ImmunoPET imaging with 89Zr-DFO-REGN3767 in patients with advanced solid cancer prior to and during treatment with cemiplimab with or without platinum-based chemotherapy

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This study has been transitioned to CTIS with ID 2024-516795-15-00 check the CTIS register for the current data. Primary: i) To determine the optimal 89Zr-DFO-REGN3767 protein dose and optimal PET imaging timepoint. ii) To evaluate the...

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

Summary

ID

NL-OMON51900

Source
ToetsingOnline

Brief title
LAG-3 PET imaging in advanced solid tumors

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Cancer, metastases

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Regeneron Pharmaceuticals Inc.

Intervention

Keyword: Cancer, Immune checkpoint inhibitor, LAG-3, Positron emission tomography

Outcome measures

Primary outcome

• Comparison of standardized uptake values in tumor lesions and tumor-to-blood ratios at different time points and different 89Zr-DFO-REGN3767 antibody dose levels.

• To evaluate the biodistribution and PK of 89Zr-DFO-REGN3767 antibody by measuring standardized uptake value (SUV) on 89Zr-DFO-REGN3767 PET scans in patients with histologically or cytologically documented locally advanced or metastatic solid tumors who based on available clinical data may benefit from treatment with cemiplimab with or without platinum-based chemotherapy.

• Safety evaluation through summaries of adverse events, changes in laboratory test results and changes in vital signs after exposure to 89Zr-DFO-REGN3767.

Secondary outcome

• Comparison of tracer uptake, expressed as standardized uptake values, in different tumor lesions within and between patients on 89Zr-PET scans.

• Correlation of tumor tracer uptake with tumor and immune cell LAG3 expression as assessed by immunohistochemistry on a tumor biopsy sample.

• Correlation of tumor tracer uptake with response to cemiplimab with or without platinum-based chemotherapy, according to RECIST v1.1.

• Assessment of change in tumor and normal organ tracer uptake after 2 cycles

of cemiplimab with or without chemotherapy

Study description

Background summary

The rapidly evolving fields of tumor immunology and cancer immunotherapy have resulted in several Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved immune checkpoint inhibitors (ICI) for different tumor types. However, not all patients respond to these drugs. Moreover, immunotherapeutic drugs require careful management of potential side effects. Therefore, it would be of major interest to be able to know whether a specific treatment induces an immune response.

The dynamic tumor microenvironment and tumor heterogeneity have raised significant interest in objectifying the status of the microenvironment. Still, the ability to monitor changes in the immune status of metastatic cancers is limited. Current methods to monitor lymphocytes from whole blood or biopsies from heterogeneous tumors do not necessarily reflect the dynamic and spatial information required to monitor immune responses to therapeutic intervention. Moreover, these responses may elicit whole body changes in immune cell numbers and localization. Molecular imaging can noninvasively monitor whole-body systemic and intratumoral alterations. Assessing abundance and localization of immune cells before and during therapy would increase the understanding of the dynamics of immunotherapeutic mechanisms, with the potential to provide translatable methods for predicting and/or assessing responses.

The immune checkpoint lymphocyte activation gene-3 (LAG-3, cluster of differentiation (CD)223)) is a cell surface molecule expressed on activated T cells, natural killer (NK) cells, B cells and several additional hematopoietic cell types including plasmacytoid dendritic cells. The fully human anti-LAG-3 antibody fianlimab (REGN3767) has been radiolabeled with deferoxamine (DFO) Zirconium-89 (89Zr). In a preclinical mouse model, this tracer visualized LAG-3 expressing intratumoral T cells after co-implantation of human Raji Burkitt lymphoma cells with human peripheral blood mononuclear cells.1 89Zr-DFO-REGN3767 positron emission tomography (PET) allows visualization of the 89Zr-DFO-REGN3767 antibody uptake in tumor and lymphoid tissues which might be an early marker of immune response that could guide ICI treatment. Chemotherapy is thought to increase LAG-3 expression. Such a tracer might be extremely informative regarding T cell behavior during established ICI therapy with anti-programmed cell death protein 1 (PD1) antibody with or without platinum-based chemotherapy.

