A Phase I/IIa open-label, multi-center study to evaluate the safety, tolerability, whole-body distribution, radiation dosimetry and anti-tumor activity of [177Lu]-NeoB administered in patients with advanced solid tumors known to overexpress gastrin-releasing peptide receptor (GRPR)

Published: 30-04-2019
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This study has been transitioned to CTIS with ID 2023-507170-41-00 check the CTIS register for the current data. Primary:Phase I: • To identify the maximum tolerated dose (MTD) and/or Recommended Phase II dose (RP2D) of [177Lu]-NeoB Phase IIa:•...

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

Summary

ID

NL-OMON54819

Source
ToetsingOnline

Brief title
NeoRay

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced solid tumors, gastrin-releasing peptide receptor

Health condition

Advanced solid tumors known to overexpress GRPR

Research involving
Human

Sponsors and support

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

Intervention

Keyword: [177Lu]-NeoB, GRPR, Phase I, Tumors

Outcome measures

Primary outcome

Efficacy:

Tumor assessment per RECIST v1.1, RANO (applicable for GBM only)

Key safety assessments:

Incidence and severity of Adverse Events (AEs) and Serious Adverse Events

(SAEs), including changes in laboratory values, vital signs, and

Electrocardiograms (ECGs) for [177Lu]-NeoB; Incidence and severity of Adverse

Events (AEs) and Serious Adverse Events (SAEs) for [68Ga]-NeoB.

Secondary outcome

Other:

PK for all patients as well as distribution and radiation dosimetry for at

least the first 3 patients treated at each dose level of [177Lu]-NeoB in phase

I, the first 6 patients treated in cohorts A, B, and C, and all patients

treated in cohort D in Phase IIa.

Study description

Background summary

Gastrin-releasing-peptide (GRP) is a bombesin-like peptide growth factor implicated in the regulation of numerous central and peripheral functions. By binding to an extracellular GRP receptor (GRPR), it activates an intracellular G-protein that triggers further downstream events. Beside its physiological widespread role, GRP has been demonstrated to be a potent mitogen for normal and neoplastic tissues and may be involved in growth dysregulation and carcinogenesis. In fact, upregulation of GRP/GRPR has been reported in several cancers, including colon, stomach, pancreas, gastrointestinal (GI), uterus, ovaries, head and neck squamous cell cancer and in various central nervous system (CNS) malignancies with the strongest signal been observed for gastrointestinal stromal tumors (GIST), breast, lung (small cell and non-small cell), prostate cancer and glioblastoma (GBM).

Peptide receptor agonists have initially been the GRPR ligands of choice for tracer development. However, more recently, GRPR antagonists have demonstrated greater tumor uptake and better image contrast.

The ligand NeoB, a high affinity antagonist for GRPR, can be radiolabelled with either Gallium 68, for diagnostic use, or with Lutetium 177, for therapy. [68Ga]-NeoB has already been assessed in a Phase I/IIa clinical trial aimed at evaluating the safety, biodistribution, dosimetry and preliminary diagnostic performance of [68Ga]-NeoB in patients with advanced Tyrosine Kinase Inhibitor (TKI)-treated Gastro Intestinal Stromal Tumor (GIST) (EudraCT Number: 2016-002053-38).

[68Ga]-NeoB was well tolerated, no related adverse events have been reported in this study.

Additionally, a Phase II study was recently conducted to evaluate the preliminary diagnostic performance of [68Ga]-NeoB in adult patients with malignancies known to overexpress GRPR (EudraCT Number: 2017-003432-37), and no adverse events related to [68Ga]-NeoB were reported.

Study objective

This study has been transitioned to CTIS with ID 2023-507170-41-00 check the CTIS register

for the current data.

