Phase II study of preliminary diagnostic performance of [68Ga]-NeoBOMB1 in adult patients with malignancies known to overexpress Gastrin Releasing Peptide Receptor

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Primary Objective• To characterize preliminary targeting properties of [68Ga]-NeoBOMB1 in patients with malignancies known to overexpress GRPR.Secondary objectives• To assess safety and tolerability of a single diagnostic dose of [68Ga]-NeoBOMB1…

Ethical review	Approved WMO
Status	Completed
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON46627

Source
ToetsingOnline

Brief title
A68GA201

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Cancer, Malignancies known to overexpress GRPR

Research involving
Human

Sponsors and support

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

Intervention

Keyword: [68Ga]-NeoBOMB1, Cancer, Diagnostic Radiopharmaceutical, Gastrin Releasing Peptide Receptor

Outcome measures

Primary outcome

Primary Study Endpoint

•*Number and location of tumour lesions detected by [68Ga]-NeoBOMB1 overall and

for

each tumour type

•*Calculation of the ratio tumour/background SUV and calculation of percentage

absorbed dose in tumour overall and for each tumour type.

Secondary outcome

Secondary Study Endpoints

•*Standard safety parameters (clinical monitoring, laboratory, ECG)

•*Tolerability and safety of the administration of a diagnostic dose of

[68Ga]-NeoBOMB1

in patients with malignancies known to overexpress GRPR as determined by absence

of:

- increased number of SAEs compared to other peptide-based radiotracers;

- clinically relevant changes of physiological parameters (blood pressure, heart

rate, ECG findings)

•*Generation of decay corrected tissue TACs from [68Ga]-NeoBOMB1 PET/CT images in normal organs, tumour lesions.

•*Quantification of urinary excretion of [68Ga]-NeoBOMB1

•*Calculation of half-life of [68Ga]-NeoBOMB1 in blood

•*Generation of non-decay-corrected TACs from [68Ga]-NeoBOMB1 PET/CT images in normal organs, tumour lesions

•*Calculation of residence times in organs and tumour lesions of [68Ga]-NeoBOMB1

•*Calculation of absorbed doses and effective whole body dose of [68Ga]-NeoBOMB1

•*Calculation of the SUV of each lesion

•*Number and location of tumour lesion detected by [68Ga]-NeoBOMB1 in comparison with comparable standard imaging modalities such as FDG-PET

•*Calculation of the [68Ga]-NeoBOMB1 PET overall, positive and negative on a lesion-by-lesion basis as well as on a patient basis relative to the standard imaging overall and for each tumour type

•*Comparison of number of patients with tumour lesions detected and number of tumour lesions detected by [68Ga]-NeoBOMB1 with cytology and/or histopathology from archival and/or recent biopsy specimens

•*Calculation of the [68Ga]-NeoBOMB1 PET sensitivity and specificity on a lesion-bylesion basis for all lesions with associated biopsy data, and on a patient basis relative

to histopathology / cytology data

Exploratory Study Endpoints

•*Absorbed tumour doses of [177Lu]-NeoBOMB1 extrapolated from 68Ga-dosimetric

data

and definition of dose limiting organ for radionuclide therapy

Study description

Background summary

GRP is a bombesin-like peptide growth factor implicated in the regulation of numerous central and peripheral functions. By binding to a GRP extracellular receptor (GRPR), it activates an intracellular G-protein that triggers further chain reactions. 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 breast, prostate, colon, lung (small cell and non-small cell), stomach, pancreas, uterus, ovaries, head and neck squamous cell cancer and in various central nervous system malignancies.
For instance, GRPR expression has been investigated in primary and metastatic breast cancer among different molecular subtypes. GRPR overexpression was most strongly associated with estrogen receptor (ER) positivity and found in over 75% of the primary tumour samples and in over 90% of their metastatic lymph nodes.

In parallel, a massive GRP receptor overexpression has been demonstrated in prostate tissues that are already neoplastic or in the process of malignant transformation (i.e. prostatic intraepithelial neoplasias). In this specific case, GRP receptors have been thought of as markers for early molecular events in prostate carcinogenesis and useful in differentiating prostate hyperplasia from prostate neoplasia.

In the lung, GRP has been found in the pulmonary neuroendocrine cells and is responsible for lung development and maturation. Nevertheless, GRP has also been reported in relation to growth dysregulation and carcinogenesis on non-small cell lung cancer (NSCLC) proliferation. In fact, increased levels of GRP

have led to increased release of pro-ligands for epidermal growth factor receptor (EGFR) with subsequent activation of EGF and mitogen-activated protein kinase downstream pathways.

Presence of GRP and/or expression GRPR have also been investigated in colorectal cancer samples (primary tumour, lymph nodes and metastatic lesions) where over 80% samples expressed GRP/GRPR as opposed to adjacent normal healthy epithelium.
Overall, the literature accounts with a growing body of evidence suggesting that GRPR might be a valuable target.
Peptide receptor agonists have long been the ligands of choice for tracer development and utilization in nuclear medicine thanks to their high radioactive accumulation inside the target cells after receptor-radioligand complex internalization. However, GRPR antagonists have been compared to GRPR agonists and showed greater tumour uptake and better image contrast. Furthermore, GRPR antagonists allow for a safer clinical use, since no acute biological adverse effects are expected.

The Sponsor has therefore designed the current protocol to establish whether the ligand NeoBOMB1, a high affinity antagonist for GRPR, radiolabelled with a well-established PET isotope, Gallium-68 (68Ga) is a suitable radiotracer for in vivo detection of GRPR-expressing malignancies, currently focusing on breast, prostate, lung (small cell and non-small cell) and colon-rectum.

