A First-In-Human study of 89ZR-DFO-REGN5054 (anti-CD8) Positron Emission Tomography in patients with solid malignancies treated with cemiplimab

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The primary objective:To determine the safety and tolerability of 89Zr*DFO*REGN5054 alone and in combination with cemiplimab.Secondary ObjectivesFor Part A:• To characterize the radioactivity pharmacokinetic (PK) profile of 89Zr DFO REGN5054• To...

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

Summary

ID

NL-OMON53715

Source
ToetsingOnline

Brief title
89ZR-DFO-REGN5054 PETscan study in patient with cemiplimab treated cancer

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, tumor

Research involving
Human

Sponsors and support

Primary sponsor: Regeneron Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Regeneron Pharmaceuticals;Inc.

Intervention

Keyword: anti-CD8 PET tracer, cemiplimab, imaging solid tumors

Outcome measures

Primary outcome

The co-primary endpoints are:

-For Part A, the primary endpoint is the incidence of treatment-emergent

adverse events (TEAEs).

-For Part A and B, the incidence and severity of TEAEs.

Secondary outcome

For Part A:

- Clinical dosimetry based on tissue radiation absorbed dose and effective dose

calculated from PET image acquisition data and 89Zr-DFOREGN5054 activity

concentration in blood on days 1, 5, and 8

- Serum imaging agent activity concentration, expressed as standardized uptake

value (SUV), with calculation of area under the curve (AUC) through day 8

(AUC0-7)

For Part A and Part B:

- 89Zr-DFO-REGN5054 uptake across CD8-expressing normal tissues and tumors at

the time of imaging

- Blood pool uptake of 89Zr-DFO-REGN5054 with subsequent calculation of SUV

tumor-to-blood ratios at the time of imaging

- Association of 89Zr-DFO-REGN5054 autoradiographic signal intensity

distribution with CD8 expression in tumor tissues at baseline

For Part B:

- Association of 89Zr-DFO-REGN5054 uptake with CD8 expression in tumor tissues

at baseline

- Association of tumor-to-blood ratio of 89Zr-DFO-REGN5054 with CD8 expression

in tumor tissues at baseline

Study description

Background summary

89Zr-DFO-REGN5054 is an investigational tracking substance (tracer), which means it has not yet been approved by a health authority for imaging of tumors. 89Zr-DFO-REGN5054 is being studied as an agent for imaging tumors and will be administered by infusion (through the vein).
89Zr-DFO-REGN5054 is an antibody labeled with tiny amounts of a radioactive atom called Zirconium-89 (89Zr). 89Zr can be detected from outside the body with positron emitting tomography scans (PET scans), with machines similar to CT scanners. 89Zr-DFO-REGN5054 binds to a substance in the body called CD8, located on immune cells called T-cells. 89Zr-DFO-REGN5054 may image CD8, which is present on T-cells in tumors, and could in this way possibly provide useful information on which tumors are more likely to respond to certain new anti-cancer therapies, where the body's immune cells are activated to kill tumor cells.
Cemiplimab is a PD-1 antibody immune checkpoint inhibitor, which is approved in Europe by the EMA (European Medicines Agency) for the treatment of a type of skin cancer called metastatic (widespread) cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC for patients who cannot be treated with intended curative surgery or curative radiation. Cemiplimab has not been approved for the treatment of any other types of cancer. Therefore, if you have a type of cancer other than CSCC, the treatment with cemiplimab is still considered to be investigational.

Study objective

The primary objective:
To determine the safety and tolerability of 89Zr*DFO*REGN5054 alone and in

combination with cemiplimab.

Secondary Objectives
For Part A:
• To characterize the radioactivity pharmacokinetic (PK) profile of 89Zr DFO REGN5054
• To establish an adequate mass dose and activity dose of 89Zr-DFO-REGN5054 and optimal post-infusion time for imaging
For Parts A and B:
• To evaluate the association of CD8 expression in tissue biopsies (via IHC) with tumor 89Zr*DFO*REGN5054 uptake in vivo (via PET) and ex vivo (via autoradiography)
• To evaluate the uptake of 89Zr*DFO*REGN5054 in tumors, normal CD8 expressing tissues, and blood

The exploratory objectives of the study are:
• To evaluate the association of 89Zr-DFO-REGN5054 signal at baseline and on treatment with tumor response after cemiplimab treatment
• To evaluate the association between 18F-fluorodeoxyglucose (18F-FDG) and 89Zr DFO REGN5054 uptake in tumor lesions
• To characterize association of 89Zr-DFO-REGN5054 signal at baseline and on treatment with the mRNA and protein biomarkers of tumor infiltrating lymphocyte density and effector function
• To assess anti-tumor activity of cemiplimab

