Molecular imaging of zirconium-89-labeled atezolizumab as a tool to investigate atezolizumab biodistribution in diffuse large B-cell lymphoma

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Primary objective:• To evaluate biodistribution of 89Zr-atezolizumab in patients with high risk DLBCL at diagnosis.Secondary objective:• To assess the heterogeneity of 89Zr-atezolizumab tumor uptake in high-risk DLBCL before R-CHOP.• To correlate...

Ethical review	Approved WMO
Status	Pending
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Observational invasive

Summary

ID

NL-OMON48775

Source
ToetsingOnline

Brief title
PDL1 imaging in DLBCL

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
diffuse large B-cell lymphoma, lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: HOVON

Source(s) of monetary or material Support: Firma Roche,Hoffmann-La Roche

Intervention

Keyword: atezolizumab, DLBCL, immunoPET, molecular imaging

Outcome measures

Primary outcome

• Description of 89Zr-atezolizumab biodistribution in DLBCL by measuring standardized uptake value (SUV) on the 89Zr-atezolizumab-PET scans

Secondary outcome

• Tumor and immune cell PD-L1 expression analysis in an archival pre-treatment biopsy, will be correlated to 89Zr-atezolizumab tumor uptake, evaluated by measuring standardized uptake value (SUV) on 89Zr-atezolizumab-PET-scans

• Correlation analysis of tumor 89Zr-atezolizumab uptake, evaluated by measuring standardized uptake value (SUV) and sPD-L1 levels in patient serum, assessed using ELISA

• Correlation analysis of tumor 89Zr-atezolizumab uptake, evaluated by assessing immune signature by GEP

• Correlation analysis of 89Zr-atezolizumab uptake and MRD status

• Correlation analysis between 89Zr-atezolizumab off-target uptake and atezolizumab toxicity

• Analysis of predictive value of 89Zr-atezolizumab imaging in DLBCL patients

Exploratory study endpoints:

• Establish baseline characteristics and dynamics for T-cell repertoire and

microbiome after R-CHOP

Study description

Background summary

Patients with a high-risk diffuse large B-cell lymphoma (DLBLC) with an international prognostic score (IPI) > 2, have a high risk of relapse even after achieving a metabolic complete remission with R-CHOP chemo-immunotherapy. Outcome after relapse is dismal. In patients with varies types of relapsed lymphoma checkpoint inhibition have shown promising results.
In order to improve outcome patients with a high risk DLBCL will be treated in the HOVON 151 trial (EudracT 2017-002605-35) with the monoclonal antibody directed against the immune checkpoint program death ligand 1 (PDL1) atezolizumab for 1 year after achieving a complete metabolic remission with R-CHOP.
The observed percentage of PD-L1 positive tumor cells in DLBCL cases ranges from 13 to 31%. For PD-1/PD-L1 checkpoint inhibition PD-L1 tumor surface expression was proposed as a potential predictive marker. Despite higher overall response rates in PD-L1 positive malignancies compared to PD-L1 negative tumors, responses are seen in PD-L1 negative patients nevertheless. PD-L1 status from resected specimens showed a poor correlation to the PDL1 status from matched biopsies. Furthermore it has been shown that PDL1 expression in tumor biopsies changes with treatment. Therefore, PDL1 expression assessed by one single biopsy might not be representative.
Molecular imaging can be used for the noninvasive assessment of biodistribution of monoclonal antibodies. Atezolizumab has previously successfully been labeled with the radionucleotide Zirconium-89 (89Zr) and studied in solid malignancies (EudracT 2015-000996-29). The results of atezolizumab biodistribution can help to get a better understanding of the response mechanisms, the relation with minimal residual disease, the relation with the status of the T-cell and NK-cell repertoire and toxicity of programmed death ligand 1 (PD-L1) checkpoint

inhibition. Possibly in the future this will facilitate optimal patient selections. Sequential 89Zr-atezolizumab PET scans can provide information on the dynamics of atezolizumab biodistribution over time. In combination with repeated characterization of tumor tissue and blood samples, these results can give inside in the primary and acquired resistance.
In this parallel study of the HOVON 151 trial 89Zr-atezolizumab-PET-scans will be used to evaluate 20 DLBCL patients before induction (R-CHOP) therapy, at the start of atezolizumab consolidation and at suspected relapse.

Study objective

Primary objective:

• To evaluate biodistribution of 89Zr-atezolizumab in patients with high risk DLBCL at diagnosis.

Secondary objective:

• To assess the heterogeneity of 89Zr-atezolizumab tumor uptake in high-risk DLBCL before R-CHOP.
• To correlate 89Zr-atezolizumab biodistribution with PD-L1 expression on tumor cells and cells in the micro-environment as assessed by immunohistochemistry (IHC) on archival tumor biopsies, soluble PD-L1 (sPD-L1) measurements and PD-L1 RNA expression (GEP).
• To evaluate 89Zr-atezolizumab biodistribution in metabolic complete remission following R-CHOP and assess the relation with minimal residual disease.
• To assess the 89Zr-atezolizumab biodistribution at relapse after treatment with atezolizumab for patients treated in the HOVON 151 trial.
• Correlate 89Zr-atezolizumab tumor uptake dynamics and biodistribution to potential adverse reactions of atezolizumab treatment for patients treated in the HOVON 151 trial

Exploratory objectives:

• To establish the baseline characteristics for the T-cell and NK-cell repertoire and dynamics induced by R-CHOP.
• To establish the baseline characteristics for the microbiome and the dynamics induced by R-CHOP.

Study design

Phase II, multicenter, prospective, non-randomized trial:

Part A: 21 eligible patients will undergo a baseline 89Zr-atezolizumab-PET-scans before R-CHOP therapy.

