A phase II, open label, multi-center study of 89Zr-DF-Crefmirlimab for CD8 positron emission tomography in patients with locally advanced or metastatic solid tumours

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This study has been transitioned to CTIS with ID 2024-515885-15-00 check the CTIS register for the current data. Main objectives:• To evaluate whole body distribution of 89Zr-Df-crefmirlimab in cancer patients prior to and during treatment with an...

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON56589

Source
ToetsingOnline

Brief title
CD8 PET imaging in metastatic solid tumours

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
locally advanced or metastatic solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: IMI

Intervention

Keyword: 89Zr-DF-Crefmirlimab, PET imaging

Outcome measures

Primary outcome

Evaluation of the biodistribution and PK of 89Zr-Df-crefmirlimab antibody, through measuring standardized uptake value (SUV) on 89Zr-Df-crefmirlimab PET scans in patients with histologically or cytologically documented locally advanced or metastatic solid tumours. Correlation of tumour tracer uptake with tumour and immune cell CD8 expression, as assessed by immunohistochemistry. Changes in tumour volumetry, mpMRI parameters and MRI based texture metrics during immune checkpoint inhibitor treatment will also be measured.

Secondary outcome

• Local and systemic signs and symptoms of infusion reactions, incidence of adverse events per NCI CTCAE v5.0 criteria, changes in laboratory test results, vital signs and 12-lead electrocardiogram (ECG) findings.

• mpMRI parameters such as Ktrans derived from DCE-MRI; f, D derived from IVIM-DWI and DDKI and K derived from DK-MRI with tumour and immune cell CD8 expression as well as T cell infiltration.

• 89Zr-Df-crefmirlimab PET measurements (expressed as standardized uptake values) with radiologic response to treatment, according to (i)RECIST v1.1 criteria.

Study description

Background summary

The rapidly evolving fields of tumour immunology and cancer immunotherapy have resulted in several Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved immune checkpoint inhibitors for different tumour types. These monoclonal antibody-based therapies exert their effect by blocking inhibitory ligand-receptor interactions of immune checkpoints, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) receptor, or its ligand (PD-L1). However, not all patients respond to these drugs. Moreover, immunotherapeutic drugs can elicit severe side effects. Therefore, it would be of major interest to be able to know whether a specific treatment induces an immune response.
The dynamic tumour microenvironment and tumour heterogeneity have raised significant interest in elucidating the status of the microenvironment, but 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 tumours 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 accumulation and localization. Molecular imaging and functional MRI techniques can noninvasively monitor whole body systemic and intratumoural alterations. Assessing changes in abundance and localization of immune cells 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.
For this purpose, ImaginAb has developed 89Zr-Df-crefmirlimab, an 80 kDa minibody (Mb) with a high affinity for the CD8 glycoprotein. The minibody is conjugated with deferoxamine (Df) and radiolabeled with the positron emitting radionuclide Zirconium-89 (89Zr). 89Zr-Df-crefmirlimab was designed to enable whole body PET imaging of CD8+ cells.
Noninvasive serial whole-body monitoring of the tumour immune response to therapy by means of imaging immune cells might provide major insights. By performing 89Zr-Df-crefmirlimab PET scans prior to and during treatment with an anti-PD-1 antibody, nivolumab or cetrelimab (JNJ-63723283), the radioactivity uptake in primary and metastatic tumour lesions and normal organ distribution can be evaluated. 89Zr-Df-crefmirlimab 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 2024-515885-15-00 check the CTIS register for the current data.

Main objectives:
• To evaluate whole body distribution of 89Zr-Df-crefmirlimab in cancer patients prior to and during treatment with an anti-PD-1 antibody.
• To evaluate pharmacokinetics (PK) of 89Zr-Df-crefmirlimab in patients prior to and during treatment with an anti-PD-1 antibody.
• To correlate tumour tracer uptake with immune cell CD8 expression as assessed by immunohistochemistry.
• To evaluate changes in tumour volumetry, mpMRI parameters and MRI based texture metrics during treatment with an anti-PD-1 antibody.

Secondary objectives:
• To evaluate the safety of repeat doses of 89Zr-Df-crefmirlimab.
• To correlate mpMRI parameters such as Ktrans derived from DCE-MRI; f, D derived from IVIM-DWI and DDKI and K derived from DK-MRI with tumour and immune cell CD8 expression as well as T cell infiltration.
• To correlate response to treatment with nivolumab or cetrelimab, according to the RECIST v1.1 and iRECIST criteria with 89Zr-Df-crefmirlimab uptake in tumour lesions.

Study design

This is a multi-center, single-arm trial designed to evaluate the safety and imaging characteristics of 89Zr-Df-crefmirlimab in patients with locally advanced or metastatic solid tumours prior to and during PD-1 antibody therapy.

Intervention

89Zr-Df-crefmirlimab will be administered followed by a PET scan 24 hours later. All patients will undergo a 89Zr-Df-crefmirlimab PET scan at baseline and after 4 weeks of treatment with the PD-1 antibody. All patients participating in this imaging trial will undergo at least one tumour biopsy. The biopsy procedure(s) will be performed after the 89Zr-Df-crefmirlimab PET scan at baseline and/or after the 89Zr-Df-crefmirlimab PET on-treatment. After the first PET scan and tumour biopsy the patients will start treatment with PD-1 antibody nivolumab 360 mg or cetrelimab 900 mg loading dose followed by 600 mg in 3-weekly cycles.

