A phase III multi-center, randomized, open-label study to evaluate the efficacy and safety of Lutathera in patients with Grade 2 and Grade 3 advanced GEP-NET

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This study has been transitioned to CTIS with ID 2023-507443-10-00 check the CTIS register for the current data. The pivotal Phase III NETTER-1 study showed that Lutathera with best supportive care (30mg octreotide long-acting) provided a...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Endocrine and glandular disorders NEC
Study type	Interventional

Summary

ID

NL-OMON55150

Source
ToetsingOnline

Brief title
NETTER2

Condition

- Endocrine and glandular disorders NEC
- Endocrine neoplasms malignant and unspecified

Synonym
GEP-NETs (gastro-entero-pancreatic neuroendocrine tumors), including the stomach, intestines, pancreas and liver., progressive malignant tumors that can occur in various organs

Research involving
Human

Sponsors and support

Primary sponsor: Advanced Accelerator Applications Internationals SA
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Advanced GEP-NET, Lutathera, Phase 3, PRRT

Outcome measures

Primary outcome

To demonstrate that Lutathera is superior to active comparator in delaying the

time-to-first occurrence of progression or death (PFS) as first line treatment.

Secondary outcome

Key Secondary Objectives:

- To demonstrate the superiority of Lutathera, compared to active comparator,

in terms of objective response

- To demonstrate the superiority of Lutathera, compared to active comparator,

in terms of time to deterioration in selected QoL items/scales

Other Secondary Objectives:

- To evaluate the efficacy of Lutathera, compared to active comparator, in

keeping the disease under control

- To evaluate the efficacy of Lutathera, compared to active comparator, in

terms of duration of response

- To evaluate the safety and tolerability of Lutathera

- To evaluate the effect of Lutathera on survival

Study description

Background summary

The study drug contains a radioactive compound called lutetium. The radioactive lutetium delivers strong radiation directly into tumor cells and works by causing death of the cancerous tissues. The intent of giving the drug internally into a vein is that it should focus the cell killing effects of the radiation by binding to tumors. Due to the rapid excretion it will have less effect on healthy tissue.

Treatment with the study drug is called Peptide Receptor Radionuclide Therapy (PRRT). This PRRT treatment is based on the administration of a radioactive product. PRRT is a form of targeted treatment that is performed using a small radioactive molecule.

The study drug can be administered in combination with octreotide long-acting. Octreotide long-acting binds to and prevents tumor cells from secreting hormones and other substances that may cause symptoms such as flushing, diarrhea, and tummy cramps. It gives relief of symptoms in patients with grade 2 or grade 3 GEP-NETs (gastro-entero-pancreatic neuroendocrine tumors).

Both treatments, the study drug and octreotide long acting, are used to try and stop grade 2 or grade 3 GEP-NETs (gastro-entero-pancreatic neuroendocrine tumors) from getting worse and perhaps to even reduce the size of tumor(s).

Study objective

This study has been transitioned to CTIS with ID 2023-507443-10-00 check the CTIS register for the current data.

The pivotal Phase III NETTER-1 study showed that Lutathera with best supportive care (30mg octreotide long-acting) provided a significant increase in PFS to patients with progressive midgut carcinoid tumors (at enrollment) compared to patients treated with high dose (60 mg) octreotide long-acting. The NETTER-1 patient population included 34.5% of patients with G2 NET (65.5% G1), while G3 NETs were excluded. Only patients progressive on SSAs were eligible (2nd line), SSA-naïve patients were excluded.

The aim of the NETTER-2 study is to determine if Lutathera in combination with octreotide long-acting prolongs PFS in GEP-NET patients with high proliferation rate tumors (G2 and G3), when given as a 1st line treatment in comparison to treatment with high dose (60 mg) octreotide long-acting. SSA-naïve patients are eligible, as well as patients previously treated with SSAs in the absence of progression.

Based on extensive experience with Lutathera as well as octreotide LAR in adult GEP NET patients, and the relevance of the molecular target in adolescent GEP NET patients, the study will be open to adolescents aged >= 15 years and >40 kg body weight (BW); younger patients are not expected to present with the disease meeting the severity criteria for this trial.

