A phase I/II study of lutetium (177Lu)-lilotomab satetraxetan (Betalutin®) antibody-radionuclide-conjugate for treatment of relapsed non-Hodgkin lymphoma.

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PART B (FL phase IIb *PARADIGME*):Primary objective:Randomised section of Part B- To evaluate the efficacy of the *40/15* dose regimen (40 mg lilotomab / 15 MBq/kg Betalutin) compared with *100/20* dose regimen (100 mg/m2 lilotomab/ 20 MBq/kg...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas non-Hodgkin's unspecified histology
Study type	Interventional

Summary

ID

NL-OMON55476

Source
ToetsingOnline

Brief title
LYMRIT-37-01 (3185/0002)

Condition

- Lymphomas non-Hodgkin's unspecified histology

Synonym
Non-Hodgkin's lymphoma; Lymfcancer

Research involving
Human

Sponsors and support

Primary sponsor: Nordic Nanovector ASA
Source(s) of monetary or material Support: industry

Intervention

Keyword: Betalutin, Lymph cancer, Non-Hodgkin B-cell lymphoma

Outcome measures

Primary outcome

ENDPOINTS - PART B (phase IIb)

Primary endpoint:

• Overall response rate (ORR) as assessed by an independent review committee

based on Cheson criteria (version 2014).

Secondary outcome

ENDPOINTS - PART B (phase IIb)

Secondary endpoints:

Efficacy:

• ORR by investigator assessment.

• CRR by independent review and investigator assessment.

• DoR by independent review and investigator assessment.

• DoCR by independent review and investigator assessment.

• PFS by independent review and investigator assessment.

• OS.

• Change from baseline in the sum of the product of the greatest perpendicular

diameters (SPD) of target lymph nodes as documented radiographically.

Safety:

• Incidence and severity of AEs.

Exploratory endpoints:

• Changes in quality of life (QoL) as reported by patients using the FACT-Lym questionnaire (Version 4).

• Pharmacokinetic assessments e.g. total lilotomab antibodies measurements in serum (total lilotomab antibodies pharmacokinetics) and total radioactivity measurements in blood (Betalutin pharmacokinetics).

Study description

Background summary

Non-Hodgkin lymphoma is a disease that can be treated effectively with chemotherapy and immunotherapy, but relapses will occur, and there is therefore a need for new types of treatment.

Antibodies are proteins that can be found in your blood or other body fluids. They are important elements of the body*s defence system. Some antibodies can recognize specific parts of cancer cells that they can bind to. By doing so, the antibodies will activate processes that can destroy the cancer cells. Previous research has shown that in many cases antibodies with a radioisotope attached (radioimmunotherapy) have been effective. This process is called radiolabelling. The radioisotope that is attached to the antibody will help with killing the cancer cells by adding radiation.

In this study, a new type of radioimmunotherapy called Betalutin® will be tested. Betalutin® is made by using a new antibody, called lilotomab, and attaching a radioactive molecule (radioisotope) called Lutetium-177. The radioisotope Lutetium-177 may be more suitable for radioimmunotherapy than the radioisotopes that have previously been used for non-Hodgkin lymphoma. The

Betalutin® binds to an area on the surface of the cancer cells called CD37. This treatment is intended to target the cancer cells with the radioactivity, thereby irradiating them inside the body.

Study objective

PART B (FL phase IIb *PARADIGME*):

Primary objective:
Randomised section of Part B
- To evaluate the efficacy of the *40/15* dose regimen (40 mg lilotomab / 15 MBq/kg Betalutin) compared with *100/20* dose regimen (100 mg/m2 lilotomab/ 20 MBq/kg Betalutin) based on an Independent Review Committee (IRC) assessment of tumour response rates in adult patients with relapsed rituximab/anti-CD20-refractory follicular lymphoma.

Selected regimen for further development:
- To evaluate the overall response rate (ORR) of the regimen selected for further development based on the Independent Review Committee (IRC) assessment of tumour response rates in adult patients with relapsed rituximab/anti-CD20 refractory FL.

Study design

PART B (phase IIb)-*PARADIGME*
Open label, randomised 1:1 (stratified for double-refractory patients, where double-refractory is defined as refractory to both an anti-CD20 therapy and an alkylating agent therapy - see Section 9.1.7.2 for full definition) to receive one of the 2 RP2Ds (40 mg lilotomab + 15 MBq/kg Betalutin (referred to as *40/15*) or 100 mg/m2 lilotomab + 20 MBq/kg Betalutin (referred to as *100/20*). The patients will receive a single dose of rituximab 375 mg/m2 on Day -14, and then sequential administration of lilotomab followed by Betalutin within 4 hours on Day 0. Once 50 patients have been treated (approximately 25 per arm) an interim analysis (IA) will be performed for futility (see *Statistical Methods and Planned Analysis*).