Noninvasive serial whole-body monitoring of the tumor immune response to therapy by means of imaging activated immune cells might provide major insights. By performing 89Zr-DFO-REGN3767 PET scans prior to and during treatment with anti-PD-1 antibody cemiplimab with or without platinum-based chemotherapy, the radioactivity uptake in primary and metastatic tumor lesions and normal organ distribution can be evaluated. 89Zr-DFO-REGN3767 PET can serve as a potential complementary tool for patient and treatment selection in the future as well as could potentially lead to early treatment decisions.

Study objective

This study has been transitioned to CTIS with ID 2024-516795-15-00 check the CTIS register for the current data.

Primary: i) To determine the optimal 89Zr-DFO-REGN3767 protein dose and optimal PET imaging timepoint. ii) To evaluate the pharmacokinetics (PK) of 89Zr-DFO-REGN3767 by measuring standardized uptake value (SUV) on 89Zr-DFO-REGN3767 PET scans in patients with histologically or cytologically documented locally advanced or metastatic solid tumors who based on available clinical data, may benefit from treatment with the PD1 antibody cemiplimab +/- platinum- based chemotherapy. iii) To evaluate the safety of 89Zr-DFO-REGN3767.

Secondary: i) To assess the heterogeneity of 89Zr-DFO-REGN3767 antibody tumor uptake within a lesion and between lesions. ii) To correlate tumor tracer uptake with tumor and immune cell LAG3 expression as assessed by biopsy. iii) To correlate the tumor tracer uptake with response to cemiplimab antibody with or without platinum-based chemotherapy. iv) To assess change in tumor and normal organ uptake after 2 cycles of cemiplimab with or without chemotherapy

Study design

An investigator-initiated, single-center (University Medical Center Groningen (UMCG)), open-label clinical trial designed to evaluate the safety, in vivo biodistribution and tumor / organ pharmacodynamics of the PET tracer 89Zr-DFO-REGN3767 in patients with histologically documented locally advanced or metastatic solid tumors who according to the opinion of the investigator, based on available clinical data, may benefit from cemiplimab with or without platinum-based chemotherapy.

Intervention

Part A will serve to find the optimal tracer dose and the optimal interval between tracer injection and PET scanning. Approximately 4 cohorts of about 2-3 patients each will undergo 89Zr-DFO-REGN3767 PET imaging at 4 time points (day of 89Zr-DFO-REGN3767 injection, day 2, day 4 and day 7 after injection). Depending on the tumor saturation and scanning results, additional patients can

be included. At least six patients will be enrolled at the dose level considered appropriate for further testing; additional patients may be enrolled at that dose level if considered necessary to collect additional imaging and/or safety data prior to starting part B. After completion of imaging, patients will receive the PD1 antibody cemiplimab at a dose of 350 mg every 3 weeks with or without platinum-based chemotherapy.
Part B, using the optimal protein tracer dose and at the optimal PET scan timepoint, will serve to evaluate the PK and imaging characteristics of 89Zr-DFO-REGN3767 before and during treatment with cemiplimab with or without platinum-based chemotherapy. In part B, approximately 22 patients will be enrolled to undergo 89Zr-DFO-REGN3767 PET imaging twice; the first 89Zr-DFO-REGN3767 PET scan will be performed at baseline, before starting therapy. The second 89Zr-DFO-REGN3767 PET scan will be performed early in cycle 2 (within 7 days after administration of cycle 2), to minimize morphological changes in tumors responding to the therapy. In part B, one cohort of 11 patients will be treated with cemiplimab every 3 weeks and another cohort of 11 patients will be treated with cemiplimab every 3 weeks with platinum-based chemotherapy. All patients participating in the imaging trial part A and B will undergo at least one tumor biopsy. The biopsy procedure will be performed after the last 89Zr-DFO-REGN3767 PET scan that occurs before the start of treatment. In addition, in part B, on-treatment tumor biopsies will be performed if possible, at the end of the second 89Zr-DFO-REGN3767 PET scan period.

