Opname en biodistributie van 89Zirconium gelabeld ipilimumab in melanoompatiënten die behandeld worden met ipilimumab

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON27886

Source
NTR

Brief title
Zirconipi

Health condition

Immuno_PET
Melanoma (melanoom)
Ipilimumab
Immunotherapy (imuumtherapie)
89Zirconium

Sponsors and support

Primary sponsor: VU University Medical Center
Source(s) of monetary or material Support: Bristol-Myer Aquibb

Intervention

Outcome measures

Primary outcome

The detection of 89Zr-ipilimumab in tumor lesions (after first injection of ipilimumab) and in week 4 (after second injection of ipilimumab). Tumor lesions will be defined using a diagnostic CT-scan or MRI. The short axis diameter of a measurable tumor lesion is ¡Ý1 cm. The five largest lesions will be used for evaluation:

- Visual: present/absent; present being as focally enhanced uptake on the immuno-PET scan with optimal contrast (72-144 hours post injection).

- Quantitative: measured in mean and peak Standardized Uptake Value (SUVmean and SUVpeak) of the tumor lesions with the highest antibody uptake, using automatic delineated tumor volumes of interest (VOI's). Targeting is defined as SUVtumor/SUVblood >1.

Secondary outcome

1. Clinical outcome:

- Response after starting therapy with ipilimumab at 12 and 24 weeks and every 12 weeks thereafter. For melanoma patients response will be assessed by CT-scan using the mWHO and irRC.

- Overall survival.

2. The detection of 89Zr-ipilimumab in normal tissue in week 1 (after first injection if ipilimumab) and in week 4 (after second injection of ipilimumab):

- visual: Description of the biodistribution.

- quantitative: The % uptake (of total injected) 89Zr-ipilimumab in normal tissue, measured in VOI¡¯s.

- comparison between uptake (SUVmean and SUVpeak) of 89Zr-ipilimumab after the first injection of ipilimumab and after the second injection 3 weeks later.

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 at 6 time points (whole blood sample): pre-treatment, at t = 60 minutes and t = 72 hours after first and after second injection of ipilimumab.

- Correlation between CTLA-4+CD4+ expression of PBMCs and uptake of 89Zr-ipilimumab in tissues.

- Pharmacokinetics of 89Zr-ipilimumab. The concentration of ipilimumab in blood samples will be measured at t = 5, 30, 60, 120 minutes and 72, 144 hours after injection of 89Zr-ipilimumab in the first three patients.

- The SUV in tumor lesions will be compared to the SUV in blood. Specific uptake of ipilimumab in tumor lesions is defined as SUVtumor/SUVblood >1.

Study description

Background summary

Rationale:

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.

To visualize molecular interactions we use a novel technique in which positron emission tomography (PET) is combined with labeled monoclonal antibodies. Because ipilimumab induces activation of T-lymphocytes we hypothesize that uptake of 89Zr-ipilimumab in tumor

lesions and normal tissue is different (i.e. higher) after the second administration of ipilimumab (3 weeks after first injection). Therefore immuno-PET scans will be performed after the first and after the second injection of ipilimumab.

Objective:

Part one: The primary objective is:

1. To assess uptake (visual and quantitative) of 89Zr-ipilimumab in tumor lesions and biodistribution at two timepoints (at start of ipilimumab therapy and after the second injection 3 weeks later).

The secondary objectives are:

1. To determine the correlation between tumor targeting of ipilimumab and response to therapy.

2. To assess uptake (visual and quantitative) of 89Zr-ipilimumab in normal tissues.

3. To determine de correlation between organ targeting and toxicity

Study objective

We hypothesize that differences in response to ipilimumab treatment are due to variability in the pharmacokinetics and ¡¡ìCdynamics of the antibody. Thus, we hypothesize that patients who do not respond to CTLA-4 blockade therapy, have insufficient drug levels in tumor tissue. Because ipilimumab induces upregulation of T-lymphocytes we hypothesize that uptake of 89Zr-ipilimumab in tumor lesions and normal tissue is different (i.e. higher) after the second administration of ipilimumab (3 weeks after first injection). Therefore immuno-PET scans will be performed after the first and after the second injection of ipilimumab.

Study design

- The detection of 89Zr-ipilimumab in tumor lesions (after first injection of ipilimumab) and in week 4 (after second injection of ipilimumab).

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

- The detection of 89Zr-ipilimumab in normal tissue in week 1 (after first injection if ipilimumab) and in week 4 (after second injection of ipilimumab)

Intervention

Metastatic melanoma patients, who are treated with ipilimumab (3 mg/kg), will be infused with 89Zr-labeled ipilimumab within 2 hours after injection of the first and second standard 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. An immuno-PET scan will be obtained at 1, 72 or 144 hours postinjection (optimal timepoint to be determined using the results of extra immuno-PET scans in the first 3 metastatic melanoma patients). All tissue concentrations of ipilimumab, measured by immuno-PET scan, will be related to blood concentration. This procedure will be repeated 3 weeks later when the patient receives the second injection of ipilimumab. Side effects will be monitored. After 12 weeks CT-scans will be made to assess response using the mWHO (modified WHO) and irRC (immune related Response Criteria) 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 after the second injection of ipilimumab. 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.

Contacts

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Eligibility criteria

Inclusion criteria

- Advanced/metastatic melanoma.

- Scheduled for treatment with ipilimumab.

- Age ¡Ý 18 years.

- Histological or cytological documentation of cancer is required.

- WHO Performance Status of 0 or 1.

- At least 1 measurable lesion.

- Signed informed consent must be obtained prior to any study procedures.

- Patients must be able to adhere to the study appointments and other protocol requirements.

Exclusion criteria

- Previous exposure to ipilimumab.

- Pregnant or breast-feeding subjects.

- Concurrent anticancer chemotherapy, immunotherapy or investigational drug therapy during the study or within 4 weeks after starting the study drug.

- Radiotherapy of target lesions during study or within 4 weeks after starting the study drug. Palliative radiotherapy will be allowed.

- Major surgery within 28 days of start of study drug.

- Substance abuse, medical, psychological or social conditions that may interfere with the subject¡¯s participation in the study or evaluation of the study results.

- Any condition that is unstable or could jeopardize the safety of the subject and their compliance in the study.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other

Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2017
Enrollment:	29
Type:	Anticipated

Ethics review

Positive opinion

Date:	27-01-2017
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 53144
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL6104
NTR-old	NTR6445
CCMO	NL54099.029.15
OMON	NL-OMON53144

Study results