Study design

Overall, 222 patients will be randomized (2:1 randomization ratio) to receive treatment with Lutathera (7.4GBq/200 mCi x 4 administrations every 8± 1 weeks; cumulative dose: 29.6 GBq/800mCi) plus octreotide long-acting (30 mg every 8 weeks during Lutathera treatment and every 4 weeks after last Lutathera treatment) or high dose octreotide long-acting (60 mg every 4 weeks). Randomization will be stratified by Grade (G2 vs G3) and tumor origin (pNET vs other origin). The primary endpoint of the study is PFS centrally assessed (target HR=0.5; 90% power, 1-sided α=2.5%). The primary analysis will be performed after 99 PFS events (99 evaluable and centrally confirmed disease progressions or death events) have occurred. The study consists of a Screening Phase, a Treatment Phase, an optional Treatment Extension Phase (cross-over), an optional Re-treatment Phase and a Follow up Phase.

Screening Phase
The screening phase must be shortened as much as possible, in order to treat the patients possibly within 2 weeks after the consent signature. The randomization must be performed immediately after all eligibility criteria are verified. As Lutathera production and shipment will take circa 12 days to be arranged, if a patient is randomized in the Lutathera arm, Lutathera first dose must be ordered immediately after randomization. The baseline CT/MRI scan should be taken possibly on the same day as randomization or immediately before (within 1 week) to ensure that it reflects the disease status closely before the therapy start.

Treatment Phase
During the Treatment Phase, objective tumor response will be assessed at W16±1, W24±1 and then every 12±1 weeks from the randomization date, according to RECIST 1.1 criteria (central + local assessment up to first progression, then only local assessment).

Duration of the Treatment Phase:
Before the PFS primary analysis (i.e. 99 evaluable and centrally confirmed disease progressions or death events), patients continue the Treatment Phase until progression; after the PFS primary analysis, the Treatment Phase duration is limited to 72 weeks. At any time during the study (before or after the PFS primary analysis) any progressive patient (based on central imaging assessment) immediately ceases the Treatment Phase and proceeds to the Follow-up Phase. In addition, patients randomized in the control arm have the option, if eligible, to enroll for post-progression cross-over with Lutathera).

Optional Treatment Extension Phase (cross-over)
In the control arm, any patient with radiological progression according to RECIST (based on central assessment) has the option to enroll for post-progression cross-over, upon signature of a new informed consent, to receive maximum 4 cycles of Lutathera (7.4 GBq/200 mCi x 4 cycles; cumulative dose: 29.6 GBq / 800mCi) plus 30 mg octreotide long acting every 8 weeks. If RECIST progression occurs after Week 72 post the primary end point analysis, the decision to enroll the patient in the cross-over phase will be based on local assessment. The time window to start Lutathera during the cross-over phase is within 4 years after the last patient has been randomized.

Optional Re-treatment Phase
Patients in the Lutathera arm with radiological progression based on RECIST criteria in central assessment will be offered enrollment in the optional re-treatment phase upon signature of a new informed consent. If RECIST progression occurs after Week 72 post the primary end point analysis, the decision to enroll the patient in re-treatment will be based on local assessment. The criteria to enter the re-treatment phase include achievement of stabilization of disease or radiological response to Lutathera initial treatment for at least 6 months after receiving the 4th Lutathera dose and good safety/tolerability. If a patient*s response has changed from PR/CR to SD within 6 months after the 4th Lutathera dose, the patient is still eligible for re-treatment, provided there is no documented progression within 6 months. Patients who received other systemic treatments for GEP-NET after progression (except somatostatin analogues) are not eligible for re-treatment. The time window to start re-treatment in this study is within 4 years after the last patient has been randomized. In the re-treatment phase, patients will initially receive 2 administrations of
Lutathera 7.4 GBq/200 mCi at 8-week interval. Based on the physician*s judgment of the clinical benefit derived from the first 2 doses, up to 2 additional doses of Lutathera may be administered. A maximum of 4 cycles of Lutathera is allowed during the re-treatment period. All safety and efficacy assessments in the re-treatment period will be performed locally (SRI images must also be submitted to the central images reading center possibly within 1 month) and following the schedule in the initial treatment period. Assessments will be continued until disease progression is documented by investigator or until End of Study, whichever occurs first.

Follow up Phase
At the end of the Treatment Phase or after discontinuation for any cause (including disease progression), all patients will continue to be followed up to 3 years to continue data collection for the secondary endpoints of the study, such as long term safety and overall survival. Patients included in the optional crossover or re-treatment phase will be followed up at least 6 months and up to 3 years (or until EoS, whatever comes first). During the Follow-up Phase, serious adverse events and adverse events of special interest (AESI) related to the study treatment as well as AESI of

secondary hematological malignancies irrespective of causality, will be reported. Anti-tumor treatments administered after progression/discontinuation, disease status based on local CT/MRI assessment, and OS data will be collected every 6 months in both arms.

