver metastasis or a primary biliary tumor) and
* Total bilirubin *1.5 × ULN or *3 × ULN with documented liver involvement (patients with Gilbert*s
Disease may be enrolled with prior Sponsor approval).
12. Adequate renal function, with estimated glomerular filtration rate *30 mL/minute.
13. Ability to swallow capsules and comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
14. Willingness of men and women of reproductive potential to observe conventional and effective birth control for the duration of treatment and for 3 months following the last dose of study treatment.
Notes:
* A postmenopausal woman will be defined as having no menses for 12 months without an alternative medical cause. Male sterility will be defined as only men sterilized surgically. For male patients with a pregnant partner, a condom should be used for contraception. For male patients with a non-pregnant female partner of child-bearing potential and woman of child-bearing potential one of the following birth control methods with a failure rate of less than 1% per year when used consistently and correctly are recommended:
a. Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally
b. Progestogen-only hormonal contraception associated with inhibition of ovulation given orally, by
injection, or by implant
c. Intrauterine device (IUD)
d. Intrauterine hormone-releasing system (IUS)
e. Bilateral tubal occlusion
f. Vasectomized partner
g. Sexual abstinence
* Birth control methods unacceptable for this clinical trial are:
a. Periodic abstinence (calendar, symptothermal, or post-ovulation methods)
b. Withdrawal (coitus interruptus)
c. Spermicide only
d. Lactational amenorrhea method

Exclusion criteria

Exclusion Criteria for Dose Escalation and Dose Expansion:
1. For NSCLC patients, an additional known oncogenic driver. Examples include targetable mutation in EGFR, targetable rearrangement involving ALK or ROS1, or KRAS (dose expansion only). Such patients may be enrolled to Cohort 5 with prior Sponsor approval.
2. Investigational agent or anticancer therapy within 5 half-lives or 2 weeks (whichever is shorter) prior to planned start of LOXO-292. In addition, no concurrent investigational therapy is permitted.
Notes:
* Refer to Section 6.3.2 of the main protocol for allowable concurrent therapies.
* LOXO-292 may be started within less than 5 half-lives or 2 weeks of prior therapy if considered by
the Investigator to be safe and within the best interest of the patient, with prior Sponsor approval.
3. Major surgery (excluding placement of vascular access) within 4 weeks prior to planned start of
LOXO-292.
4. Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study
treatment, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least 4 weeks prior to the first dose of study treatment.
5. Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy.
6. Symptomatic primary central nervous system (CNS) tumor or metastases; symptomatic leptomeningeal carcinomatosis; untreated spinal cord compression.
Exception: Patients with CNS primary tumor, brain metastases, or treated spinal cord compression are eligible if neurological symptoms have been stable for 14 days prior to the first dose of LOXO-292, there has been no increase in steroid dose for 14 days prior to the first dose of LOXO-292 to manage CNS symptoms, and no CNS surgery or radiation has been performed for 28 days (14 days after last radiation with stereotactic radiosurgery [SRS]).
7. Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of LOXO-292 or prolongation of the QT interval corrected for heart rate (QTcF) >470 msec on at least 2/3 consecutive ECGs, and mean QTcF >470 msec on all 3 ECGs, during Screening. Correction of suspected drug-induced QTcF prolongation may be attempted at the Investigator*s discretion if clinically safe to do so.
8. Active uncontrolled systemic bacterial, viral, or fungal infection, which in the opinion of the Investigator makes it undesirable for the patient to participate in the trial. Screening for chronic conditions is not required.
9. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug.
10. Uncontrolled symptomatic hyperthyroidism or hypothyroidism.
11. Uncontrolled symptomatic hypercalcemia or hypocalcemia.
12. Current treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or

inducers (refer to Appendix C of the main protocol).
13. Current treatment with proton pump inhibitors (PPIs) (refer to Appendix F of the main protocol).
Note:
* Treatment with PPIs must be stopped 1 or more weeks prior to the first dose of LOXO-292. For
recommended alternatives, refer to Section 6.3.3 of the main protocol).
14. Pregnancy or lactation.
15. Active second malignancy other than minor treatment of indolent cancers.

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	LOXO-292

Ethics review

Approved WMO

Date:	03-09-2018
Application type:	First submission

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-05-2019
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2017-000800-59-NL
ClinicalTrials.gov	NCT03157128
CCMO	NL65249.031.18