Intervention

Investigational Products (PART A and B):
Betalutin is an antibody-radionuclide-conjugate (ARC) composed of the radioisotope lutetium-177 (177Lu), the linker p-SNC-benzyl-DOTA (also referred as satetraxetan) and the murine anti-human CD37 immunoglobulin G1 (IgG1) antibody, lilotomab. The active moiety is the beta-particle emitting nuclide 177Lu. Lutetium-177 has a physical half-life of 6.7 days. The antibody lilotomab recognises epitopes on the human CD37 antigen, which is abundant on the cell surface of tumours of B-cell origin, including non-Hodgkin lymphoma

(NHL). Betalutin is prepared as a solution for intravenous administration. The amount of Betalutin (also referred as lutetium (177Lu) lilotomab satetraxetan) injected per patient will depend on dose level and patient*s weight; however, the dose is capped for patients who weigh more than 130 kg (patients heavier than 130 kg will receive the dose for a 130 kg patient). The concentration of lilotomab satetraxetan in the Betalutin formulation is 0,78 mg/mL, and the amount injected is dependent on how many days after production the product is given, up to a maximum of 18 mg of lilotomab. Betalutin will be supplied in vials containing a ready-to-use solution.
The investigational medicinal product (IMP) will be referred to as Betalutin or lutetium (177Lu)-lilotomab satetraxetan in the protocol.

Rituximab, a chimeric anti-CD20 antibody, will be used to clear the circulating normal peripheral B lymphocytes in the blood and in the spleen before administering Betalutin. This may secure better access for Betalutin to less accessible compartments such as lymph nodes and larger tumour masses. Rituximab targets CD20 and will not block the binding of Betalutin to CD37 on the B-lymphocytes or tumour cells.
Pre-medication consisting of an antipyretic and antihistamine should be administered before infusion of rituximab. The types of pre-medication will be in accordance with each hospital*s routine, including any use of corticosteroids. For detailed guidance on use of rituximab and possible side effects, see the summary of product characteristics or prescribing information.

Lilotomab, is a murine anti-human CD37 antibody, and the same antibody, as used in Betalutin, that will be used to block the binding on remaining B-cells, in the lymphoid organs following the rituximab pre treatment. Administration of lilotomab will be performed within 4 hours before administration of Betalutin on Day 0. Pre-medication consisting of an antipyretic and antihistamine medication should be administered before infusion of lilotomab.

Study burden and risks

Please refer to appendix D of the subject information sheet

Contacts

Public
Nordic Nanovector ASA

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Oslo NO-0884
NO
Scientific

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NO

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria: PART B (phase IIb) , 1. Histologically confirmed (by WHO classification) relapsed non-Hodgkin B-cell FL (grade I-IIIA).
2. Male or female aged >= 18 years.
3. Received at least 2 prior systemic anti-neoplastic or immunotherapy-based regimens (maintenance therapy following a CR/PR is not considered to be a separate line of therapy). Systemic regimens including agents such as idelalisib or other PI3K inhibitors qualify as a prior line of therapy.
4. Prior therapy must have included a rituximab/anti-CD20 agent and an alkylating agent which may be been administered in separate regimens.
5. Patients must be refractory to any at least one previous regimen that contained rituximab or an anti-CD20 agent, with refractoriness defined as:
i. no response (no CR or PR) during therapy, or
ii. a response (CR/PR) lasting less than 6 months after the completion of a regimen of rituximab/anti-CD20 therapy (including occurrence of progressive disease (PD) during rituximab/anti-CD20 maintenance therapy, or within 6 months of completion of maintenance therapy).
6. WHO performance status of 0-2.
7. Life expectancy of >= 3 months.
8. Bone marrow tumour infiltration < 25% (in biopsy taken from a site not previously irradiated).
9. Measurable disease by CT or MRI: longest diameter (LDi) > 1.5 cm for nodal

