Programmed death ligand 1 (PD-L1) PET imaging in patients with (Diffuse) Large B-cell lymphoma who are treated with CD19-directed CAR T-cell therapy: a pilot study.

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This study has been transitioned to CTIS with ID 2024-518422-32-01 check the CTIS register for the current data. Primary objectives: The first primary objective is to study the expression of PD-L1 in normal tissue and lymphoma lesions before CAR T-...

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

Summary

ID

NL-OMON56151

Source
ToetsingOnline

Brief title
PD-L1 PET-imaging during 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: PUSH call 2020; Cancer research fund UMCG

Intervention

Keyword: (Diffuse) Large B-cell lymphoma, CAR T-cell therapy, PD-L1, PET-imaging

Outcome measures

Primary outcome

Primary parameters

- to study the expression of PD-L1 in normal tissue and lymphoma lesions before CD19-directed CAR T-cell therapy in LBCL patients by 89Zr-atezolizumab PET/CT imaging and to correlate pretreatment 89Zr-atezolizumab uptake to response to CD19-directed CAR T-cell therapy and thereby identify clinically relevant PD-L1 expression. Heterogeneity of 89Zr-atezolizumab uptake will be evaluated by measuring standardized uptake value (SUV) on the 89Zr-atezolizumab PET/CT scan.

- To study whether the amount of 89Zr-atezolizumab uptake, measured by the intensity of 89Zr-atezolizumab PET/CT imaging (SUV), can be used to differentiate between lymphoma activity and treatment-related inflammatory reaction (histiocytic/sarcoid-like reaction) in patients with an end-of-treatment 18F-FDG-positive PET/CT signal.

Secondary outcome

Secondary parameters:

- To correlate the pretreatment 89Zr-atezolizumab distribution to CAR T-cell peak expansion and persistence.

- To correlate the pretreatment 89Zr-atezolizumab uptake to CAR T-cell therapy related grade 1-5 adverse events (cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS)).
- To correlate tumor 89Zr-atezolizumab uptake with tumor and tumor infiltrating cell PD-L1 expression as assessed by immunohistochemistry on a fresh contemporaneous tumor biopsy.
- To compare the 89Zr-atezolizumab distribution in irradiated versus non-irradiated lymphoma lesions in patients who require radiotherapy as a bridging strategy prior to CAR T-cell infusion. If possible, these results will be compared to tumor and immune cell PD-L1 expression as assessed by immunohistochemistry on a fresh contemporaneous tumor biopsy of an irradiated lymphoma lesion.
- To determine the incidence of a treatment-related inflammatory signal on 18F-FDG-PET/CT scan (histiocytic/sarcoid-like reaction) after CAR T-cell therapy.

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 therapy and their prognosis is extremely poor.
Possible mechanisms of non-responsiveness include loss of CD19 expression on the tumor cells, upregulation of immune checkpoint proteins such as programmed death-ligand 1 (PD-L1, CD274) or impaired T-cell function due to an immunosuppressive microenvironment. However the role each of these mechanisms play in the case of a diminished or non-response to CAR T-cell therapy is not yet defined.
Engagement of the PD-1/PD-L1 pathway is known to result in the reduction of T-cell activation, proliferation, and survival. Moreover, PD-L1 expression can be altered by radiotherapy, used as bridging therapy in CAR T-cell therapy. Hypothetically, patients with high or upregulated PD-L1 expression are more likely to be non-responders to CAR T-cell therapy and these patients might benefit from additional PD-1/PDL-1 blocking therapy. However, the exact role of PD-L1 expression in CAR T-cell therapy is not yet defined.
Currently, predicting tumor PD-L1 expression is not optimal, because it requires invasive sequential biopsies that are often subject to the errors and limitations of invasive tissue collection. Recently, positron-emission tomography computed topography (PET/CT) imaging with 89Zr-atezolizumab (formerly known as 89Zr-MPDL3280A), a PET-labeled antibody against PD-L1, was found to correlate better with response to immune checkpoint inhibition than immunohistochemistry- or RNA-sequencing-based predictive biomarkers in different solid tumors. By performing a 89Zr-atezolizumab-PET/CT scan prior to CD19-directed CAR T-cell therapy PD-L1 expression could be defined in a non-invasive manner.
Additionally, repeated 89Zr-atezolizumab-PET/CT scan in the case of a suspected relapse or non-response might distinguish between lymphoma activity and a treatment-related inflammatory reaction without the need to take invasive biopsies. Fluor-18-deoxyglucose (18F-FDG)-PET/CT scans are currently used for the diagnosis, staging, and evaluation of response in patients with NHL. However, response assessment with 18F-FDG-PET/CT may regularly be false-positive as a result of pseudo-progression or local immune activation (histiocytic or sarcoid-like reactions). Most often these reactions are mediated by macrophages/histiocytes which are known to express PD-L1 at high levels on their cell surface compared to lower levels on malignant B-cells. Therefore, a 89Zr-atezolizumab could be used to differentiate between a relapse/non-response or a treatment-related inflammatory reaction.

