SAMENVATTING HOVON 151 imaging

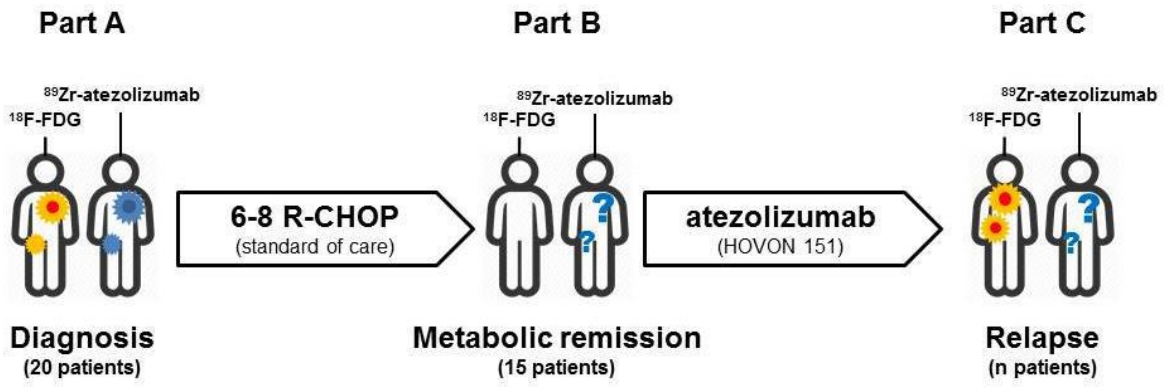
TITEL

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

INDICATIE

Patients with stage II-IV high risk diffuse large B-cell lymphoma, defined as international prognostic index > 2, age 18-75 years.

SCHEMA



In **Part A**, 20 eligible patients will undergo a baseline ^{89}Zr-atezolizumab-PET-scans before R-CHOP therapy.
In **Part B**, an estimate of 15 patients who achieved CR after R-CHOP therapy will undergo a second ^{89}Zr-atezolizumab-PET-scan.
After participation within the imaging trial all eligible patients will be allowed to enter the HOVON 151 treatment trial.
In **Part C**, patients with suspected relapse in the HOVON 151 trial will undergo one additional ^{89}Zr-atezolizumab-PET-scan.

INCLUSIE 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 B)
- Ann Arbor stages II-IV (see appendix D)
- IPI ≥ 3 at diagnosis (see appendix F)
- 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

EXCLUSIE CRITERIA

Diagnosis

- All histopathological diagnoses other than DLBCL-NOS according to the WHO classification, revision 2016 (see appendix B), 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:

$$CrCl = \frac{(140 - \text{age [in years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ for females})}{(0.815 \times \text{serum creatinine [µ mol/L]})}$$

- Inadequate hematological function: hemoglobin < 5.5 mmol/L ANC < 1.0x109/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 antitumor necrosis factor (anti-TNF) agents within 2 weeks prior to date of registration; inhaled corticosteroids and mineralocorticoids are allowed.