lesion, LDi > 1.0 cm for extra nodal lesion on an assessment performed during the screening period.
Criteria 10 and 11 must be satisfied within 72 hours of the administration of rituximab:
10. ANC >= 1.5 x 109/L.
11. Platelet count >= 100 x 109/L.
Criteria 12 to 15 must be verified at time of eligibility review within 2 weeks prior to rituximab administration:
12. Haemoglobin >= 9.0 g/dL.
13. Total bilirubin <=1.5 x upper limit of normal (ULN) (except patients with documented Gilbert*s syndrome [< 3.0 mg/dL]).
14. Liver enzymes: Aspartate transaminase (AST); Alanine transaminase (ALT) or ALP <= 2.5 x ULN (or <= 5.0 x ULN with liver involvement by primary disease).
15. Adequate renal function as demonstrated by a serum creatinine < 1.5 x ULN.
16. Women of childbearing potential must:
a) understand that the study medication is expected to have teratogenic risk.
b) have a negative serum beta human-chorionic gonadotropin (ß-HCG) pregnancy test at screening.
c) commit to continued abstinence from heterosexual intercourse (excluding periodic abstinence or the withdrawal method) or begin a highly effective method of birth control with a Pearl-Index < 1%, without interruption, from 4 weeks before starting study medication, throughout study medication therapy and for 12 months after end of study medication therapy, even if she has amenorrhoea. Apart from abstinence, highly effective methods of birth control are:
i. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
ii. Progestogen-only hormonal contraception associated with inhibition of ovulation ((oral, injectable, implantable)
iii. Intrauterine device (IUD).
iv. Intrauterine hormone-releasing system (IUS).
v. Bilateral tubal occlusion.
vi. Vasectomised partner.
17. Male patients must agree to use condoms during intercourse throughout study treatment administration and for 12 months following administration of Betalutin.
18. The patient is willing and able to comply with the protocol, and agrees to return to the hospital for follow-up visits and examination.
19. The patient has been fully informed about the study and has signed the informed consent form.
20. Negative HAMA test at screening.
21. Negative test at screening for Hepatitis B (negative HBsAG and anti-HBC), Hepatitis C and HIV.

Exclusion criteria

Exclusion Criteria: PART B (phase IIb),
1. Prior hematopoietic allogenic stem cell transplantation.
2. Patients with a prior autologous stem cell transplanted (SCT) are excluded unless at least two years have elapsed since transplantation.
3. Evidence of histological transformation from FL to diffuse large B-cell lymphoma (DLBCL) at time of screening (transformation to grade IIIB that was successfully treated with recurrence of grade I-IIIA initial clone is accepted).
4. Previous total body irradiation.
5. Prior anti-lymphoma therapy (chemotherapy, immunotherapy or other systemic agent including any investigational agent) within 4 weeks prior to start of study treatment (corticosteroid treatment at doses of <= 20 mg/day, topical or inhaled corticosteroids, granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor [GM-CSF] are permitted up to 2 weeks prior to start of rituximab).
6. Patients who are receiving any other investigational medicinal products.
7. Patients with known or suspected CNS involvement of lymphoma.
8. History of malignancy other than FL within 5 years prior to screening,(i.e. patients with cancer diagnosed within 5 years prior to screening or who were diagnosed prior to 5 years and were not in CR or were on treatment within 5 years prior to screening), with the exception of malignancies with a negligible risk of metastasis or death (e.g. 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localised prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.
9. Pregnant or breastfeeding women.
10. Exposure to another CD37 targeting drug.
11. A known hypersensitivity to rituximab, lilotomab, Betalutin or murine proteins or any excipient used in rituximab, lilotomab, or Betalutin.
12. Has received a live-attenuated vaccine within 30 days prior to enrolment.
13. Evidence of severe or uncontrolled systemic diseases:
a. Uncontrolled infection including evidence of ongoing systemic bacterial, fungal, or viral infection (excluding viral upper respiratory tract infections) at the time of initiation of study treatment.
b. Pulmonary conditions e.g. unstable or uncompensated respiratory disease.
c. Hepatic, renal, neurological, or metabolic conditions - which in the opinion of the investigator would compromise the protocol objectives.
d. Psychiatric conditions e.g. patients unlikely to comply with the protocol, e.g. mental condition rendering the patient unable to understand the nature, scope, and possible consequences of participating in the study.
e. History of erythema multiforme, toxic epidermal necrolysis, or Stevens-Johnson
syndrome.
f. Cardiac conditions in the previous 24 weeks (before date of consent), including

i. history of acute coronary syndromes (including unstable angina).
ii. class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
iii. known uncontrolled arrhythmias (except sinus arrhythmia).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-11-2019
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Betalutin
Generic name:	Betalutin
Product type:	Medicine
Brand name:	Lilotomab
Generic name:	Lilotomab
Product type:	Medicine
Brand name:	Rituximab 100mg
Generic name:	MabThera (Roche) 100mg

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Rituximab 500mg
Generic name:	MabThera (Roche) 500mg
Registration:	Yes - NL 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:	20-07-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-03-2020
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-01-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-05-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-02-2022
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)

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	EUCTR2011-000033-36-NL
ClinicalTrials.gov	NCT01796171
CCMO	NL65124.042.18

Study results

Date completed:	16-03-2020
Actual enrolment:	1

Summary results
Trial is onging in other countries