A phase 1-2 immunoPET imaging study with ZED88082A in patients before and during treatment with 1) MPDL3280A or 2) PD-1 antibody plus or minus ipilimumab

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Primary objectives: To evaluate safety of ZED88082A in combination with CED88004S. To determine appropriate ZED88082A/CED88004S dosing and PET imaging time-points. To evaluate pharmacokinetics (PK) of ZED88082A/CED88004S in patients before and...

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

Summary

ID

NL-OMON49728

Source
ToetsingOnline

Brief title
CD8 PET imaging study before and during immunotherapy

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: Genentech Inc.

Intervention

Keyword: Cancer, CD8, Checkpoint inhibitor, Positron emission tomography

Outcome measures

Primary outcome

Assessment of safety of ZED88082A/CED88004S.

Appropriate ZED88082A/CED88004S dosing and appropriate PET imaging time-points.

Description of ZED88082A/CED88004S PK by measuring standardized uptake value (SUV) on the ZED88082A/CED88004S-PET scans 0, 2, 4 and/or 7 days after ZED88082A/CED88004S injection before and during immune checkpoint inhibitor treatment.

Assessment of immunogenicity by ADA formation.

Secondary outcome

i. Heterogeneity of ZED88082A tumor uptake, evaluated by measuring standardized uptake value (SUV) on the ZED88082A/CED88004S-PET scans 0, 2, 4 and/or 7 days after ZED88082A/CED88004S injection.

ii. Safety assessment of side effects as defined according to NCI CTCAE v4.03 considered possibly related to ICI will be correlated to ZED88082A normal organ uptake, evaluated by measuring standardized uptake value (SUV) on the ZED88082A/CED88004S-PET scans performed at baseline and during ICI treatment 0,

2, 4 and/or 7 days after ZED88082A/CED88004S injection. For patients in part A and B1, data on AEs possibly related to ICI will be recorded within the MPDL3280A treatment trial. For melanoma patients in part B2, AEs possibly related to ICI will be separately recorded in the electronical case record form of this imaging trial. Data will be derived from the electronical medical dossier in a prospectively observational way, assessed by investigators or treating physicians* initiative and graded according to CTCAEv4.03.

iii. Immune cell CD8 expression and tumor and immune cell PD-L1 expression analyses, as well as evaluation of other markers of lymphocytic infiltration in a tissue biopsy will be correlated to ZED88082A tumor uptake, evaluated by measuring standardized uptake value (SUV) on the ZED88082A/CED88004S-PET scan 0, 2, 4 and/or 7 days after ZED88082A/CED88004S injection.

iv. ZED88082A normal organ uptake, evaluated by measuring standardized uptake value (SUV) on the ZED88082A/CED88004S-PET scans 0, 2, 4 and/or 7 days after ZED88082A/CED88004S injection will be correlated to ZED88082A/CED88004S blood kinetics. Aliquots of whole blood and serum samples will be measured for 89Zr-activity in an isotope well counter and corrected for decay to assess ZED88082A concentrations. Whole blood and serum activity will be expressed as standardized uptake value (SUV). Serum samples will also be collected regularly during the study to measure concentrations of ZED88082A/CED88004S. PK parameters will be derived from the serum concentrations. These will include at least:

• Maximum serum concentration (Cmax)

• Time to reach maximum serum concentration (tmax)

• Area under the concentration-time curve (AUC)

• Serum concentration at the time of the ZED88082A/CED88004S-PET scans (CPET)

v. Assessment of dosimetry, by calculations of radioactivity in Bq or mSv of ZED88082A concentration in tumor target tissue, blood and other organs of interest with regards to injected dose (ID), derived from measurements of standardized uptake value (SUV) on ZED88082A/CED88004S-PET and direct analysis of blood 89Zr-activity.