Study burden and risks

For this study, patients have to make a maximum of 9 extra visits to the clinic for screening, to receive 89Zr-DFO-REGN3767 injection, to have up to 4 PET-scan visits, and the biopsies taken before and/or after starting treatment with cemiplimab with or without platinum-based chemotherapy. In practice, most procedures will be combined with visits to the hospital in the context of clinical care to minimize the burden.
89Zr-DFO-REGN3767 is a radioactive compound and therefore, will cause radiation burden to the patient. The projected effective dose after receiving 37 MBq of 89Zr-DFO-REGN3767 is about 18 mSv. Each PET scan will be made with a low dose attenuation correction CT scan, which has an effective dose of 1.5 mSv. Thus, patients in part A undergoing 4 PET/CT scans, will receive an exposure of approximately 18 + (4x1.5) = 24 mSv. Patients in part B will receive two 37 MBq doses of 89Zr-DFO-REGN3767 and undergo 2 PET/CT-scans. The radiation exposure will be approximately (2x18) + (2x1.5) = 39 mSv.
Besides PET imaging, patients will be asked to provide a total of 11 blood samples in part A (86 mL) and 12 samples in part B (96 mL). A tumor lesion will be biopsied. Based on a literature review, the risk of tumor biopsies is considered low, with a small risk of significant or major complications or death. To keep this risk as low as possible only patients that have safely accessible tumor lesions will be included in the study.
The risk associated with 89Zr-DFO-REGN3767 is considered very low based on extensive preclinical testing and preliminary data of an ongoing phase 1 trial

where REGN3767 is given (NCT03005782, EudraCT 2016-002789-30). This study will enroll patients who have exhausted standard therapy and are believed by the investigator to potentially benefit from PD1 antibody with or without platinum-based chemotherapy. Available clinical data will be used to inform the investigator*s decision. Although patients that have a standard treatment option of ICI therapy plus or minus chemotherapy do not directly benefit from this study, results from this study will be valuable for our understanding of the tumor immune response and will guide further prospective research and hopefully treatment decisions.

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. Age >= 18 years at the time of signing informed consent.

2. Patients with histologically confirmed diagnosis of locally advanced or metastatic solid cancer types who, according to the opinion of the investigator, based on available clinical data, may benefit from PD1 antibody with or without platinum-based chemotherapy.
3. At least 1 lesion that is accessible per investigator*s assessment and eligible for biopsy according to standard clinical care procedures.
4. Measurable disease, as defined by standard RECIST v1.1. Previously irradiated lesions should not be counted as target lesions except for lesions that have progressed after radiotherapy.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Life expectancy >= 12 weeks.
7. Adequate organ and bone marrow function as defined below:
a. Hemoglobin >=9.0 g/dL
b. Absolute neutrophil count >=1.5 x 109/L
c. Absolute lymphocyte count >=0.75 x 109/L
d. Platelet count >=100 x 109/L
e. Serum creatinine <=1.5 x upper limit of normal (ULN) or estimated glomerular filtration rate > 30 mL/min/1.73 m2. A 24-hour urine creatinine collection may substitute for the calculated creatinine clearance to meet eligibility criteria.
f. Adequate hepatic function:
i. Total bilirubin <=1.5 x ULN (<=3 x ULN if liver tumor involvement); Patients with Gilbert*s syndrome do not need to meet total bilirubin requirements, provided their total bilirubin is unchanged from their baseline. Gilbert*s syndrome must be documented appropriately as past medical history.
ii. Aspartate aminotransferase (AST) <=2.5 x ULN (<=5 x ULN if liver tumor involvement)
iii. Alanine aminotransferase (ALT) <=2.5 x ULN (<=5 x ULN if liver tumor involvement)
iv. Alkaline phosphatase (ALP) <=2.5 x ULN (<=5 x ULN if liver or bone tumor involvement)
8. Signed informed consent.
9. Willingness and ability to comply with all protocol required procedures.