Study design

This is a phase 1, first-in human (FIH) trial evaluating 89Zr-DFO-REGN5054 as an imaging agent to evaluate intra-tumoral expression of CD8 on T-cells at baseline and in the context of cemiplimab therapy.
The study comprises 2 parts, Part A and Part B. Part A is a dose-finding and safety study in which subjects receive a single 89Zr-DFO-REGN5054 dose, followed by serial PET/computed tomography (CT) scans over a 7-day period. Part A will evaluate dosimetry and establish an adequate mass dose of 89Zr DFO-REGN5054 and an optimal post-infusion imaging time. In Part B, subjects will receive 2 doses of 89Zr-DFO-REGN5054. CD8 immuno-positron emission tomography (iPET) signal will be measured after 89Zr DFO REGN5054 infusion at the defined mass dose and at a post-infusion imaging time point (both determined in Part A) at baseline and post-cemiplimab administration, for comparison with CD8 IHC and tumor response. Subjects who enroll in study Part A will not be eligible to participate in study Part B.
Subjects in both Part A and Part B will receive cemiplimab therapy after the first 89Zr-DFO-REGN5054 PET/CT scan until confirmed progression or for up to 102 weeks (~2 years) followed by a 90-day follow-up period.
Tumor burden will be assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and immune-based Response Evaluation Criteria in Solid Tumors (iRECIST) at the end of each treatment cycle, through

cycle 4 and every other cycle thereafter.
Part A
For Part A, 7 ascending 89Zr-DFO-REGN5054 mass dose cohorts are planned (2 mg, 5 mg, 10 mg, 20 mg, 40 mg, 60mg, and 80 mg), with up to 6 subjects per cohort. Subjects will receive 89Zr-DFO-REGN5054 on day 1, followed by 3 PET/CT scans over the course of 1 week (days 1, 5, and 8). The first 2 subjects in each mass dose cohort will be monitored in the medical facility for at least 24 hours after 89Zr DFO REGN5054 infusion. A minimum of 1 week will be required between completion of the first 89Zr-DFO-REGN5054 administration for the initial 2 subjects at each dose level to allow for evaluation of acute toxicity. Evaluation of 89Zr-DFO-REGN5054 safety will continue for at least 7 days following infusion of the imaging agent until the day 8 PET/CT scan, prior to cemiplimab therapy. Cemiplimab treatment will then be initiated, at a fixed dose of 350 mg Q3W, any time up to 7 days after the last 89Zr-DFO-REGN5054 PET/CT scan and/or the optional biopsy.
Dose Escalation Strategy
For each mass dose cohort in Part A, an initial 2 subjects will be dosed with 89Zr-DFO-REGN5054, with a minimum 1-week interval between the dosing of each subject.
Upon completion of the day 8 PET scan for the second subject at a given mass dose, a Dose Escalation Review meeting will take place. Upon review of all available imaging, 89Zr-DFO-REGN5054 serum activity concentration, clinical dosimetry, and safety data on these subjects, a decision will be made to undertake 1 of the following:
• Expand the cohort to up to 6 subjects , based on adequate safety and adequate blood pool serum 89Zr-DFO-REGN5054 activity and
uptake in CD8-expressing normal tissues (spleen).
• Ascend to the next mass dose cohort, based on adequate safety but inadequate serum 89Zr-DFO-REGN5054 activity concentration and
uptake in CD8-expressing normal tissues (spleen) and/or tumor uptake.
• Proceed with the next mass dose cohort at a lower mass dose, based on inadequate uptake in CD8-expressing normal tissues (spleen,
marrow) and/or tumor uptake, but adequate serum 89ZrDFOREGN5054 activity concentration. This lower mass dose will allow for
evaluation of potential competition from unlabeled antibody,
resulting in dampening of the iPET signal at higher mass doses.
Upon completion of dosing of each cohort (up to 6 subjects), a Dose Escalation Review meeting will take place to review all available safety and imaging data to decide on one of the following:
• Ascend to the next mass dose cohort,
• Close Part A and proceed with Part B, based on any given cohort of up to 6 subjects with adequate serum 89Zr-DFO-REGN5054 activity
concentration, uptake in CD8 expressing normal tissues, and/or tumor uptake at the optimal time point post infusion.
In the event of occurrence of 1 or more adverse events of special interest (AESIs) or serious adverse events (SAEs) assessed as related to 89Zr*DFO*REGN5054 by the investigator, the study will be suspended for safety