Primary:
Phase I:
• To identify the maximum tolerated dose (MTD) and/or Recommended Phase II dose (RP2D) of [177Lu]-NeoB

Phase IIa:
• Cohort A, B, C: To assess the Disease Control Rate (DCR) of [177Lu]-NeoB at the RP2D
• Cohort D: To assess the PK as well as the biodistribution and radiation dosimetry of [177Lu]-NeoB in patients with moderately impaired renal function

Secondary:
Phase I:
• To assess the PK as well as the biodistribution and radiation dosimetry of each dose level of [177 Lu]-NeoB
• To assess the preliminary anti-tumor activity of [177Lu]-NeoB

Phase IIa:
• Cohort A, B, C: To assess quality of life of patients via EORTC QLQ-C30 Questionnaire
• Cohort A, B, C: To assess the PK as well as the biodistribution and radiation dosimetry of [177Lu]-NeoB
• Cohort A, B, C: To further assess the anti-tumor activity of [177Lu]-NeoB

Phase I and IIa:
• To characterize the safety and tolerability of [177Lu]-NeoB
• To further characterize the safety and tolerability of [68Ga]-NeoB

Exploratory Objectives:
Phase I:
• To evaluate the biodistribution of [68Ga]-NeoB and [177Lu]-NeoB

Phase IIa:
• Cohort D: To further assess the anti-tumor activity of [177Lu]-NeoB

Phase I and IIa:
• To compare SUVr ranges with qualitative [68Ga]-NeoB uptake to define as positive or negative on GRPR overexpressing tumor lesions

Study design

This is a Phase I study which consists of a dose escalation. The design of the Phase I, open label dose finding study was chosen to establish a safe and tolerated dose of [177Lu]-NeoB to be used in Phase IIa in patients with selected advanced solid tumors known to overexpress GRPR and with [68Ga]-NeoB

lesion uptake.

The dose escalation will follow a Bayesian optimal interval (BOIN) design. Dose escalation decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study.

Only patients with a [68Ga]-NeoB tumor lesion uptake, as defined in inclusion criteria, on PET/CT or PET/MRI scan performed at screening will be enrolled into the study and will receive treatment with [177Lu]-NeoB. The methodology to discriminate [68Ga]-NeoB uptake as positive or negative on tumor lesions is described in the Imaging Acquisition Manual.

Since [68Ga]-NeoB is not approved yet and is therefore considered as an IMP2 in this protocol, a safety follow-up will be performed via phone call in an interval of 2(+1) days after [68Ga]-NeoB administration.

An interval of at least 2 weeks between [68Ga]-NeoB and [177Lu]-NeoB administration is required.

A total of up to 7 dose levels in the dose escalation of [177Lu]-NeoB will be evaluated. At each cohort/dose level of at least 3 patients will be enrolled at the same time. This is deemed acceptable due to the advanced tumor status of the population, the low dose of 1.85 GBq (50 mCi) in cycle 1 Cohort 1 and the safety margin (40% and 20% of the estimated cumulative dose) applied in Cohorts 2 and 3. The dosimetry data obtained from three evaluable patients in cycle 1 Cohort 1 will be used to establish the Estimated Cumulative Dose (ECD). This ECD will be used to define the dose of subsequent cycles for patients treated in Cohort 1 as described in Section 6.4.3 of the Protocol.

For further information please refer to the protocol.

Intervention

The IV administration of [68Ga]-NeoB 50 µg, kit for radiopharmaceutical preparation (IMP2), administered 1 time.

The IV administration and subsequent dose escalation and -modification of [177Lu]-NeoB (IMP1), administered 2/3 times.

See the protocol section 6 for a detailed description on dose determination and administration in relation to the different cohorts.

Study burden and risks

Subjects will be asked to come to the doctor*s study site between 15-20 times over about 15 months. In addition, subjects will be called twice over the phone

at the end of the study to check if they have some side effects linked to the study treatment and to know what type of new treatment they are taking. Each visit should take about 2 hours except the visits where subjects will receive the study products and will have body scans for which the visit will be longer. For the first treatment administration of [177Lu]-NeoB, subjects will have to stay at the hospital all day with an overnight until the day after.
These visits also include physical examinations, electrical tracing of the heart (ECG), echocardiograms, body scans, vital signs measurements and taking blood and urine samples.

When taking blood samples the subject might experience pain, lightheaded, additional bleeding (at the site of blood draw), temporary discomfort, bruising, and infection (rarely).
During ECG's the subject may experience temporary discomfort (pulling skin/hair when removing the sensors), develop minor skin irritation from the ECG patch adhesive.
Slow intravenous infusion; for practical and radioprotection reasons, a cannula is inserted through the skin into a vein. The insertion feels like a sharp scratch and the related risks are infection, inflammation of the vein, infiltration, extravasation and embolism.

