A Multicenter, Randomized, Open-label, Phase 3 Trial Comparing selpercatinib (LOXO-292) to Physicians Choice of Cabozantinib or Vandetanib in Patients with Progressive, Advanced, Kinase Inhibitor Naïve, RET-Mutant Medullary Thyroid Cancer (LIBRETTO-531)

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Primary* To compare TFFS of patients with progressive, advanced, kinase inhibitor naïve, RET-mutant MTC treated with LOXO-292 versus cabozantinib or vandetanib.Secondary* To compare other efficacy outcomes, based on RECIST 1.1 criteria, observed in...

Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49573

Source
ToetsingOnline

Brief title
J2G-MC-JZJB (LIBRETTO 531)

Condition

- Other condition

Synonym
Medullary Thyroid Cancer; Thyroid cancer

Health condition

Oncology - Thyroid

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: LOXO-292, Medullary Thyroid Cancer, Randomized, Selpercatinib

Outcome measures

Primary outcome

* TFFS by BICR

Secondary outcome

* PFS by BICR

* TFFS by investigator

* TFFS by investigator

* ORR by investigator and BICR

* DoR by investigator and BICR

* OS

* PFS2 by investigator

* Safety per CTCAE v5.0 (including but not limited to): incidence and severity

of TEAEs, SAEs, deaths, and clinical laboratory abnormalities.

* FACT-GP5

* PRO CTCAE

Study description

Background summary

Medullary thyroid cancer (MTC) accounts for 1% to 2% of thyroid cancers in the United States (SEER 2018). The majority of MTCs are sporadic, with approximately 10% hereditary due to a germline activating mutation in the RET gene. Most sporadic MTCs harbor activating RET mutations as well. The clinical course of MTC is highly heterogeneous, varying from indolent tumors that remain unchanged for many years to aggressive cancers associated with high mortality. Although surgery can be curative for the approximately 85% of patients who present with localized disease, approximately 50% develop recurrent disease. Metastatic MTC is incurable. Treatment with the multikinase inhibitors (MKIs) cabozantinib or vandetanib is the standard treatment for patients with symptomatic and/or progressive metastatic MTC. However, the efficacy of these MKIs is ultimately limited by incomplete inhibition of RET in tumors in patients, significant toxicity from stronger inhibition of other targets and poor pharmacokinetics (PK). As a result, most patients treated with these agents experience significant toxicities requiring dose interruptions, reductions (35% to 79%), and/or treatment cessation (12% to 16%) (Wells et al. 2012, Elisei et al. 2013). LOXO-292 is a highly potent and specific small molecule inhibitor of the RET kinase, with minimal inhibition of other kinase and non-kinase targets. A Phase 1/2 study (LIBRETTO-001) was designed to assess the safety, PK and anti-tumor activity of LOXO-292 in patients with RET-altered solid tumors. The Phase 1 portion of the study has been completed and the Phase 2 portion is ongoing. Initial data from Phase 1 was recently presented (Drilon et al. 2018; Oxnard et al. 2018; Wirth et al. 2018). As of 02 April 2018, 82 patients were treated at 8 dose levels (20 mg QD to 240 mg BID). Treatment-emergent adverse events (TEAEs) were monitorable and reversible. A dose of 160 mg BID has been selected for Phase 2. The investigator-assessed overall response rate (ORR) and confirmed ORR (cORR) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 in patients with RET mutant MTC were 59% (n = 17/29) and 56% (n = 15/27, respectively, with 94% (n = 16/17) of responses ongoing with a median follow up of 7.6 months (8.4 months for responders). Given its manageable toxicity profile and evidence of durable antitumor activity in patients with advanced RET mutant MTC, LOXO-292 may be of benefit in delaying treatment failure and disease progression and improving survival in patients with progressive, advanced MTC who have not previously received cabozantinib or vandetanib.

Study objective

Primary
* To compare TFFS of patients with progressive, advanced, kinase inhibitor naïve, RET-mutant MTC treated with LOXO-292 versus cabozantinib or vandetanib.