Study description

Background summary

The rapidly evolving fields of tumor immunology and cancer immunotherapy have recently resulted in several FDA and EMA approved immune checkpoint inhibitors for several tumor types. However, not all patients respond to these drugs, so it may be advantageous to combine current immune checkpoint inhibitors with other 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 tumor microenvironment and tumor heterogeneity have therefore raised significant interest in objectifying 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 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.
Currently, CD8+ cytotoxic T-cells are considered to play a critical effector

role in anti-tumor immunity. Analysis of tumor-infiltrating lymphocytes (TIL) has demonstrated the importance of tumor immune microenvironment and indicated that the presence of cytotoxic CD8+ T cells can predict overall survival in several tumor types. Noninvasive serial whole body monitoring of the tumor immune response to therapy by means of imaging CD8+ cytotoxic T-cells might thus provide major insights. RED88822 is an one-armed anti-CD8 antibody, which is called CED88004S when DFO-conjugated and ZED88082A when it is 89Zr-labeled-DFO-conjugated, that was designed to enable whole body PET imaging of CD8+ T-cells. By performing ZED88082A/CED88004S-PET scans prior to treatment with immune checkpoint inhibitors, the radioactivity uptake in primary and metastatic tumor lesions and normal organ distribution can be evaluated and ZED88082A/CED88004S-PET serve as a potential complementary tool for patient and treatment selection in the future. Repeat ZED88082A/CED88004S-PET imaging during ICI treatment will provide information about systemic and intratumoral alterations in response to immunotherapy.

Study objective

Primary objectives: To evaluate safety of ZED88082A in combination with CED88004S. To determine appropriate ZED88082A/CED88004S dosing and PET imaging time-points. To evaluate pharmacokinetics (PK) of ZED88082A/CED88004S in patients before and during ICI treatment. To evaluate immunogenicity/anti-drug antibodies (ADA) of ZED88082A/CED88004S in patients before and during ICI treatment.

Secondary objectives: i) To assess heterogeneity of ZED88082A/CED88004S tumor uptake. ii) To correlate normal organ ZED88082A/CED88004S uptake to (serious) adverse events (possibly) related to ICI treatment. iii) To correlate tumor ZED88082A/CED88004S uptake with tumor and immune cell CD8-expression as assessed by a fresh contemporaneous tumor biopsy. iv) To correlate ZED88082A/CED88004S normal tissue kinetics with ZED88082A/CED88004S blood kinetics. v) To assess dosimetry.

Study design

This is a phase-1 first in human, open-label, single-center, single-arm trial designed to evaluate the PK of ZED88082A/CED88004S-PET in patients prior to and during treatment with checkpoint inhibitors. The study is divided in two parts:

Part A contains initial safety assessment, dose finding and PET-scan scedule finding of ZED88082A/CED88004S-PET.
Part B contains evaluation of pharmacokinetics of the tracer ZED88082A/CED88004S in patients before and during checkpoint inhibitor therapie.

Intervention

In part A of this imaging trial, a dose finding study will be performed to establish safety, to assess the appropriate protein dose for PET-scanning (consisting of a fixed dose of ZED88082A and if required with limited amount of *cold* CED88004S for proper imaging performance), and to assess the appropriate PET scanning interval. Approximately 4 cohorts of about 2-3 patients each will undergo ZED88082A/CED88004S-PET imaging at 4 time points (day of ZED88082A/CED88004S injection, day 2, day 4 and day 7 after injection). Afterwards, eligible (non melanoma) patients will be allowed to enter the MPDL3280A treatment trial (MPDL3280A-treatment-IST-UMCG) provided they continue to meet the eligibility criteria to receive this drug. Patients with melanoma may receive standard treatment with PD-1 antibody plus or minus ipilimumab. The purpose of part B of the study is to analyze the PK of ZED88082A/CED88004S before and during treatment with ICIs in patients, with appropriate ZED88082A/CED88004S protein dosing and at appropriate PET scanning time point as determined in part A.