The potential risks issued from [177Lu]-NeoB are of two types: radioactivity side effects and risks related to the nature of drug.
The most common radioactivity side-effects expected in patients being treated with [177Lu]-NeoB is the decrease of blood cells, most importantly, red blood cells, platelets, and other blood cells such as white blood cells. A decrease in the various blood cell types may put one at risk for bleeding, fatigue, shortness of breath, and infection.
The radioactive substance may affect other organs, especially pancreas, kidneys and bone marrow. To check the possible adverse effects of treatment with the [177Lu]-NeoB on these organs, the function of these organs will be assessed throughout the study duration by taking blood and urine tests.
Other secondary effects could be nausea and vomiting - usually during the first 24 hours and abdominal pain - during the treatment administration. Possible delayed (> first 24 hours) side effects of the radiation include fatigue and temporary hair loss. Other sides-effects reported are: irritation at the injection site, diarrhea or constipation, slow or fast heart-beat, abnormal liver function, loss of appetite, loose feces (stools), shortness of breath.

PET (Positron Emission Tomography): one will receive an intravenous injection of a radioactive substance ([68Ga]-NeoB) and between 1 hour and 3 hours later one will lie still on a bed while the PET machine takes pictures of the body for about 15 minutes. The risks of this procedure are related to the radioactive substance: the radioactivity will disappear by itself soon after the end of the exam; the amount of radiation of this procedure is similar to that from a CT scan exam.
SPECT (Single-Photon Emission Computed Tomography): if one is among the first 3

patients included in each cohort of the first part of the study (Phase I), one will receive via intravenous injection a radioactive substance ([177Lu]-NeoB), and will lie on a bed while the SPECT machine takes pictures of the body. The risks of this procedure are related to the radioactive substance: the radioactivity will disappear by itself progressively after the end of the exam; the amount of radiation of this procedure is similar to that from a CT scan exam.
CT (Computed Tomography): the CT scan is often combined with the SPECT or PET and is low-dose CT scan. The contribution of low-dose CT scan will result in a theoretical radiation dose of 7 mSv max. Other risks of this procedure are only related to the IV (nausea for a short time and, in rare cases, allergic reactions).
MRI (Magnetic Resonance Imaging): the MRI can be used as an alternative to the CT scan, especially if your tumor lesions are located in the brain. During the scan, a MRI contrast (a type of dye) will be injected into a vein in the arm. The dye will be injected through the cannula that is already in place or a new one. The risks of this procedure are only related to the dye injection (nausea for a short time and, in rare cases, allergic reactions).

Considering the risks, precautions, possible benefits, and the situation of possible participants; the benefit-risk balance of administering [177Lu]-NeoB within the overall clinical context defined in the clinical trial appears to weight in favor of patient*s benefit.

See protocol section 4 for a full description on the risks and benefits.

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. Signed informed consent must be obtained prior to participation in the study.,
2. Adult patients (age >= 18 years old) with any of the following advanced or metastatic solid tumors:
• For Phase I: breast cancer, lung cancer, prostate cancer, GIST, GBM
• For Phase IIa:
a. Cohort A: Breast cancer with histology as follows: HR- positive with ER > 10% of nuclei stain, HER-2 negative and HER-2 low based on current practice and medical history.
b. Cohort B: Prostate cancer
c. Cohort C: GIST
d. Cohort D: patients affected by any advanced/metastatic solid tumor type suspected to overexpress GRPR including recurrent GBM, and with moderate impaired renal function defined as creatinine clearance (calculated using the Cockcroft-Gault formula, or measured) >= 30mL/min and < 60mL/min.,
3. At least one measurable lesion per RECIST 1.1 RANO (applicable for GBM only) criteria detected on the low-dose CT/MRI (for GBM MRI only) acquired together with the [68Ga]-NeoB PET. The same identified measurable lesion shows [68Ga]-NeoB uptake on PET/CT or PET/MRI. If the only matching lesion is located in the bone, the patient will still be eligible.,
4. Patients for whom no standard therapy is available, tolerated or appropriate in both Phase I and Phase IIa. Specifically in the Phase IIa breast cancer cohort, patients need to have completed at least one prior treatment of endocrine therapy (including CDk4/6i) and at least one prior chemotherapy (unless contraindicated) in the metastatic setting. Patients with prior treatment with trastuzumab deruxtecan, alpelisib or elascestrant are also eligible. In case of confirmed presence of deleterious or suspected deleterious germline BRCA1 or BRCA2 mutation, the patient must also have already received a PARP inhibitor based therapy.