Part B: An estimate of 15 patients who achieved CR after R-CHOP therapy will undergo a second 89Zr-atezolizumab-PET-scan.

After participation within the imaging trial all eligible patients will be allowed to enter the HOVON 151 treatment trial.

Part C: Patients with suspected relapse in the HOVON 151 trial will undergo one additional 89Zr-atezolizumab-PET-scan.

Study burden and risks

For this 89Zr-atezolizumab imaging side study patients have to make max. 4 extra visits to the clinic for screening, to receive tracer injection and 1 PET scan in each Part of the study (A,B and C). Because of the minimal modifications accompanying the labeling process of atezolizumab, the toxicity profile of 89Zr-atezolizumab is expected to be similar to that of atezolizumab. Based on the experience of the trial in solid malignancy, 89Zr-atezolizumab is unlikely to pose a toxicological threat, because the tracer is administered at a non-therapeutic dose of 11 mg. 89Zr-atezolizumab-PET-scans implement a radiation burden of 19.5 mSv. Besides PET imaging, patients will be asked to give in total 2 additional blood samples (20 mL) and a fecal sample which will give minor discomfort. The risk associated with the 89Zr-atezolizumab-PET-scans seems minor and although patients do not directly benefit from this 89Zr-atezolizumab imaging study, results of this study will be valuable for our understanding of the tumor immune response and will guide further prospective research. After participation within the 89Zr-atezolizumab imaging study all patients will be allowed to enter the HOVON 151 treatment trial, provided they continue to meet the eligibility criteria to participate in the HOVON 151 trial and to receive atezolizumab. The HOVON 151 trial aims at improving DFS in high-risk DLBCL patients with atezolizumab consolidation.

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

Inclusion criteria, • Age 18-75 (inclusive) years
• Patients with a confirmed histologic diagnosis of diffuse large B-cell lymphoma (DLBCL-NOS)
based upon a representative histology specimen according to the WHO classification, revision 2016
(see appendix A)
• Ann Arbor stages II-IV
• Negative pregnancy test at study entry
• Patient is willing and able use adequate contraception during and until 5 months after the last
protocol treatment.
• Written informed consent
• Patient is capable of giving a written informed consent

Exclusion criteria

Diagnosis
• All histopathological diagnoses other than DLBCL-NOS according to the WHO classification, revision 2016, including:
- High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 translocations
- Testicular large B-cell lymphoma
- Primary mediastinal B cell lymphoma
- Transformed indolent lymphoma
- Post-transplant lymphoproliferative disorder, Organ dysfunction

• Clinical signs of severe pulmonary dysfunction
• Clinical signs of heart failure (NYHA classification II-IV)
• Symptomatic coronary artery disease or cardiac arrhythmias not well controlled with medication.
• Myocardial infarction during the last 6 months
• Significant renal dysfunction (serum creatinine >= 150 umol/l or clearance <= 30ml/min
Creatinine clearance may be calculated by Cockcroft -Gault formula:
CrCl = (140 - age [in years]) x weight [kg] (x 0.85 for females) / (0.815 x serum creatinine [µmol/L])
• Inadequate hematological function: hemoglobin < 5.5 mmol/L ANC < 1.0x10^9/L or platelets < 75x10^9 /L
• Spontaneous INR > 1.5, aPTT >33
• Significant hepatic dysfunction (total bilirubin >= 1.5x upper limit of normal (ULN) or transaminases >= 2.5 x ULN), unless related to Gilberts syndrome.
• Clinical signs of severe cerebral dysfunction
• Patients with a history of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant and adversely affecting compliance to study drugs
• Major surgery within the last 4 weeks, Known or suspected infection
• Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection or any major episode of infection requiring treatment with IV antibiotics or hospitalization within 4 weeks before date of registration.
Suspected active or latent tuberculosis needs to be confirmed by positive interferon gamma (IFN-γ) release assay
• Patients known to be HIV-positive
• Active chronic hepatitis B or C infection
• Administration of a live, attenuated vaccine within 4 weeks before date of registration or anticipation that such a live attenuated vaccine will be required during the study and for a period of 5 months after discontinuation of atezolizumab., Auto-immune
• Any active or history of documented autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener*s granulomatosis, Sjögren*s syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
The following exceptions are allowed: Patients with autoimmune-related hypothyroidism or type 1 diabetes mellitus who are on stable treatment.
• History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest CT scan at screening.
• Patients with uncontrolled asthma or allergy, requiring systemic steroid treatment
• Regular treatment with corticosteroids within the 4 weeks prior to date of registration, unless administered for indications other than NHL at a dose equivalent to < 30 mg/day prednisone/prednisolone., General

• Serious underlying medical conditions, which could impair the ability of the patient to participate in the trial (e.g. ongoing infection, uncontrolled diabetes mellitus, gastric ulcers, active autoimmune disease)
• Current participation in another clinical trial interfering with this trial
• History of active cancer during the past 5 years, except basal cell carcinoma of the skin or stage 0 cervical carcinoma
• Life expectancy < 6 months
• Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule, Prior treatment
• Prior treatment with atezolizumab, or anti PD-1 or PDL-1 antibodies.
• Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA4 therapeutic antibodies.
• Treatment with systemic immunostimulatory agents (including but not limited to IFN, interleukin [IL]-2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to date of registration.
• Treatment with systemic immunosuppressive medications, including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor (anti-TNF) agents within 2 weeks prior to date of registration; inhaled corticosteroids and mineralocorticoids are allowed.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2019
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	89Zr-Atezolizumab
Generic name:	89Zr-Atezolizumab

Ethics review

Approved WMO Date:	26-09-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-01-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-03-2020
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	EUCTR2017-003511-20-NL

Register	ID
CCMO	NL63047.042.18