Secondary
* To compare other efficacy outcomes, based on RECIST 1.1 criteria, observed in patients with progressive, advanced, kinase inhibitor naïve, RET-mutant MTC treated with LOXO-292 versus cabozantinib or vandetanib.
* To evaluate the safety and tolerability of LOXO-292 compared to cabozantinib or vandetanib.
* To compare the tolerability of LOXO-292 versus cabozantinib or vandetanib
* To assess/evaluate performance of local RET laboratory tests compared to a single, central test.
* To assess the PK of selpercatinib in the patient population.

Study design

This is a global, multicenter, randomized (2:1), open-label, Phase 3 study comparing LOXO-292 (treatment Arm A) to physicians choice of cabozantinib or vandetanib (treatment Arm B) in patients with progressive, advanced, kinase inhibitor naïve, RET-mutant MTC.
Patients will be stratified based on:
* RET mutation: M918T vs. other
* Geographic region: North America vs. Europe vs. Asia
* Intended treatment if randomized to control arm: cabozantinib vs. vandetanib
Patients with histologically confirmed, unresectable, locally advanced, or metastatic MTC who have not received previous treatment with a kinase inhibitor are eligible. Patients are required to have radiologic progressive disease per RECIST 1.1 at screening compared with an image obtained within the prior 14 months and to have a documented RET mutation in tumor or germline DNA. Both radiographic progression and RET mutation must be confirmed by the sponsor prior to patient randomization. Patients will be randomized in a 2:1 ratio to receive LOXO-292 (treatment Arm A) or physicians choice of cabozantinib (treatment Arm B1) or vandetanib (treatment Arm B2). Patients assigned to the control arm cannot switch from cabozantinib to vandetanib or from vandetanib to cabozantinib during the study. Treatment will continue until disease progression, unacceptable toxicity, or death. Patients randomized to Arm B who discontinue treatment and who have radiographic disease progression that is confirmed by blinded independent central review (BICR) may be eligible for crossover to LOXO-292 if they meet the eligibility criteria for crossover (see Section 5.2.1).

Intervention

Arm A: Intervention LOXO-292, twice daily
Arm B1: Intervention Cabozantinib, once daily
Arm B2: Intervention Vandetanib, once daily

Cycle length is 28 days for all treatment arms.

Study burden and risks

During the study, you will visit the hospital approximately 4 times per month, the frequency of study visits may be higher than visits required as routine practice by your doctor for looking after your illness, however these are required for study participation. A visit will take approximately 1 hour during the treatment period. The follow-up visits will take 30 minutes to 1 hour.

Venapunction : Yes
Biopsy: Possible

For more information see section E6 and Section J in this form, or the protocol.

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

1. Are of an acceptable age to provide informed consent according to local regulations and
are at least 18 years of age (patients as young as 12 years of age will be allowed if
permitted by local regulatory authorities and institutional review boards).
2. Histologically confirmed, unresectable, locally advanced and/or metastatic MTC and no
prior history of treatment with kinase inhibitors for advanced/metastatic disease. Prior
systemic or radiation therapy in the adjuvant setting may be allowed with discussion and
approval by the Lilly CRS/CRP.
3. Radiographic progressive, measurable disease per RECIST 1.1 (Eisenhauer et al. 2009) at
screening compared with a previous image taken within the prior 14 months as assessed
by the BICR.
4. A RET gene alteration identified in a tumor, germline DNA or blood sample, as defined
in Appendix 6 of the protocol. The RET alteration result should be generated from a laboratory with
CLIA, ISO/EIC, CAP, or other similar certification. Lilly should be contacted to discuss
test results from labs where such certification is not clearly demonstrated to determine
eligibility. In all cases, a redacted Molecular Pathology Report or other report(s)
describing tumor and/or germline RET (and other) alteration analysis should be submitted to Lilly or designee during/prior to eligibility.
a. Mandatory provision of an unstained, archived tumor tissue sample in a quantity
sufficient to allow for retrospective central analysis of RET mutation status (for
confirmation). Please refer to Section 8.8.1 for details.
b. Participants must have adequate unstained, archived tumor tissue sample, as