End of the Study
The End of Study is after 4 years have elapsed from the randomization of the last patient or 6 months after the last cross-over or re-treatment dose in the study, whichever occurs last. The time window to start cross-over or re-treatment with Lutathera in this study is within 4 years after the last patient
has been randomized. For patients in the Lutathera arm who progress beyond this window, access to re-treatment with Lutathera may be granted via Post Study Drug Supply (PSDS) programs.

Intervention

In this study, approximately 222 patients with advanced G2-3 GEP-NET will be randomized (2:1 randomization ratio) to receive treatment with Lutathera (7.4 GBq or 200 mCi x 4 administrations every 8± 1 weeks; cumulative dose: 29.6 GBq or 800 mCi) plus octreotide long-acting standard dose (30 mg every 8 weeks during Lutathera treatment and every 4 weeks after last Lutathera treatment) or octreotide long-acting high dose (60 mg every 4 weeks).

The investigational drug product Lutathera® (177Lu-DOTA0-Tyr3-Octreotate) will be provided by the Sponsor. The Sponsor will also provide the 2.5% Lys-Arg amino acid solution for infusion (if it can*t be compounded at the hospital Pharmacy), as well as octreotide long-acting (Sandostatin® LAR Depot) for the entire duration of the Treatment Phase (and optional Treatment Extension Phase in case of cross-over) of the study. Patients will switch to prescribed drugs in the follow up phase.

Anti-emetics, SRI imaging agents, short-acting octreotide or any other supportive care medication will not be supplied by the Sponsor.

Study burden and risks

The study load for the test subject comprises:

23 visits of approximately 4 hours (group 1) or 20 visits of approximately 2 hours during the treatment phase. The subject should stay overnight in the hospital after administration of Lutathera (minimum of 1 night).

Physical examination: combined 8 times in the screening phase and treatment phase and every 12 weeks after the treatment period.
Measuring vital functions: combined 10 times in the screening phase and

treatment phase and every 12 weeks after the treatment period. 6 times extra in the optional treatment phase.
Measuring heart ejection fraction: 1 time during screening.
Blood sample collection: 15 times combined in the screening phase and treatment phase and every 12 weeks after the treatment period (15-30 ml of blood per visit). 10 times extra in the optional treatment phase.
Pregnancy test: combined 4 times in the screening phase and treatment phase. 4 times extra in the optional treatment phase.
SRI-SCAN (PET scan): 1 time during screening (unless completed in the last 3 months before screening). 1 extra time in the optional treatment phase.
CT / MRI scan: combined 7 times in the screening phase and treatment phase and every 12 weeks after the treatment period. 3 times extra in the optional treatment phase.
ECG: 5 times in the screening phase and treatment phase. 5 times extra in the optional treatment phase. The subject is asked to complete in 3 questionnaires about the quality of his or her life.

Risks and inconveniences for the test subject
The subject is exposed to radiation and may experience physical and / or psychological discomfort from the aforementioned tests, procedures and questionnaires. For a comprehensive risk analysis, see the subjects' information section 6 "possible side effects, risks and discomforts on pages 6 and 7 and Annex D, page 19, for less common side effects. Appendix E, pages 20-21, shows the risks and inconveniences of the measurements and actions that are performed in this study. Below are the most common side effects.

Study drug treatment (study group 1) The most common side effects of radioactivity are a decrease in the number of blood cells, mainly red blood cells, platelets and other blood cells such as white blood cells. Due to a decrease in the number of different blood cells, there are risks of bleeding, fatigue, shortness of breath, and infection.

The most common side effect with amino acid solution: nausea (in approximately 1 in 4 subjects), vomiting (in approximately 1 in 10 subjects) and hyperkalaemia (an increased level of potassium in the blood).

High dose Octreotide treatment (study group 2)
The most serious side effects are allergic reactions, stomach pain, nausea / vomiting, feeling restless or dizzy, yellowing of the skin or whites of the eyes of the patient, acute pancreatitis (sudden, severe pain in the lower abdomen).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects eligible for inclusion in this study must meet all of the following criteria:
1. Presence of metastasized or locally advanced, inoperable (curative intent) histologically proven, well differentiated Grade 2 or Grade 3 gastroenteropancreatic neuroendocrine (GEP-NET) tumor diagnosed within 6 months prior to screening.
2. Ki67 index >=10 and <= 55%.
3. Patients >=15 years of age and a body weight of >40 kg at screening.
4. Expression of somatostatin receptors on all target lesions documented by CT/MRI scans, assessed by any of the following somatostatin receptor imaging (SRI) modalities within 3 months prior to randomization: [68Ga]-DOTA-TOC (e.g. Somakit-TOC®) PET/CT (or MRI when applicable based on target lesions) imaging or [68Ga]-DOTA-TATE PET/CT (or MRI
when applicable based on target lesions) imaging (e.g. NETSPOT®) or

