A phase II study evaluating the feasibility and clinical efficacy of atezolizumab consolidation treatment in high risk diffuse large B-cell lymphoma

Published: 28-03-2018
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2022-501076-26-00 check the CTIS register for the current data. Primary objective:• To evaluate the 2-year disease free survival (DFS)Secondary objectives:• To evaluate toxicity and asses the relation...

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

Summary

ID

NL-OMON52540

Source
ToetsingOnline

Brief title
HOVON 151 NHL

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, consolidation, Diffuse Large B-Cell Lymphoma, high risk

Outcome measures

Primary outcome

Primary endpoint

• Disease free survival measured from the date of registration to relapse or death from any cause whichever comes first.

Secondary outcome

• (severe) adverse events and the relation of adverse events in time to recovery of the T-cell repertoire.

• Overall survival, calculated from registration until death from any cause.

• The relationship between MRD status at the end-of-induction and end-of-consolidation therapy.

• The relation between MRD conversion and 2-years DFS and OS

• The relationship between T-cell repertoire, PDL1/HLA expression, mutational load, gene immune signature, microbiome and effect of atezolizumab on MRD conversion.

• The relation between the T-cell and NK cell repertoire and adverse events.

Study description

Background summary

In high risk diffuse large B-cell lymphoma (DLBCL), IPI-score > 2, 21% of patients will relapse within 2-years after completion of R-CHOP induction

treatment despite achieving a complete remission. Patient relapsing within a year after R-CHOP treatment have a very poor prognosis, even after second line chemotherapy, with only 15% of patients achieving a long remission. Therefore, additional therapy in first line treatment is required for these patients. The immune checkpoint inhibitor atezolizumab is a monoclonal antibody directed against the program death ligand 1 (PDL1). The PD1 and PDL1 inhibitors have shown excellent results in relapsed Hodgkin lymphoma and promising results in relapsed B-cell non Hodgkin lymphoma. Given the acceptable toxicity profile of atezolizumab, this study examines the efficacy and toxicity of atezolizumab as consolidation treatment after R-CHOP induction in DLBCL patients at high risk of relapse.

Study objective

This study has been transitioned to CTIS with ID 2022-501076-26-00 check the CTIS register for the current data.

Primary objective:
• To evaluate the 2-year disease free survival (DFS)

Secondary objectives:
• To evaluate toxicity and asses the relation of adverse events in time to recovery of the T-cell repertoire
• To evaluate the 2-year overall survival (OS)
• To evaluate minimal residual disease (MRD) status at the end of induction therapy and at various time points during consolidation treatment.
• To evaluate the recovery of the T-cell en NK cell repertoire after induction therapy and at various time points during consolidation treatment in relation to toxicity and efficacy

Exploratory objectives
• To explore the PDL1/HLA expression, mutational load, gene expression immune profile, soluble PDL1, microbiome and T-cell clonality of patients in relation to MRD status and MRD conversion.
• To explore the tumor characteristics and mutational dynamics in patients who relapse
• To assess the crossing of the blood-brain barrier of atezolizumab by measuring atezolizumab concentrations in het cerebrospinal fluid.

Study design

Phase 2, multicenter, prospective, non-randomized clinical trial.

Intervention

All patients will receive atezolizumab 1200mg intravenously every 3 weeks for

54 weeks (18 cycles)

Study burden and risks

The prognosis of DLBCL patients with an early relapse is dismal. Atezolizumab has shown promising activity in relapsed DLBCL patients. Toxicity data on atezolizumab are available for > 6000 patients and is manageable. In melanoma and lungcancer consolidation immunotherapy after chemoradiotherapy has shown a dramatic increase in survival. Assumption of this study is that atezolizumab consolidation will result in higher PFS by eradicating MRD.

Contacts

Public
HOVON

HOVON Centraal Bureau, VUmc, De Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
HOVON

HOVON Centraal Bureau, VUmc, De Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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
• Ann Arbor stages II-IV
• WHO performance status 0 - 1
• IPI >=3 at diagnosis
• Complete metabolic remission (Deauville 1-3) after 6-8 cycles of R-CHOP according to the Lugano criteria
• Negative pregnancy test at study entry
• Patient is willing and able to use adequate contraception during and until 5 months after the last protocol treatment.
• Written informed consent
• Patient is capable of giving 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 a double/triple translocation with MYC, BCL2 and/or BCL6. Please note that patients with an isolated MYC translocation or an isolated BCL2 translocation or an isolated BCL-6 translocation are eligible (single hit translocation).
- 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:
• Inadequate hematological function: hemoglobin 5.5 < mmol/L, ANC < 1.0x109/L or platelets < 75x109 /L
• Signs or know history of bleeding disorder
• 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 regsitration 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, stage 0 cervical carcinoma or cracinoma in situ (for which no systemic treatment was indicated)
• 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:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-09-2018
Enrollment:	90
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tecentriq
Generic name:	Atezolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-03-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-08-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-01-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-04-2020

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-03-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-09-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-05-2022

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-06-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-09-2022
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	CTIS2022-501076-26-00
EudraCT	EUCTR2017-002605-35-NL
ClinicalTrials.gov	NCT03463057
CCMO	NL63352.042.17