A Prospective, Randomized, Controlled, Open-label, Multicenter Trial to Evaluate Efficacy, Safety and Patient- reported Outcomes of Peptide Receptor Radionuclide Therapy (PRRT) with Lutetium (177Lu) Edotreotide compared to Best Standard of Care in Patients with Well-differentiated Aggressive Grade 2 and Grade 3, Somatostatin receptor-positive (SSTR+), Neuroendocrine Tumors of GastroEnteric or Pancreatic Origin (COMPOSE)

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This study has been transitioned to CTIS with ID 2024-510812-64-00 check the CTIS register for the current data. The purpose of this study is to investigate the efficacy and safety of the investigational drug known as Lutetium (177Lu) edotreotide in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Endocrine neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON56413

Source
ToetsingOnline

Brief title
177Lu-Edotreotide vs Best Standard of Care in Grade 2 and Grade 3 GEP-NETs

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
gastroenteropancreatic neuroendocrine tumors

Research involving
Human

Sponsors and support

Primary sponsor: ITM Solucin GmbH
Source(s) of monetary or material Support: industry sponsored trial by ITM Solucin GmbH

Intervention

Keyword: GEP-NET, Lutetium Edotreotide

Outcome measures

Primary outcome

Primary objective

To demonstrate the efficacy of PRRT with lutetium (177Lu) edotreotide in the

treatment of aggressive Grade 2 (G2: Ki67 between 15 and 20, both inclusive)

and Grade 3 (G3: Ki-67 above 20 up to 55, inclusive) SSTR+ GEP-NETs compared to

best standard of care (Investigator*s choice [from the protocol comparator

list]).

Primary endpoint

Progression-free survival (PFS), defined as the time from randomization until

adequately documented Response Evaluation Criteria in Solid Tumors (RECIST)

v1.1 disease progression (based on blinded, central assessment) or death, whichever occurs first.

Secondary outcome

Secondary objectives

1. To further demonstrate the efficacy of PRRT with lutetium (177Lu) edotreotide.

2. To assess the impact of PRRT with lutetium (177Lu) edotreotide on trial patient*s health-related quality of life (HRQL) and neuroendocrine functional tumor symptoms during and after therapy in comparison to best standard of care.

3. To assess the safety and tolerability of PRRT with lutetium (177Lu) edotreotide in trial patients compared to control treatment options.

Secondary endpoints

1. Further demonstration of efficacy:

For all endpoints based on RECIST v1.1, main analyses will be based on blinded, central assessment. Local assessments will be presented as sensitivity analyses.

1.1 Objective response rate (ORR), defined as the proportion of randomized patients with complete response (CR) or partial response (PR) (RECIST v1.1).

1.2 Overall survival (OS), defined as the time from randomization until death.

1.3 Duration of response (DoR), defined as the time from experiencing first CR or PR until the next progressive disease (PD) (RECIST v1.1).

1.4 Disease control rate (DCR), defined as the proportion of randomized patients with CR, PR or stable disease (SD) (RECIST v1.1).

1.5 Duration of disease control (DDC), defined as the time from experiencing

CR, PR or SD until the next subsequent PD (RECIST v1.1).

2. 2 HRQL (European Organization for Research and Treatment of Cancer [EORTC]

quality of life questionnaire [QLQ]-C30 and - GI.NET21)):

2.1 Maximum HRQL improvement in total scores relative to baseline.

2.2 Duration of maximum HRQL improvement, defined as the time from maximum

improvement until subsequent deterioration.

2.3 Time to HRQL deterioration, defined as the time from randomization until

first HRQL deterioration.

3. Safety and tolerability based on adverse events, laboratory data and vital

signs.

Study description

Background summary

Lutetium (177Lu) edotreotide is a type of therapy known as Peptide Receptor Radionuclide Therapy (or PRRT for short). This type of therapy is described in more detail in a later section of this document. Briefly, lutetium (177Lu) edotreotide binds to a receptor on the surface of GEP NETs called the *somatostatin receptor*. The cells of most GEP-NETs have an overload of these receptors. The participant will need to have somatostatin receptor-positive disease in order to be able to take part in the study, confirmed at entry into the study as explained later in this document.

