Uptake and biodistribution of 89Zirconium-labeled ipilimumab in ipilimumab treated patients with metastatic melanoma

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This study has been transitioned to CTIS with ID 2024-516547-11-00 check the CTIS register for the current data. To assess uptake (visual and quantitative) of 89Zr-ipilimumab in tumor lesions and biodistribution at start of nivolumab/ipilimumab...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Skin neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON53144

Source
ToetsingOnline

Brief title
Tumor uptake of 89Zirconium-ipilumumab

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: CCA- V-ICI stichting beurs

Intervention

Keyword: Immuno-PET, Immunotherapy, Ipilimumab, Melanoma

Outcome measures

Primary outcome

The primary endpoint is:

1. The detection (visual and quantitative) of 89Zr-ipilimumab in tumor lesions

(the short axis diameter of a measurable tumor lesion is >=1 cm. The five

largest lesions will be used for evaluation).

Secondary outcome

The secondary endpoints are:

1. Clinical outcome (response and survival):

- Response after starting therapy with ipilimumab at 12 and 24 weeks and every

12 weeks thereafter

- Overall survival

2. The detection (visual and quantitative) of 89Zr-ipilimumab in normal tissue

after the first injection of nivolumab/ipilimumab:

- visual

- quantitative

- Visual differences between a regular scanner, with limited field of view, and

a long axial field of view PET/CT (total body/Quadra)

3. Side effects:

- Adverse events using Common Terminology Criteria Adverse Events, version 4.0

(CTCAE 4.0)

- Correlation between side effects of ipilimumab and uptake of 89Zr-ipilimumab

in normal tissue

4. Other study parameters:

- CTLA-4+CD4+ expression of PBMCs (before start of ipilimumab and during

treatment)

- Pharmacokinetics of 89Zr-ipilimumab

Study description

Background summary

Ipilimumab, a monoclonal antibody targeting CTLA-4, is approved for the treatment of metastatic melanoma and significantly increases median overall survival. However, use of this drug is associated with immune related adverse events (IRAEs) like colitis, hepatitis, dermatitis, alveolitis and hypophysitis in 10-40% of the patients. In general IRAEs are manageable by cessation of ipilimumab in combination with treatment with corticosteroids or TNF-alpha blockade but they can be severe or even life-threatening. In addition, treatment with ipilimumab is expensive. Because of the high costs and the potential serious toxicity of ipilimumab, it is of great importance to identify biomarkers that correlate with clinical activity and can be used to select patients that will benefit from CTLA-4 blockade therapy.
We hypothesize that differences in response to treatment with ipilimumab are due to variability in the pharmacodynamics and -kinetics of the antibody. We hypothesize that patients who do not respond to treatment with ipilimumab have lower drug levels in tumor tissues as compared to patients with a good response to therapy. In addition, we hypothesize that IRAEs are associated with high drug levels in the affected tissue.

Study objective

This study has been transitioned to CTIS with ID 2024-516547-11-00 check the CTIS register for the current data.

To assess uptake (visual and quantitative) of 89Zr-ipilimumab in tumor lesions and biodistribution at start of nivolumab/ipilimumab therapy

Secondary
1. To determine the correlation between tumor targeting of ipilimumab and

response to therapy.
2. To assess uptake (visual and quantitative expressed as SUVmean and SUVpeak) of 89Zr-ipilimumab in normal tissues, with special attention to gut, lung, liver and pituitary, before start of nivolumab/ipilimumab therapy, in nivolumab/ipilimumab treated patients and to quantitatively analyse the uptake.
3. To evaluate differences in visual uptake on PET/CT between a regular scanner, with limited field of view, and a long axial field of view PET/CT (total body/Quadra)
4. To determine the correlation between organ (e.g. GI-tract, skin, liver) targeting and toxicity.
5. To determine whether tumor related pre-treatment CTLA-4 expression in CD4+ T cells in blood of metastatic melanoma patients predicts improved survival after ipilimumab treatment.
6. To determine the correlation between pre-treatment CTLA-4 expression in CD4+ T cells in blood of metastatic melanoma and uptake of 89Zr-ipilimumab in tissues.
7. To determine the correlation between inflammatory infiltrate in tumor tissue and uptake of 89Zr-ipilimumab.

Study design

Metastatic melanoma patients, who are treated with nivolumab (1 mg/kg) and ipilimumab (3 mg/kg), will be infused with 89Zr-labeled ipilimumab one week before injection of the first nivolumab/ipilimumab doses. Peripheral blood mononuclear cells (PBMCs) will be collected for immunomonitoring. Metastases as (non)-target lesions will be defined using diagnostic CT-scan. Uptake of ipilimumab in metastases will be assessed using regions of interests (ROIs) on 89Zr-PET-scans. In part 1, an immuno-PET scan will be obtained at 72, 96 and 144 hours postinjection. In part 2, one or two immuno-PET scans will be obtained on the same day at the optimal timepoint. All tissue concentrations of 89Zr-ipilimumab, measured by immuno-PET scan, will be related to blood concentration. Side effects will be monitored. After 12 weeks CT-scans will be made to assess response using RECIST 1.1 and iRECIST criteria. In addition, patients will be followed for toxicity and survival. CTLA-4+CD4+ expression of PBMCs and 89Zr-labeled ipilimumab uptake by tumors and organs will be correlated with responses, toxicity and survival.
An optional tumor biopsy will be performed pre-therapy and within 48 hours after the last immuno-PET/CT scan. Immunohistochemical analysis of the tumor lesions will be performed. The T-lymphocyte infiltration in tumors will be correlated to uptake of 89Zr-ipilimumab at immuno-PET scan.

Study burden and risks

Upon enrolment in this study, blood samples will be obtained for immunomonitoring. During therapy, follow-up will include standard laboratory analysis, immuno-PET-CT and CT-scans on regular visits to the outpatient

clinic. The radiation exposure is substantial, but acceptable in the study population. Patients do not require shielding after injection of 89Zr-ipilimumab.

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

- Metastasized melanoma or unresectable malignant melanoma
- Scheduled for treatment with nivolumab and ipilimumab
- Age > 18 years
- At least one measurable lesion
- WHO performance status 0 or 1

Exclusion criteria

- Previous exposure to ipilimumab
- Pregnant or breast feeding women
- Concurrent anticancer chemotherapy, immunotherapy or investigational drug during the study or within 4 weeks after starting study drug
- Radiotherapy on target lesions during the study or within 4 weeks after starting study drug

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-05-2017
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	89-Zirconium ipilimumab
Generic name:	ipilimumab-zirconium-89

Ethics review

Approved WMO

Date:	18-08-2015
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-12-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2023
Application type:	Amendment

Review commission: METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 27886
Source: NTR
Title:

In other registers

Register	ID
EU-CTR	CTIS2024-516547-11-00
EudraCT	EUCTR2012-003616-31-NL
CCMO	NL54099.029.15