defined in Section 8.8.1, for retrospective central confirmation of the RET result.
5. Eastern Cooperative Oncology Group (ECOG) performance status score (Oken et al.
1982) of 0 to 2.
6. Ability to swallow capsules and comply with treatment, laboratory monitoring, and
required clinic visits for the duration of study participation
7. Patients must have discontinued from previous treatments as shown in the protocol and fully
recovered. Consult with the Lilly CRS/CRP for the appropriate length of time prior to
the first dose of study treatment on additional therapies not mentioned.
8. Have adequate organ function, as defined in the protocol.
9. Patients must have normal serum potassium, calcium, and magnesium levels (may be
receiving supplements).
10. Men with partners of childbearing potential or women of childbearing potential must
agree to use a highly effective contraceptive method (for example, intrauterine device
[IUD], birth control pill, or barrier method) during treatment with study drug and for
6 months following the last dose of study drug. If a condom is used as a barrier
contraceptive, a spermicidal agent should be added as double-barrier protection. See
Appendix 3 of the protocol.
Note: Unless not allowed by local regulations, women of childbearing potential who are
abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a
same-sex relationship (as part of their preferred and usual lifestyle) must agree to either
remain abstinent or stay in a same-sex relationship without sexual relationships with
males unless they agree to use contraceptive method known to be highly effective.
Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods),
declaration of abstinence just for the duration of a trial, and withdrawal are not
acceptable methods of contraception.
11. Women of childbearing potential must have a negative pregnancy test (serum or urine,
consistent with local regulations) documented within 24 hours prior to treatment with
study drug.

12. Capable of giving signed informed assent/consent as described in Appendix 1 of the protocol, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol.

Exclusion criteria

13. An additional validated oncogenic driver in MTC if known that could cause resistance to LOXO-292 treatment. Examples include, but are not limited to RAS gene mutations and ALK gene fusions.
14. Symptomatic CNS metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Patients are eligible if neurologically stable and without increase in steroid dose for 14 days prior to the first dose of study treatment and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery (SRS).
15. Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of study treatment or prolongation of the QT interval corrected for heart rate using Fridericia*s formula (QTcF) >470 msec on more than one ECG during Screening. Correction of suspected drug-induced QTcF prolongation may be attempted at the investigator*s discretion if clinically safe to do so.
Patients who are intended to receive vandetanib if randomized to the control arm ineligible if QTcF is >450msec.
a. Note: Patients with implanted pacemakers may enter study without meeting QTc criteria due to nonevaluable measurement.
16. Active uncontrolled systemic bacterial, viral, or fungal infection or serious ongoing intercurrent illness, such as hypertension or diabetes, despite optimal treatment, a clinical diagnosis or symptoms of interstitial lung disease, or other serious medical conditions which in the medical judgment of the investigator would prevent the patient from safely participating (screening for chronic conditions is not required).
17. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug.
18. Uncontrolled symptomatic hyperthyroidism or hypothyroidism

19. Uncontrolled symptomatic hypercalcemia or hypocalcemia
20. Active hemorrhage or at significant risk for hemorrhage.
21. Other malignancy unless nonmelanoma skin cancer, carcinoma in situ of the cervix or
malignancy diagnosed >=2 years previously and not currently active. Patients receiving
adjuvant hormone therapy for breast or prostate cancer with no evidence of disease are eligible. Participants with MEN2-associated pheochromocytoma are eligible if the pheochromocytoma is, in the opinion of the investigator, documented to be stable or has been resected (and patient has fully recovered from surgery).
22. Prior systemic treatment with kinase inhibitor(s)
23. Require concomitant use of strong CYP3A4 inhibitors or inducers (see Appendix 7 of the protocol)
24. Require treatment with proton pump inhibitors (PPIs)
25. Are taking a concomitant medication that is known to cause QTc prolongation (for
examples, see Appendix 7 of the protocol)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cabozantinib
Generic name:	-
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Selpercatinib
Generic name:	LOXO-292
Product type:	Medicine
Brand name:	Vandetanib
Generic name:	-
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-03-2020
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Not approved Date:	22-09-2020
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	EUCTR2019-001978-28-NL
CCMO	NL71643.031.19