In this study, the effect of lutetium (177Lu) edotreotide (known as the *Investigational Medicinal Product* or *IMP* arm) will be compared with other drugs (known as the *control* arm) being used to treat well-differentiated G2 and G3 GEP-NETs. Several other drugs are used worldwide for this type of cancer, but in this study, treatment will be limited to one of three options which are considered to be the best standard of care in the regions the study is being run. These other treatments are described in a later section of this document. No matter which group the participant is assigned to, the quality of your medical care will be absolutely the same. If the participant is assigned to receive one of the other treatments, and if the disease worsens on that treatment, it might be decide to offer the PRRT therapy outside of this study,

if this is to be considered appropriate and beneficial.

This study is being done for research purposes to collect information on how effective and safe lutetium (177Lu) edotreotide is in patients with GEP-NETs, specifically those classified as well differentiated Grade 2 (G2: Ki-67 between 15 and 20, both inclusive) and Grade 3 (G3: Ki-67 above 20 up to 55, inclusive). Ki-67 is a protein that is found in growing, dividing cells but is absent in cells not growing. Cancer cells grow and divide rapidly and Ki-67 is considered a good marker of cell growth allowing your doctor to follow the progress of your cancer. In this study only patients with a Ki-67 of 15 to 55 will be included, as this indicates an aggressive type of GEPNETs with poorer outcomes and limited other treatment options. The safety information will look at any general changes in the participants wellbeing.

Study objective

This study has been transitioned to CTIS with ID 2024-510812-64-00 check the CTIS register for the current data.

The purpose of this study is to investigate the efficacy and safety of the investigational drug known as Lutetium (177Lu) edotreotide in comparison with several other drugs that are already used worldwide in the treatment of neuroendocrine tumors.
It is the aim that lutetium (177Lu) edotreotide will slow or stop tumor progression or even reduce tumor size, thereby increasing survival and improving symptoms in patients with neuroendocrine tumors, specifically those which originate in the stomach or intestines (gastroenteric) or the pancreas.

Study design

This is a prospective, randomized, controlled, open-label, multi-center, international, Phase III clinical trial to evaluate the efficacy, safety and patient-reported outcomes of PRRT with lutetium (177Lu) edotreotide compared to best standard of care (investigator*s choice [from the protocol comparator list]) in patients with unresectable or metastatic, histologically confirmed, well-differentiated aggressive G2 (Ki-67 between 15 and 20, both inclusive) and G3 (Ki-67 above 20 up to 55, inclusive) SSTR+ GEP NETs.

Intervention

All successfully screened patients will be randomized in a 1:1 manner to receive:

- PRRT with lutetium (177Lu) edotreotide (7.5 ± 0.7 GBq), administered as an IV infusion for 6 cycles or until diagnosis of disease progression (101 patients),
For a given patient, trial treatment dosing should be discontinued in case of a

persistent Dose Modifying Toxicity (DMT) or if the patient withdraws consent to continue with treatment.

Each dosis contains a mass dose of 150 µg of edotreotide (DOTATOC).
Treatment may be delayed by up to a maximum of 4 to 16 weeks depending on the cycle if required due to safety concerns.

The cumulative lutetium (177Lu) edotreotide dose will be up to 45 GBq, which is estimated not to exceed, on average, a
cumulative renal absorbed radiation dose of 23 Gy, as calculated based on a blinded analysis of the dosimetry data of the first
dose administered in the COMPETE trial
(https://clinicaltrials.gov/ct2/show/NCT03049189).

or
- In the best standard of care (control) arm, each patient will receive an Investigator*s choice of therapy from the following list: CAPTEM (capecitabine-temozolomide), everolimus or FOLFOX (folinic acid, fluorouracil and oxaliplatin). The choice and treatment process will be based on individual risk-benefit assessment, institutional protocols, the local Prescribing Information, local regulations or the local guidelines.

Also in this arm, the treatment should be discontinued in case of progression, persistent DMT or if the patient withdraws consent.

Study burden and risks

There are risks, discomforts, and inconveniences associated with any research study. Side effects may be experienced from taking part in this study, although not everybody does. Side effects are mostly reversible and not all require treatment. It is very important that any side effects, reactions, or discomforts experienced between visits to the hospital are mentioned to the study doctor or nurses.

Any drug may cause an allergic reaction. These symptoms, as they may be signs of a severe allergic reaction: sudden swelling of your lips, face, throat, or tongue, severe rash, and/or difficulty swallowing or breathing should be reported right away to the study doctor or nurses.

