A phase 2 immunoPET imaging study with ZED88082A/CED88004S in patients with Large B-cell lymphoma before and after CD19-directed CAR T-cell therapy

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Primary objectives:The objective is to study the distribution of CD8+ T-cells before and after CAR T-cell therapy in the patient by ZED88082A/CED88004S-PET imaging. We will correlate the pretreatment CD8+ T-cell distribution and CD8+ CAR T-cell...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON51886

Source
ToetsingOnline

Brief title
CD8 PET imaging study before and after CAR T-cell therapy

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Large B-cell lymphoma, lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Genentech Inc

Intervention

Keyword: CAR T, CD8, imaging, Large B-cell lymphoma

Outcome measures

Primary outcome

Primary endpoints:

- To determine the whole-body biodistribution of the ZED88082A tracer in normal tissues and tumor lesions before and after CAR T-cell therapy.

Secondary outcome

Secondary endpoints:

- Assess safety and dosimetry ZED88082A/CED88004S uptake in the setting of CD19-directed CAR T-cell therapy

- Correlative expression analysis between ZED88082A tracer standard uptake volume (SUV) parameters in the tumor, CD8 expression in tumor biopsy, and response to CAR T-cell therapy.

- To perform correlative expression analysis between SUV parameters of ZED88082A tracer in the tumor, CD8 expression in tumor biopsy, and SUV parameters in the tumor and whole-body and CAR T-cell persistence, peak level and CAR T-cell phenotype as measured in the peripheral blood.

- Correlative expression analysis between ZED88082A tracer SUV parameters in the tumor, and grade 1-5 adverse events to CAR T-cell therapy, including cytokine release syndrome and neurotoxicity.

- Correlative expression analysis between ZED88082A tracer uptake in irradiated versus non-irradiated lymphoma lesions in patients who require radiotherapy as

bridging strategy prior to CAR T-cell infusion.

Study description

Background summary

Anti-CD19 Chimeric Antigen Receptor (CAR)-T cell therapy has changed the treatment landscape of patients with (Diffuse) Large B-cell Lymphoma (LBCL) and other types of Non-Hodgkin Lymphoma (NHL). Patients with LBCL who do not respond to first-line therapy, have a relapse within 6 months (primary refractory), or after second-line therapy, including high-dose chemotherapy and autologous stem cell rescue, have a poor prognosis and only 6% of these patients have a long-term survival. The recent results of 3 pivotal studies with 3 different anti-CD19 CAR T-cell products administered to patients with relapsed/refractory (R/R) LBCL resulted in high response rates and long-term remissions in almost half of the patients. Unfortunately, some patients do not respond to CAR T-cell. Moreover, CAR T-cell therapy can elicit severe side effects. Therefore, it would be of major interest to know whether CAR T-cell therapy induces an immune response in a specific patient. The dynamic lymphoma microenvironment and tumor heterogeneity have therefore raised significant interest in objectifying the status of the microenvironment in the setting of CAR T-cell therapy, but the ability to monitor changes in the immune status of lymphoma and CAR T-cell therapy is very scarce. 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 and side effects. Preinfusion of CAR product T-cell subsets with a definable polyfunctional profile has been associated with a favorable outcome of CAR T-cell therapy in NHL. In addition, biopsies taken from lymphoma lesions demonstrated that the best responses after CD19-directed CAR T-cell therapy were noted in patients where the CAR T-cells were able to infiltrate the tumor and in patients who did have a higher expansion of CD3+/CD8+ CAR T cells in peripheral blood. It is, therefore, of high interest to determine the distribution of CD8+ T-cells within the tumor and elsewhere in the body, before and after CAR T-cell therapy. Noninvasive serial whole-body monitoring of the lymphoma immune response to CAR T-cell therapy using imaging CD8+ cytotoxic T-cells might thus provide major insights. RED88822 is a 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 CAR T-cells, the radioactivity uptake in lymphoma 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 after CAR T-cell treatment will provide information about systemic and intratumoral alterations in response to CAR T-cell therapy.

