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

Published: 17-12-2020
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This study has been transitioned to CTIS with ID 2023-506782-56-00 check the CTIS register for the current data. To compare PFS of patients with progressive, advanced, kinase inhibitor naïve, RET-mutant MTC treated with selpercatinib versus...

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

Summary

ID

NL-OMON54458

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

Progression Free Survival (PFS) by Blinded Independent Committee Review (BICR)

- PFS by BICR

Secondary outcome

1. Treatment Failure Free Survival (TFFS) by BICR (TFFS by BICR)

2. TFFS by investigator

3. PFS by investigator

4. ORR: Percentage of Participants with Complete Response (CR) or Partial

Response (PR) by BICR

5. Duration of Response (DoR) by BICR

6. Overall Survival (OS)

7. PFS2 by Investigator

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

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

9. Proportion of time with high-side-effect bother based on FACT-GP5

10. RET mutation status

11. Predose plasma concentrations at Day 8 of Cycle 1, and at Day 1 of Cycles 2

through 6.

Study description

Background summary

Medullary thyroid cancer (MTC) accounts for 1% to 2% of thyroid cancers in the United States, with approximately 1000 new cases per year (SEER 2018). The majority of MTCs are sporadic, with approximately 20% to 25% hereditary due to a germline activating mutation in the RET gene.

Patients with RET-mutant MTC comprise a population with high unmet need. Chemotherapy is ineffective for MTC. Therefore, there is an urgent need to identify new targeted therapies that potently inhibit RET-mutant MTC, while sparing other kinase and nonkinase off-targets that contribute to significant toxicity

Selpercatinib 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 MTC that harbor RET alterations and/or depend on RET activation. This Phase 3 study is required to confirm the benefit from selpercatinib seen in patients with advanced/metastatic MTC in the LIBRETTO-001 trial and to better understand this benefit in the context of other available treatments for advanced/metastatic MTC.

Study objective

This study has been transitioned to CTIS with ID 2023-506782-56-00 check the CTIS register for the current data.

To compare PFS of patients with progressive, advanced, kinase inhibitor naïve, RET-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib.

Study design

This is a global, multicenter, randomized (2:1), open-label, Phase 3 study comparing selpercatinib (treatment arm 1) to physicians choice of cabozantinib or vandetanib (treatment arm 2) in patients with progressive, advanced, kinase

inhibitor naïve, RET-mutant Medullary Thyroid Cancer (LIBRETTO-531).

Intervention

Arm A: Intervention Selpercatinib, 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

Benefit: Selpercatinib 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 MTC that harbor RET alterations and/or depend on RET activation. Given its manageable toxicity profile and evidence of durable antitumor activity in patients with advanced RET mutant MTC, Selpercatinib may be of benefit in delaying treatment failure and disease progression.

Risk: The most common toxicities associated with Selpercatinib are monitorable and reversible and include dry mouth, diarrhea, hypertension, fatigue, constipation, AST/ALT elevation, headache, nausea, peripheral edema, and increased blood creatinine.

Burden: Patients receiving the treatment would be advised to avoid grapefruit juice, usage of certain medications. Additionally, patients treated with Vandetanib would be advised to avoid sun exposure during the study and for up to 4 months after the end of the study.
During the study patients will be exposed to the burden of increase monitoring of vital signs, therefor more frequent hospital visits and invasive procedures, such as: venapunction, biopsy and radiation procedures.

Due to the manageable toxicity profile of Selpercatinib and evidence of durable antitumor activity in patients with advanced RET-mutant MTC, the expected benefits of the researched treatment outweigh the potential risks.

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

- Age: All patients of 16 years of age and older, after giving assent / Legally designated representative/ participant written consent.
- Histologically confirmed, metastatic MTC
- Radiographic progressive, measurable disease per BIRC at screening compared with a previous image taken within the prior 14 months as assessed by the BICR. Patients with measurable or non-measurable but evaluable disease are eligible; however, patients with non-measurable disease may not have disease limited to bone sites only.
- A RET gene alteration in tumor, genomic DNA or blood.
-Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2.
- Adequate hematologic, hepatic and renal function
- Patients must have serum potassium, calcium, and magnesium levels above the lower limit of normal (may be receiving supplements) and not clinically significantly above the upper limit of normal.
- Major surgery (excluding biopsy and placement of vascular access) within 4 weeks prior to planned start of study treatment.
- Radiotherapy within 2 weeks of the first dose of study treatment (within 4 weeks if >25% bone marrow irradiated).
- Willingness of men and women of reproductive potential to observe conventional and effective birth control for the duration of treatment and for 4 months after the last dose of study drug
-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
*not be breastfeeding during treatment and for at least 4 months after the last dose of study drug.
- Written informed consent

Exclusion criteria

- Additional validated oncogenic driver in MTC if known
- Symptomatic primary CNS tumor, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression.
- 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
- Active uncontrolled systemic bacterial, viral, or fungal infection or serious ongoing intercurrent illness, such as hypertension or diabetes, despite optimal treatment. Screening for chronic conditions is not required
- Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug
- Uncontrolled symptomatic hyperthyroidism or hypothyroidism.
- Uncontrolled symptomatic hypercalcemia or hypocalcaemia.
- Active haemorrhage or at significant risk for haemorrhage.
- Current treatment with strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers.
- Prior systemic treatment with kinase inhibitor (s) (Refer to Section 5.1, Inclusion Criteria 2b).
-Are taking a concomitant medication that is known to cause QTc prolongation.
- Life expectancy <= 3 months.
- Current treatment with proton pump inhibitors (PPIs)
- Known hypersensitivity to any of the excipients of vandetanib or cabozantinib
- Pregnancy or breastfeeding
- Other malignancy unless nonmelanoma skin cancer, carcinoma in situ of the cervix or malignancy diagnosed >=2 years previously and not currently active

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:	Recruiting
Start date (anticipated):	08-06-2021
Enrollment:	8
Type:	Actual

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
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vandetanib
Generic name:	-
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	17-12-2020
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	23-02-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	10-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-06-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	04-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-10-2023
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2023-506782-56-00
EudraCT	EUCTR 2019-001978-2-NL
ClinicalTrials.gov	NCT04211337
CCMO	NL75905.031.20