Somatostatin Receptor scintigraphy (SRS) with 111In-pentetreotide (Octreoscan® SPECT/CT), SRS with [99mTc]-Tektrotyd, [64Cu]-DOTA-TATE PET/CT (or MRI when applicable based on target lesions) imaging.
5. The tumor uptake observed in the target lesions must be > normal liver uptake observed on planar imaging.
6. Karnofsky Performance Score (KPS) *60.
7. Presence of at least 1 measurable site of disease.
8. Patients who have provided a signed informed consent form to participate in the study, obtained prior to the start of any protocol related activities.

Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.
1. Creatinine clearance <40 mL/min calculated by the Cockroft Gault method.
2. Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <2x109/L (2000/mm3); platelets <75x109/L (75x103/mm3).
3. Total bilirubin >3 x ULN.
4. Serum albumin <3.0 g/dL unless prothrombin time is within the normal range.
5. Pregnancy or lactation.
6. A Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, are not allowed to participate in this study UNLESS they are using highly effective methods of contraception throughout the study treatment period (including cross-over and re-treatment, if applicable) and for 6 months after study drug discontinuation. Sexually active male patients, unless they agree to remain abstinent (refrain from heterosexual intercourse) or be willing to use effective methods of contraception with female partners of childbearing potential or pregnant female partners during the treatment period (including cross-over and re-treatment, if applicable) and for 6 months after study drug discontinuation. In addition, male patients must refrain from donating sperm during this same period.
7. Peptide receptor radionuclide therapy (PRRT) at any time prior to randomization in the study.
8. Documented RECIST progression to previous treatments for the current GEP-NET at any time prior to randomization.
9. Patients for whom in the opinion of the investigator other therapeutic options (eg chemo-, targeted therapy) are considered more appropriate than the therapy offered in the study, based on patient and disease characteristics.
10. Any previous therapy with Interferons, Everolimus (mTOR-inhibitors), chemotherapy or other systemic therapies of GEP-NET administered for more than 1 month and within 12 weeks prior to randomization in the study.
11. Any previous radioembolization, chemoembolization and radiofrequency ablation for GEP-NET.
12. Any surgery within 12 weeks prior to randomization in the study.
13. Known brain metastases, unless these metastases have been treated and

stabilized for at least 24 weeks, prior to screening in the study. Patients with a history of brain metastases must have a head CT or MRI with contrast to document stable disease prior to randomization in the study.
14. Uncontrolled congestive heart failure (NYHA II, III, IV). Patients with history of congestive heart failure who do not violate this exclusion criterion will undergo an evaluation of their cardiac ejection fraction prior to randomization, via echocardiography. The results from an earlier assessment (not exceeding 30 days prior to randomization) may substitute the evaluation at the discretion of the Investigator, if no clinical worsening is noted. The patient*s measured cardiac ejection fraction in these patients must be >40% before randomization.
15. QTcF > 470 msec for females and QTcF > 450 msec for males or congenital long QT syndrome.
16. Uncontrolled diabetes mellitus as defined by hemoglobin A1c value > 7.5%.
17. Hyperkaleamia >6.0 mmol/L (CTCAE Grade 3) which is not corrected prior to study enrolment.
18. Any patient receiving treatment with short-acting octreotide, which cannot be interrupted for 24 h before and 24 h after the administration of Lutathera, or any patient receiving treatment with SSAs (eg octreotide long-acting), which cannot be interrupted for at least 6 weeks before the administration of Lutathera.
19. Patients with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with the completion of the study.
20. Prior external beam radiation therapy to more than 25% of the bone marrow.
21. Current spontaneous urinary incontinence.
22. Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years.
23. Patient with known incompatibility to CT Scans with I.V. contrast due to allergic reaction or renal insufficiency. If such a patient can be imaged with MRI, then the patient would not be excluded.
24. Hypersensitivity to any somatostatin analogues, the IMPs active substance or to any of the excipients.
25. Patients who have participated in any therapeutic clinical study/received any investigational agent within the last 30 days.

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-01-2021
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lutetium (177Lu) oxodotreotide
Generic name:	Luthathera
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sandostatin LAR Depot
Generic name:	Octreotide Long-acting
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-10-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-01-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	16-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-05-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2022
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-02-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-02-2024
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
EU-CTR	CTIS2023-507443-10-00
EudraCT	EUCTR2019-001562-15-NL
ClinicalTrials.gov	NCT03972488
CCMO	NL71110.078.19