Study objective

Primary objectives:
The objective is to study the distribution of CD8+ T-cells before and after CAR T-cell therapy in the patient by ZED88082A/CED88004S-PET imaging. We will correlate the pretreatment CD8+ T-cell distribution and CD8+ CAR T-cell tumor invasion, as measured by the intensity of ZED88082A/CED88004S-PET imaging positive lesions.
Secondary objectives:
a) Assess safety and dosimetry ZED88082A/CED88004S uptake in the setting of CD19-directed CAR T-cell therapy
b) To assess heterogeneity of ZED88082A/CED88004S tumor uptake
c) To correlate normal organ ZED88082A/CED88004S uptake to (serious) adverse events (possibly) related to CAR T-cell treatment
d) To correlate tumor ZED88082A/CED88004S uptake with tumor and immune cell CD8-expression as assessed by a fresh contemporaneous tumor biopsy
e) To correlate ZED88082A/CED88004S uptake in irradiated versus non-irradiated lymphoma lesions in patients who require bridging with radiotherapy prior to CAR T-cell infusion.

Study design

This is a single-center, single-arm trial designed to evaluate the distribution of endogenous CD8+ T-cells in patients with LBCL prior to CAR T-cell therapy and after CD19-directed CAR T-cell therapy.

Intervention

In this imaging trial, the purpose is to explore the feasibility of anti-CD8 PET imaging to gain insights into the biodistribution of CD8+ T-cell before and after CD19-directed CAR T-cell therapy in R/R LBCL. Patients with R/R LBCL after 2 prior lines of therapy will receive standard of care CD19-directed CAR T-cell therapy according to the eligibility criteria as formed by the Dutch Immune Effector Cell tumor board.

Study burden and risks

For this imaging study, patients have to make a maximum of 4 extra visits to the clinic for screening, to receive ZED88082A/CED88004S injection, to have 1 PET-scan visit (1 PET will be performed during hospitalization after the CAR T-cell infusion), and the biopsies taken before and/or after starting treatment with CAR T-cell therapy.
In practice, most procedures will be combined with visits to the hospital in the context of clinical care, to minimize the burden.
The first intravenous tracer injection ZED88082A/CED88004S is on day -27 (+/- 2 days) of the CAR T-cell infusion (or on day -15 (+/- 2 days) of the CAR T-cell in case radiation therapy is planned as bridging to CAR T-cell infusion). All patients will be observed for at least 30 minutes after ZED88082A/CED88002S injection to monitor for possible acute infusion related adverse events. The subsequent ZED88082A/CED88004S-PET imaging scan is 48 hrs later followed by a biopsy. The second intravenous tracer injection ZED88082A/CED88004S is on day of CAR T-cell infusion. The second ZED88082A/CED88004S-PET imaging scan and biopsy is then scheduled on day +2. On day +4 another ZED88082A/CED88004S-PET imaging scan will be done, and in case there are measurable lesions at day +4 aonother one at day +7. During the second tracer injection and ZED88082A/CED88004S-PET imaging scans the patients are hospitalized as part of the CAR T-cell observation.
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 will receive two 37 MBq doses of ZED88082A/CED88004S and undergo to 3 à 4 low-dose CT-scans. The total radiation exposure will be approximately (2x18)+(4x1.5)=42 mSv. Besides PET imaging, patients will be asked to provide 8 blood samples (160 mL). The easiest and safest accessible tumor lesion will be biopsied at the same time points as the anti-CD8 PET scans. 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, and clinical safety data from the ongoing CD8 PET imaging study, where no ZED88082A/CED88004S infusion related adverse events have been reported to date (see IMPD). 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 proceed with CD19-directed CAR T-cell treatment, provided they continue to meet the eligibility criteria to receive CD19-directed CAR T-cells.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL

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 LBCL and subtypes according to the WHO 2016 criteria
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 Lugano criteria.
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. Signs or symptoms of infection within 2 weeks prior to ZED88082A/CED88004S injection.
2. Prior immune checkpoint inhibitor bi-specific antibody, including but not limited to anti-PD1 and anti- PD-L1 therapeutic antibodies.
3. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
4. 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.
5. Pregnant or lactating women.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-06-2021
Enrollment:	23
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:	29-03-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-04-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-02-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-12-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2023
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	EUCTR2020-004749-35-NL
CCMO	NL75607.042.20
Other	NL9034