Exclusion criteria

1. Treatment with any approved anti-cancer therapy, investigational agent, or participation in another clinical trial with therapeutic intent within 28 days prior to 89Zr-DFO-REGN3767 injection.
2. Prior ICI treatment, including but not limited to anti-PD1 and anti-PD-L1 therapeutic antibodies in the past 12 months or >= 12 months ago, in case the ICI treatment was terminated for progressive disease or toxicity.
3. Encephalitis, meningitis, or uncontrolled seizures in the year prior inclusion.
4. Any unresolved toxicity (>CTCAE grade 2) from previous anti-cancer

therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy)
5. Symptomatic, untreated brain metastasis, leptomeningeal disease, or spinal cord compression. Patients are eligible if central nervous system (CNS) metastases are adequately treated and neurologically stable for at least 2 weeks prior to enrollment.
6. Documented allergic or acute hypersensitivity reaction attributed to antibody treatments
7. Major surgical procedure other than for diagnosis within 28 days prior to 89Zr-DFO-REGN3767 injection or anticipation of need for a major surgical procedure during the course of the study.
8. For patients that will be treated with cemiplimab in combination with platinum containing chemotherapy, the following additional criteria apply:
• Leucopenia <3 x 109/L
• Estimated glomerular filtration rate < 60 mL/min/1.73 m2
• Cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), unstable angina, unstable cardiac arrhythmias, myocardial infarction < 3 months ago, or cerebrovascular accident < 6 months ago.
• Hearing loss
• Any other exclusion criteria, according to the local clinical practice guidelines for the chosen chemotherapy regimen.
9. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematous, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener*s granulomatosis, Sjögren*s syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis or glomerulonephritis.
• Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for his study.
• Patients with controlled type I diabetes mellitus on a stable dose of insulin regimen may be eligible for this study.
10. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis.
• History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
11. Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 4 weeks prior to 89Zr-DFO-REGN3767 injection.
• Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the sponsor.
• The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

12. Prior allogeneic bone marrow transplantation or solid organ transplant.
13. Active infection with human immunodeficiency virus (HIV), hepatitis B, hepatitis C or tuberculosis infection; or diagnosis of immunodeficiency
• Patients will be tested for hepatitis C virus (HCV) and hepatitis B virus (HBV) at screening.
• Patients with known HIV infection who have controlled infection (undetectable viral load (HIV ribonucleic acid (RNA) polymerase chain reaction (PCR)) and CD4 count above 350 either spontaneously or on a stable antiviral regimen are permitted. For patients with controlled HIV infection, monitoring will be performed per local standards.
• Patients with hepatitis B who have a controlled infection (serum HBV deoxyribonucleic acid (DNA) PCR below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug.
• Patients who are HCV antibody positive who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.
• Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
14. Active infection that requires systemic antibiotics within 2 weeks prior to 89Zr-DFO-REGN3767 injection.
15. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of 89Zr-DFO-REGN3767, or that may affect the interpretation of the results or render the patient at high risk from complications.
16. Receipt of a live vaccine (including attenuated) within 30 days of planned start of study medication.
17. Altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent.
18. Sponsor employee/member of the clinical site study team and/or his or her immediate family
19. Women with a positive serum chorionic gonadotropin HCG pregnancy test at the screening/baseline visit. Breastfeeding women are also excluded.
20. Women of childbearing potential* and sexually active men who are unwilling to practice highly effective contraception prior to the first dose of study therapy, during the study, and for at least 6 months after the last dose.
Highly effective contraceptive measures include:
• stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
• intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
• bilateral tubal ligation
• vasectomized partner (provided that the male vasectomized partner is the sole

sexual partner of the women of childbearing potential (WOCBP) study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure)
• and/or sexual abstinence

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-01-2022
Enrollment:	38
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	89Zr-DFO-REGN3767
Generic name:	REGN3767
Product type:	Medicine
Brand name:	Cemiplimab
Generic name:	-
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	21-12-2020
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-11-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-06-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-08-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-04-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-05-2023
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-09-2023
Application type:	Amendment
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-02-2024
Application type:	Amendment
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Approved WMO Date:	13-02-2024
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Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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Application type:	Amendment
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Approved WMO Date:	27-06-2024
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Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-07-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	CTIS2024-516795-15-00
EudraCT	EUCTR2020-004052-15-NL
ClinicalTrials.gov	NCT04706715
CCMO	NL74943.042.20