Study objective

This study has been transitioned to CTIS with ID 2024-518422-32-01 check the CTIS register for the current data.

Primary objectives:
The first primary objective is to study the expression of PD-L1 in normal tissue and lymphoma lesions before CAR T-cell therapy in LBCL patients by 89Zr-atezolizumab PET/CT imaging and to correlate the pretreatment 89Zr-atezolizumab distribution to the response to CD19-directed CAR T-cell

therapy thereby identify clinically relevant PD-L1 expression.
The second primary objective is to study whether the amount of 89Zr-atezolizumab uptake, measured by the intensity of 89Zr-atezolizumab PET/CT imaging (SUV), can be used to differentiate between lymphoma activity and a treatment-related inflammatory reaction (histiocytic/sarcoid-like reaction) in patients with an end-of-treatment 18F-FDG-positive PET/CT signal.

Secondary objectives:
a) To correlate the pretreatment 89Zr-atezolizumab distribution to CAR T-cell peak expansion and persistence.
b) To correlate the pretreatment 89Zr-atezolizumab uptake to CAR T-cell therapy related grade 1-5 adverse events (cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity (ICANS)).
c) To correlate tumor 89Zr-atezolizumab uptake with tumor and tumor infiltrating cell PD-L1-expression as assessed by immunohistochemistry on a fresh contemporaneous tumor biopsy.
d) To compare the 89Zr-atezolizumab distribution in irradiated versus non-irradiated lymphoma lesions in patients who require radiotherapy as a bridging strategy prior to CAR T-cell infusion. If possible, these results will be compared to tumor and tumor infiltrating cell PD-L1 expression as assessed by immunohistochemistry on a fresh contemporaneous tumor biopsy of an irradiated lymphoma lesion.
e) To determine the incidence of a treatment-related inflammatory signal on 18F-FDG-PET/CT scan (histiocytic/sarcoid-like reaction) after CAR T-cell therapy.

Study design

This is a single-center, single-arm pilot study designed to evaluate the expression of PD-L1 in patients with LBCL and its role in non-responsiveness to CAR T-cell therapy in a non-invasive manner. Moreover, we aim to study the possibility of PD-L1 PET/CT imaging to distinguish between lymphoma activity and a treatment-related inflammatory signal (histiocytic/sarcoid-like reaction) in case of a relapse or non-response after CAR T-cell therapy.

Intervention

In this imaging trial, the purpose is to explore the feasibility of anti-PD-L1 PET/CT imaging in patients to gain insights into clinically relevant PD-L1 expression in the setting of CD19-directed CAR T-cell therapy. A 89Zr-atezolizumab PET/CT scan will be performed prior to CAR T-cell therapy. Moreover, in case of a suspicion of relapse or non-response after CAR T-cell therapy, a second 89Zr-atezolizumab PET/CT scan will be performed to investigate if this scan can be used to distuingish between lymphoma activity and a treatment-related inflammatory reaction (histiocytic/sarcoid-like reaction) Patients with R/R LBCL will receive standard of care CD19-directed

CAR T-cell therapy according to the eligibility criteria as formed by the Dutch National CAR-T tumor board.