Study burden and risks

For this study, patients are expected to make a maximum of 9 extra visits to the clinic for screening, to receive 89Zr-Df-crefmirlimab infusion, to have 2 PET-scan visits, and the biopsies taken before and/or after starting treatment with PD-1 antibody. In practice, most procedures will be combined with visits to the hospital in the context of clinical care, to minimize the burden. 89Zr-Df-crefmirlimab is a radioactive compound and therefore, will cause radiation burden to the patient. The projected effective dose after receiving

37 MBq of 89Zr-Df-crefmirlimab is about 23.7 mSv. For patients scanned with PET/CT scanners a low dose attenuation correction CT scan, which has an effective dose of 1.5 mSv, will be carried out. Thus, patients undergoing 2 PET/CT scans, will receive an exposure of approximately (2x23.7) + (2x1.5) = 50.4 mSv. The attenuation correction CT will not be acquired for patients having PET/MR making the total effective dose 47.4 mSv for these patients. Besides PET imaging, patients will be asked to provide up to 12 blood samples (60 mL total). Tumour lesions will be biopsied. Based on a literature review, the risk of tumour 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 tumour lesions will be included in the study.
The risk associated with repeat 89Zr-Df-crefmirlimab PET imaging is considered moderate. Patients that exhausted standard therapy and, according to the opinion of the investigator, based on available clinical data, may benefit from anti-PD1 therapy (nivolumab or cetrelimab) by participating in this trial. Although patients that have a standard treatment option of ICI therapy do not directly benefit from this study, results from this study will be valuable for our understanding of the tumour immune response and will guide further prospective research and hopefully treatment decisions. Close oversight of study conduct will be provided through safety review team meetings. Additionally, irAEs will be monitored throughout the study with appropriate guidance provided to investigators for their assessment and management.

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 principal investigator, based on available clinical data, may benefit from anti-PD1 antibody therapy. 3. Disease progression following first-line therapy or any subsequent treatment line or no superior standard line of therapy available. 4. At least 1 lesion that is accessible per investigator*s assessment and eligible for biopsy according to standard clinical care procedures. 5. 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 administered at least 3 months earlier. 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 7. Life expectancy >= 12 weeks. 8. Adequate organ and bone marrow function as defined below: a. Hemoglobin >=9.0 g/dL b. Absolute neutrophil count >=1.0 x 109/L c. Absolute lymphocyte count >=0.75 x 109/L d. Platelet count >=75 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 tumour 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 tumour involvement) iii. Alanine aminotransferase (ALT) <=2.5 x ULN (<=5 x ULN if liver tumour involvement) iv. Alkaline phosphatase (ALP) <=2.5 x ULN (<=5 x ULN if liver or bone tumour involvement) 9. Signed informed consent. 10. Willingness and ability to comply with all protocol required procedures. 11. For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception (i.e., one that results in a low failure rate (< 1% per year) when used consistently and correctly)).

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-Df-crefmirlimab infusion and nivolumab or cetrelimab treatment.
2. 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.
3. Prior ICI treatment, including but not limited to anti-PD1, anti-PD-L1 and anti-CTLA4 therapeutic antibodies.
4. Major surgical procedure other than for diagnosis within 28 days prior to 89Zr-Df-crefmirlimab infusion or anticipation of need for a major surgical procedure during the course of the study.
5. 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.
6. Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis factor agents) within 4 weeks prior to 89Zr-Df-crefmirlimab infusion.
• 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.
7. Prior allogeneic bone marrow transplantation or solid organ transplant.
8. 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 that is 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.
9. Receipt of a live vaccine (including attenuated) within 30 days of planned start of study medication.
10. Evidence of an active infection that requires systemic antibiotics within 2 weeks prior to 89Zr-Df-crefmirlimab infusion.
11. Evidence of an active COVID 19 infection. This infection has to be documented in the case record form. When at least 2 weeks recoverd from COVID 19, this is not an exclusion criterion anymore.
12. 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-Df-crefmirlimab, or that may affect the interpretation of the results or render the patient at high risk from complications.
13. Altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent.
14. Sponsor employee/member of the clinical site study team and/or his or her immediate family
15. Women with a positive serum chorionic gonadotropin HCG pregnancy test at the screening/baseline visit. Breastfeeding women are also excluded.
16. 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.
17. Contraindications for MRI scan
18. Patients who have any splenic disorders, or had splenectomy, that could compromise protocol objectives

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2024
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	89Zr-DF-Crefmirlimab
Generic name:	89Zr-DF-Crefmirlimab
Product type:	Medicine
Brand name:	Cetrelimab
Generic name:	Cetrelimab
Product type:	Medicine
Brand name:	Nivolumab
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-02-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-02-2024

Application type:	First submission
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	CTIS2024-515885-15-00
EudraCT	EUCTR2022-002689-34-NL
CCMO	NL82656.042.23
Other	volgt