Study objective

Primary Objective
• To characterize preliminary targeting properties of [68Ga]-NeoBOMB1 in patients with malignancies known to overexpress GRPR.

Secondary objectives
• To assess safety and tolerability of a single diagnostic dose of [68Ga]-NeoBOMB1 administered as an intravenous bolus injection.
• To assess the bio-distribution, pharmacokinetics, radiation dosimetry, and absorbed doses in critical organs for [68Ga]-NeoBOMB1 in a limited set of patients.
• To establish the optimal threshold, expressed as Standardized Uptake Value (SUV), to discriminate Positron Emission Tomography (PET) imaging positive results from negative ones.
• To estimate the [68Ga]-NeoBOMB1 PET lesion-based and patient-based imaging performance relative to a comparable standard imaging.
• To estimate the [68Ga]-NeoBOMB1 PET diagnostic performance lesion-based and patient-based relative to the GRPR histopathology findings (e.g. IHC)

Exploratory objective
• To evaluate absorbed tumour doses for potential application of

[177Lu]-NeoBOMB1.

Study design

This is a Phase II, multi-center, open label, single dose study in patients with tumour types known to overexpress GRPR, including breast, prostate, colorectal, non-small cell lung (NSCL) and small-cell lung (SCL) cancer. Population will be divided into two groups:

• a Phase-II dosimetry group, accounting with 10 patients (splitted into breast cancer: n=5 female patients and prostate cancer: n=5 male patients) who will undergo several assessments to confirm previous data on tracer bio-distribution, radiation dosimetry, residence time for critical organs, and absorbed dose critical organs for [68Ga]-NeoBOMB1. Venous whole blood and urine samples will be collected for activity-based pharmacokinetics characterization;
• a Phase-II non-dosimetry group, accounting with 40 patients splitted into :
* Breast cancer: n=5
* Prostate cancer: n=5
* Colorectal cancer: n=10.
* NSCLC: n=10
* SCLC: n=10

Patients included in the non-dosimetry group will undergo one early and one late whole-body PET-imaging acquisition, with no blood and urine sampling. Only prostate tumour patients will undergo an additional early 5-min static PET scan to better assess lymphe node metastases.
GRPR expression must be assessed while the study is ongoing within 4 weeks after IMP injection by Immunohistochemistry staining from archival or recent biopsy specimens (not older than 6 months prior to IMP injection).
The objectives of the study will be applicable for the whole study population excepted the secondary objective relative to the biodistribution and dosimetry that will be applicable only for the dosimetry group.

Intervention

Each study subject will receive a single dose (5.5mL) of study product by IV injection on visit "Day 1"

Study burden and risks

The study subjects will undergo a physical examination and are expected to not become pregnant or make their partner pregnant. Furthermore, ECGs, blood draws and urine collections will be performed. The study product will be administered by IV injection. PET/CT will be performed.
The amount of blood draws varies per group. In total there will be 4 to 5 blood draws. The total volume of these blood draws is approximately 66 to 91 mL of

blood.

The amount of PET/CT scans varies per group. There will be 2 to 4 scans. The estimated total dose of radiation is approximately 13.9 mSV with a low dose CT and 29.6 mSV with a high dose CT.

The risk of participation is approximated as low and is limited to potential side-effects of the study product and the accompanying tests. The study product is tolerated well as indicated by current findings. The results of the study can attribute to an improved diagnostic method to detect (refractory) GRPR malignancies.

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

• Subjects must be at least 18 years of age
• Subjects must have signed and dated an informed consent prior to any study-specific procedures.
• Subjects with histologically-confirmed tumour, for whom a less than 6-month-old biopsy has been performed.
• Dosimetry group:
- Luminal breast cancer
- Adenocarcinoma of the prostate
• Non-dosimetry group:
- Luminal breast cancer
- Adenocarcinoma of the prostate
- Small-cell lung cancer
- Non-small cell lung cancer
- Colorectal carcinoma
• At least one malignant lesion detected via functional or morphological imaging (PET combined to appropriate tracer according to tumour type, CT, MRI) within 3 months prior to the administration of [68Ga]-NeoBOMB1.
• The Eastern Cooperative Oncology (ECOG) performance status 0-2.
• Subjects must agree to use highly effective methods of contraception (female partners of male participants should use highly effective methods of contraception) during the trial.

Exclusion criteria

• Renal insufficiency or an estimated Glomerular Filtration Rate (eGFR) <50 ml/min/1.73m2..
• Haematological toxicity grade > 2 (Toxicity Grading Scale in vaccine clinical trials)
• Participation in any other investigational trial within 30 days of study entry.
• Subjects with positive pregnancy test (Urine dipstick), and/or currently breast-feeding
• Concurrent severe illness or clinically relevant trauma within 2 weeks before the administration of the investigational product that might preclude study completion or interfere with study results.
• Concurrent bladder outflow obstruction or unmanageable urinary incontinence.
• Known or expected hypersensitivity to 68Gallium, NeoBOMB1, or any excipient present in [68Ga]-NeoBOMB1.
• Any condition that precludes raised arms position
• Prior administration of a radiopharmaceutical within a period corresponding to 8 half-lives of the radionuclide.
• History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	11-04-2018
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	[68Ga]-NeoBOMB1
Generic name:	[68Ga]-NeoBOMB1

Ethics review

Approved WMO

Date:	14-12-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	11-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	26-06-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-05-2019
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
EudraCT	EUCTR2017-003432-37-NL
CCMO	NL63628.078.17

Study results

Date completed: 05-07-2019

Results posted: 28-04-2020

First publication
30-03-2020