Study burden and risks

For this imaging study, patients have to make a maximum of 6 extra visits to the clinic for screening, 89Zr-atezolizumab injection, a PET/CT-scan visit and a biopsy taken within 7 days of the PET-scan visit when feasible. In case of an end-of-treatment positive 18F-FDG PET/CT signal two visits are needed for the second 89Zr-atezolizumab injection and the PET/CT-scan. The biopsy taken afterwards is part of standard procedure of care, but will only be performed when feasible.
In case of bridging with radiotherapy and depending on the accessibility of the tumor lesions, patients will be asked if they are willing to undergo an extra biopsy. In practice, most procedures will be combined with visits to the hospital in the context of clinical care, to minimize patient burden.
The intravenous tracer injection 89Zr-atezolizumab is between day -19 to day -10 of the CAR T-cell infusion (depending on time needed for bridging strategy). All patients will be observed for at least 30 minutes after 89Zr-atezolizumab injection to monitor for possible acute infusion related adverse events. The subsequent 89Zr-atezolizumab PET/CT imaging scan is 7 days (day -15 to day -6) after tracer infusion. The PET/CT-imaging is followed by a biopsy within 7 days, but the biopsy will always take place before day -5 when biopsy is considered safe. Optimal time point for the 89Zr-atezolizumab-PET/CT-scan is determined in the first 3 patients, as they received a 89Zr-atezolizumab-PET/CT-scan on day 4 and 7.
In case of an end-of-treatment 18F-FDG-positive PET/CT signal another 89Zr-atezolizumab injection will be given followed by a 89Zr-atezolizumab PET/CT imaging and a biopsy within 7 days (standard procedure).
The radiation burden following administration of 37 MBq of 89Zr-atezolizumab is 18.1 mSv, in addition to 1.0 mSv per low-dose attenuation correction CT-scan. Thus, patients will receive 37 or 74 MBq doses of 89Zr-atezolizumab and undergo to 1 or 2 low-dose CT-scans. The radiation exposure will be 19.1 mSv per imaging round. Besides PET/CT imaging, patients will be asked to provide 12 blood samples (108 mL), which are taken in combination with standard clinical and outpatient care. The easiest and safest accessible tumor lesion will be biopsied within 7 days of the 89Zr-atezolizumab PET/CT scans when considered feasible. 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 89Zr-atezolizumab is considered acceptable based on extensive preclinical testing of separate components and clinical safety data from the first-in-human 89Zr-atezolizumab-study where only one low-grade adverse event (pruritus, grade 1) has been reported. 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

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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. Histologically confirmed LBCL and associated subtypes, defined by WHO 2016 classification
2. Eligibility for CAR T-cell therapy must be approved by the Dutch National Tumor Board.
3. Measurable disease, as defined by Lugano criteria
4. Signed informed consent.
5. Age >=18 at the time of signing informed consent.

6. Ability to comply with the protocol.

Exclusion criteria

1.Signs or symptoms of active infection within 2 weeks prior to 89Zr-atezolizumab injection, unless treated to resolution.
2.History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
3.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-atezolizumab, or that may affect the interpretation of the results or render the patient at high risk from complications.

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):	18-05-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	18F-FDG
Generic name:	18F-FDG
Product type:	Medicine

Brand name:	89Zr-atezolizumab
Generic name:	89Zr-MPDL3280A
Product type:	Medicine
Brand name:	MPDL3280A
Generic name:	Atezolizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Yescarta
Generic name:	axicabtagene ciloleucel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-03-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-04-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-07-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-04-2024

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
EU-CTR	CTIS2024-518422-32-01
EudraCT	EUCTR2021-005192-39-NL
ClinicalTrials.gov	NCT05404048
CCMO	NL79465.042.21