Side Effects of Lutetium (177Lu) Edotreotide
One common side effect is the reduction of blood cells that leads to an increased risk of bleeding, faster exhaustion, shortness of breath, and infections. These side effects are relatively common but are mostly temporary.

Further possible side effects include sickness, vomiting and abdominal pain during drug administration, fatigue, changes in appetite afterwards, constipation, diarrhea, dizziness, restlessness, discomfort in your upper

abdomen, and tumor pain. In one study participant, lutetium (177Lu) edotreotide administration caused a pulmonary embolism (a pulmonary embolism is a clot of material that blocks blood from getting to the lungs).

Precaution measures are implemented to downsize the discomfort and burden as much as possible.

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

1. Provided written informed consent.
2. Patients aged >= 18 years (fully mature per local regulations).
3. Histologically confirmed diagnosis of unresectable or metastatic, well-differentiated GEP-NETs, with a Ki-67 index between 15 and 55, inclusive.

4. In the Investigator*s opinion, eligible to receive treatment with at least one of the following: CAPTEM, everolimus or FOLFOX.
5. At least 1 measurable site of disease per RECIST v1.1 using contrast computed tomography (CT)/magnetic resonance imaging (MRI).
6. SSTR+ disease.
7. All patients need to undergo an FDG PET scan within 2 months prior to randomization and as close as possible to the PET SRI.
8. Patients may be treatment naive (first-line received in COMPOSE trial) or have a maximum of one prior line of systemic therapy, including SSAs (second-line received in COMPOSE trial).
9. Karnofsky-score >= 60.

Exclusion criteria

1. Known hypersensitivity to 177Lu, edotreotide, DOTA, any of the comparators, or any excipient or derivative (e.g. rapamycin).
2. Known hypersensitivity to lysine, arginine, or any excipient of the nephroprotective AAS given concurrently with the lutetium (177Lu) edotreotide infusion.
3. Prior external beam radiation therapy (EBRT) to GEP-NET lesions or liver directed selective internal radiation therapy within 12 weeks before randomization.
4. Prior selective internal radiation therapy.
5. Prior PRRT.
6. Received chemotherapy, mammalian target of rapamycin (mTOR) inhibitors, vascular endothelial growth factor (VEGF) pathway inhibitors, immunotherapy, interferon, chemo-embolization, bland embolization, cyclosporine A, locoregional treatment (e.g. cytoreduction surgery, radiofrequency ablation [RFA], liver directed intra-arterial intervention) or SSAs within 4 weeks prior to randomization into the trial.
7. Any major surgery within 4 weeks prior to randomization in the trial.
8. Therapy with an investigational compound and/or medical device within 30 days or 7 half-life periods (whichever is longer) prior to randomization. Live attenuated vaccines should not be administered during the trial treatment and over the next 3 months after the last treatment dose.
9. Patients with known brain metastases, unless these metastases have been treated and stabilized for at least 24 weeks prior to randomization. Patients with brain metastases must have a head CT or MRI with contrast to document stable brain disease.
10. Other known malignancies, (except non-invasive skin cancer, superficial bladder cancer and carcinoma of the cervix in situ), unless definitively treated and proven no evidence of recurrence for 3 years.
11. Serious non-malignant disease (e.g. psychiatric, infectious, autoimmune, metabolic or dementia), that may interfere with the objectives of the trial or with the safety or compliance of the patient, as judged by the Investigator.

12. Renal, hepatic, cardiovascular, or hematological organ dysfunction, potentially interfering with the safety of the trial treatments.
13. Current spontaneous urinary incontinence preventing safe administration of the IMP, in the investigator's opinion.
14. Pregnancy and breast-feeding
15. Patients not able to declare meaningful informed consent on their own or any other vulnerable population to that sense.

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):	24-03-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	177Lu-Edotreotide
Generic name:	177Lu-Edotreotide
Product type:	Medicine
Brand name:	Capecitabine
Generic name:	Capecitabine

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Everolimus
Generic name:	Everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Fluorouracil
Generic name:	Fluorouracil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Folinic acid
Generic name:	Folinic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Temozolomide
Generic name:	Temozolomide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	02-11-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2022
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	CTIS2024-510812-64-00
EudraCT	EUCTR2021-001086-20-NL
CCMO	NL77964.029.21