review in a Dose Escalation Review meeting, followed by a decision to undertake 1 of the following:
• Resume the study as planned if it is determined by the sponsor and confirmed by this committee that the index AESIs/SAEs are unlikely related to 89Zr*DFO*REGN5054.
• Expand the current cohort up to 6 subjects for further safety evaluation.
• Terminate the study.
In addition, an occurrence of 1 or more AESIs/SAEs, assessed as related to 89Zr*DFO*REGN5054 by the investigator, will trigger a review of the safety data by the Regeneron Safety Oversight Committee (RSOC)
Part B
Part B subjects will be imaged twice using the safe and well tolerated 89Zr DFO-REGN5054 dose and optimal post-infusion imaging time determined in Part A. Subjects will receive 89Zr-DFO-REGN5054 infusion on day 1, followed by a PET/CT scan at the optimal post-infusion imaging time. A mandatory tumor biopsy will be performed following the PET/CT scan prior to initiation of cemiplimab therapy. Any time up to 7 days after the first PET/CT scan, cemiplimab will be administered at a fixed dose of 350 mg Q3W. Approximately 4 weeks (up to 8 weeks) after the initial dose of cemiplimab, a second dose of 89Zr DFO REGN5054 will be administered, and a subsequent PET/CT scan will be performed. In addition, a biopsy of the tumor (optional) may be performed following this PET/CT scan.

Intervention

For Part A, 89Zr*DFO*REGN5054 will be administered intravenously (IV) at a single mass dose of 2 mg, 5 mg, 10 mg, 20 mg, 40 mg, 60 mg and 80 mg. For Part B subjects will be administered 89Zr-DFO-REGN5054 at the defined mass dose determined in Part A.
Cemiplimab will be administered IV at dose of 350 mg every 3 weeks (Q3W)

Study burden and risks

Taking into account the measures implemented in the protocol to minimize important risks to subjects, the potential for therapeutic benefit, evaluation of cemiplimab in subjects with advanced or metastatic solid CD8 tumors is justified.

89Zr-DFO-REGN5054 is a positron-emitting radioimmunoconjugate, specific for human CD8 that is being developed for immuno-PET imaging. 89Zr-DFO-REGN5054 has not yet been administered to humans. Therefore, there are no identified risks with clinical use. The potential risks to study participants are considered minimal and there is adequate risk minimization described in the protocol. The findings from nonclinical studies demonstrate an adequate safety margin for the planned mass dose range of 89Zr-DFO-REGN5054 in humans. The radiation exposure is expected to be similar to that of other immuno-PET tracers. Taken together,

these data justify the evaluation of 89Zr-DFO-REGN5054 as an immuno-PET agent in humans.

Based on the currently available safety information for cemiplimab, and other anti-PD-1/PD-L1 antibodies, the identified risks and minimization measures, and the emerging preliminary activity of cemiplimab in solid malignancies (including CSCC, NSCLC and cervical), the benefit-risk is considered favorable for continued clinical studies in these and other indications.

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.Advanced or metastatic solid tumors that may respond to anti-programmed cell death 1 (PD-1) immunotherapy

2. Measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria
3. Eastern Cooperative Oncology Group (ECOG) performance status of <=1
4. Adequate organ and bone marrow function as defined in the protocol
5. Willing and able to comply with clinic visits and study-related procedures (including required tumor biopsy for Part B
NOTE: Other protocol defined inclusion criteria apply.

Exclusion criteria

1. Currently receiving another cancer treatment in another studyor inadequate time since last therapy, as defined in the protocol
2. Has not yet recovered from acute toxicities from prior therapy; exceptions defined in the protocol
3. Prior treatment with a blocker of the PD-1/Programmed death ligand 1 (PD-L1) pathway
4. Currently receiving or has received chimeric antigen receptor (CAR-T) cell therapy
5. Symptomatic or untreated brain metastases, leptomeningeal disease, or spinal cord compression
6. Known history of or any evidence of interstitial lung disease, active, noninfectious pneumonitis (past 5 years) or active tuberculosis

PLEASE NOTE: ADDITIONAL EXCLUSION CRITERIA APPLY AND ARE OUTLINED IN THE PROTOCOL

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-02-2023

Enrollment:	50
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Libtayo
Generic name:	Cemiplimab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	REGN5054
Generic name:	REGN5054

Ethics review

Approved WMO Date:	08-03-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-11-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	19-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-06-2024
Application type:	Amendment
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
EudraCT	EUCTR2019-001604-38-NL
CCMO	NL79826.042.22