5. Patient Eastern Cooperative Oncology Group (ECOG) performance status:
For phase I: <= 2
For phase IIa: <= 1

Exclusion criteria

1. Patients who have not had resolution, except where otherwise stated in the inclusion/ exclusion criteria, of all clinically significant toxic effects of prior systemic cancer therapy, surgery, or radiotherapy to Grade <=1 (except for alopecia).
2. Creatinine clearance (calculated using Cockcroft-Gault formula, or measured):
a. < 60 mL/min or serum creatinine >1.5 x ULN* for Phase I and Phase IIa (Cohort A, B and C)
b. <30 mL/min and >= 60 mL/min for Phase IIa (Cohort D)
3. Platelet count of < 75 x 10^9/L*.
4. Absolute neutrophil count (ANC) < 1.0 x 10^9/L*.
5. Hemoglobin < 9 g/dL*.
6. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x upper limit of normal (ULN) if no demonstrable liver metastases or > 5 x ULN in the presence of liver metastases*.
7. Total bilirubin > 1.5 x ULN, except for patients with documented Gilbert*s syndrome who are eligible if total bilirubin <= 3 x ULN*.
8. Serum amylase and/or lipase > 1.5 x ULN*.
9. Known or expected hypersensitivity to [177Lu]-NeoB, [68Ga]-NeoB or any of their excipients.
10. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
* Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (New York Heart Association (NHYA) grade >= 2), uncontrolled arterial hypertension or clinically significant arrhythmia
* LVEF < 50% as determined by echocardiogram (ECHO)*
* QTcF >470 msec for females and QTcF >450 msec for males on screening electrocardiogram (ECG) or congenital long QT syndrome
* Acute myocardial infarction or unstable angina pectoris < 3 months prior to [177LU]-NeoB (IMP1) administration.
11. Patients with diabetes mellitus not stable under current treatment as judged by the investigator, or with hyperglycemia >= CTCAE version 5.0 grade 2*.
12. Patients with history of or ongoing acute or chronic pancreatitis.
13. Concurrent bladder outflow obstruction or unmanageable urinary incontinence.
14. Administration of a radiopharmaceutical with therapeutic intent within a period corresponding to 10 half-lives of the radionuclide used prior to injection of [68Ga]-NeoB.
15. Prior External Beam Radiation Therapy (EBRT) to more than 25% of the bone marrow.
16. [223Ra]-therapy within the context of diffuse bone or bone marrow

involvement (i.e. "superscan" defined as bone scintigraphy in which there is excessive skeletal radioisotope uptake [>20 bone lesions] in relation to soft tissues along with absent or faint activity in the genitourinary tract due to diffuse bone/bone marrow metastases).

18. Patients who have received prior systemic anti-cancer treatment within the following time frames:
* Cyclical chemotherapy within a period that is shorter than the cycle length used for that treatment (e.g. 6 weeks for nitrosourea, mitomycin-C) prior to starting [177Lu]-NeoB treatment
* Biologic therapy (e.g. antibodies), continuous or intermittent small molecule therapeutics, or any other investigational agents within a period which is <= 5 T1/2 or <= 14 days (whichever is shorter) prior to starting [177Lu]-NeoB treatment.
19. History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study.
20. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to [177Lu]-NeoB treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type.
21. Pregnant or breast-feeding women
22. 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 and for 7 months after study drug discontinuation. Highly effective contraception methods are discussed in the protocol.
23. Use of other investigational drugs within 30 days prior to informed consent signature.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-05-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[177Lu]-NeoB
Generic name:	-
Product type:	Medicine
Brand name:	[68Ga]-NeoB
Generic name:	-

Ethics review

Approved WMO Date:	30-04-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	04-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	26-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-04-2024
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	CTIS2023-507170-41-00

Register	ID
EudraCT	EUCTR2018-004727-37-NL
ClinicalTrials.gov	NCT03872778
CCMO	NL69020.078.19