In part B, approximately 30 patients will be enrolled to undergo ZED88082A/CED88004S-PET imaging twice; one at baseline before ICI treatment, and one during treatment with ICIs at early cycle 2, to minimize morphological changes in tumors responding to the therapy (with flexibility to adjust the timing of on-treatment scans based on an ongoing review of the data). Patients from part B1 will be treated with MPDL3280A in the MPDL3280A treatment trial (MPDL3280A-treatment-IST-UMCG). In part B2, approximately 10 melanoma patients eligible for standard of care PD-1 antibody therapy plus or minus ipilimumab will be enrolled. All patients participating in the imaging trial part A and B will undergo at least one tumor biopsy. The biopsy procedure will be performed at baseline after the last ZED88082A/CED88004S-PET scan, but before start of ICI treatment. In addition, in part B, on-treatment tumor biopsies will be performed if possible at the end of the second ZED88082A/CED88004S-PET scan period.

Study burden and risks

For this imaging study, patients have to make a maximum of 10 extra visits to the clinic for screening, to receive ZED88082A/CED88004S injection, to have up to 4 PET-scan visits, and the biopsies taken before and/or after starting treatment with ICI. The radiation burden following administration of 37 MBq of ZED88082A/CED88004S is about 18 mSv, in addition to 1.5 mSv per low-dose attenuation correction CT-scan. Thus, patients in part A undergoing 4 PET-scans, will receive an exposure of about 24 mSv. Patients in part B will receive two 37 MBq doses of ZED88082A/CED88004S and undergo up to 4 PET-scans. The radiation exposure will be approximately 42 mSv. Besides PET imaging, patients will be asked to provide in total 15 blood samples in part A (110 mL) and 11 samples in part B (98 mL). A tumor 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. The risk associated with the ZED88082A/CED88004S is considered acceptable based on extensive preclinical

testing, which showed no signs of T cell activation or inhibition. However, the first three patients in part A will be hospitalized the first night after ZED88082A/CED88004S injection in order to minimize the risk that significant side effects will occur outside of the hospital (e.g. in case of cytokine production). If the second cohort in part A concerns an escalated dose of ZED88082A/CED88004S, likewise the first three patients in this cohort will also be hospitalized for observation. Although patients 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. After participation within the imaging trial, eligible patients will be allowed to enter the MPDL3280A treatment trial (MPDL3280A-treatment-IST-UMCG), provided they continue to meet the eligibility criteria to receive MPDL3280A.

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. Subjects with histologically confirmed locally advanced or metastatic cancer for the following tumor types
* Cancer types other than melanoma; subjects meeting the eligibility criteria as formulated in the MPDL3280A treatment study protocol (MPDL3280A-treatment-IST-UMCG) are eligible for part A or part B1.
* Melanoma; subjects eligible to receive standard of care anti-PD1 therapy plus or minus ipilimumab, are eligible for part B2.
2. Tumor lesion(s) of which a histological biopsy can safely be obtained according to standard clinical care procedures.
3. Measurable disease, as defined by standard RECIST v1.1. Previously irradiated lesions should not be counted as target lesions.
4. Signed informed consent.
5. Age >=18 at the time of signing informed consent.
6. Life expectancy >=12 weeks.
7. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
8. Ability to comply with the protocol.
9. 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. Potential subjects with cancer other than melanoma will be excluded from participation in this study if they meet exclusion criteria formulated in the MPDL3280A treatment study protocol (MPDL3280A-treatment-IST-UMCG).
2. Signs or symptoms of infection within 2 weeks prior to ZED88082A/CED88004S injection.
3. Prior immune checkpoint inhibitor treatment, including but not limited to anti-PD1 and anti-PD-L1 therapeutic antibodies.
4. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
5. 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 ZED88082A/CED88004S, or that may affect the interpretation of the results or render the patient at high risk from complications.
6. Pregnant or lactating women.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	14-02-2019
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	89Zr-CED88084S
Generic name:	ZED88082A
Product type:	Medicine
Brand name:	CED88084S
Generic name:	-

Ethics review

Approved WMO

Date:	02-10-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	22-01-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	05-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-12-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-12-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-06-2020
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	EUCTR2017-004824-31-NL
CCMO	NL66782.042.18
Other	volgt