A randomized, open-label, multicenter, phase II trial evaluating the safety and activity of DCDT2980S in combination with rituximab or DCDS4501A in combination with rituximab in patients with relapsed or refractory B-cell non Hodgkin's lymphoma.

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The primary objective of the study is evaluating the safety, tolerance and anti-lymphoma activity of the anti-CD79b-MMAE conjugate (DCDS4501A) and the anti-CD22-MMAE conjugate (DCDT2980S), both given in combination with Rituximab once every 4 weeks...

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

Summary

ID

NL-OMON39673

Source
ToetsingOnline

Brief title
Genentech GO27834 study

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Non Hodgkin's Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Genentech Inc
Source(s) of monetary or material Support: Genentech Inc.

Intervention

Keyword: Non Hodgkin's Lymphoma, refractaire, relapse, safety

Outcome measures

Primary outcome

1. To assess the safety of both the combination of DCDT2980S with Rituximab or

DCDS4501A with Rituximab in patients with relapsed or refractory follicular NHL

and diffuse large B-cell lymphoma.

2. To assess the anti-lymphoma activity of both combinations.

Secondary outcome

1. To assess the incidence of antibody formation against DCDS4501A or DCDT2980S.

2. To obtain pharmacokinetic information on both combinations.

3. To study preliminary biological markers which might be predictive for the

anti-lymphoma activity of both combinations.

4. To get insight into the quality of life of the patients involved.

5. To evaluate the safety and the anti-lymphoma effect of both combinations in

the *cross over* setting.

Study description

Background summary

DCDS4501A (anti-CD79b-vc-MMAE) and DCDT2980S (anti-CD22-vc-MMAE) are antibody-cytostatic drug conjugates consisting of a humanized immunoglobulin-G1 (IgG1) anti-human-CD79b- or CD22-monoclonal antibody and monomethyl auristatine E (MMAE), a cytostatic agent with strong anti-mitotic activity. CD79b and CD22 are surface antigens which are expressed by all mature B-cells, excluding plasma cells, and most B-cell non-Hodgkin lymphomas. After binding of DCDS4501A or DCDT2980S to CD79b- and CD22-positive lymphoma cells, respectively, the conjugate will be internalized and will be split by lysosomal enzymes, releasing MMAE. Subsequently, MMAE will bind to tubuline through which the microtubuline network of the lymphoma cell will be disturbed. This will result in delayed cell division and cell growth and ultimately cell death.

Phase I studies with both of these 2 agents showed an acceptable toxicity profile and in a number of patients an anti-lymphoma response was observed. On the basis of the optimal dose established in the phase I study the randomized phase II trial is now proposed

Study objective

The primary objective of the study is evaluating the safety, tolerance and anti-lymphoma activity of the anti-CD79b-MMAE conjugate (DCDS4501A) and the anti-CD22-MMAE conjugate (DCDT2980S), both given in combination with Rituximab once every 4 weeks intravenously in the setting of the randomized phase II study.

Study design

Patients will be randomized between one of both conjugates, always in combination with Rituximab. In principle the treatments will be continued till progression of lymphoma growth occurs or in case the side effects become too severe. Maximal duration of treatment will be 1 year. If during treatment progression of lymphoma growth occurs, there is the possibility to *cross over*: the treatment changes from DCDS4501A to DCDT2980S or the other way around, with or without Rituximab. A *cross over* can also be considered if the new drug is not tolerated.

Intervention

Treatment with DCDT2980S or DCDS4501A in combination with Rtuximab

Study burden and risks

From the phase I studies with both DCDS4501A and DCDT2980S a favourable toxicity profile appeared, which has led to the development of the current randomized phase II trial.

In Section E9 the various risks for the subjects enrolled have been described extensively, to be summarized as infusion reactions, in particular during the first intravenous application, a (small) chance to develop the tumor lysis syndrome, temporary/reversible thrombocytopenia/granulocytopenia, and sensoric neuropathy.

The patient will be requested to come at regular times to the treatment center to monitor the health status, to draw blood for pharmacokinetic studies and to undergo - if necessary - a lymph node biopsy in case of *cross over* to the other new drug. This represents quite a burden to each individual patient.

Because of the fact that no good alternatives exist for this particular patient group, the study as described in the protocol including the risks and burdens for the patient seems to be justified. The ratio between the risk/burden for the patient and the possible yield of this study both for the patient himself/herself and for future patients is acceptable.

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

Signed Informed Consent Form(s)
• Age >= 18 years
• Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
• Life expectancy of at least 12 weeks
• History of histologically documented relapsed or refractory Grades 1*3a FL, or relapsed or refractory DLBCL
• Availability of an archival or freshly biopsied tumor tissue sample must be confirmed for study enrollment.
• Have a clinical indication for treatment as determined by the investigator
• Must have at least one bi-dimensionally measurable lesion (> 1.5 cm in its largest dimension by CT scan or MRI)
• Laboratory values (including patients with hepatic or renal involvement), as follows:
AST and ALT <= 2.5 × the upper limit of normal (ULN)
Total bilirubin <= 1.5 × ULN
Protocol: DCDT2980S and DCDS4501A*Genentech, Inc.
54/P GO27834
Platelet count >= 75,000/mm3 (unless thrombocytopenia clearly due to marrow involvement of NHL, and/or disease-related immune thrombocytopenia)
Absolute neutrophil count >= 1000/mm3 (without growth factor support, unless neutropenia clearly due to marrow involvement of NHL)
Total hemoglobin >= 9 g/dL (without transfusion support >14 days prior to screening, unless anemia clearly due to marrow involvement of NHL)
Serum creatinine <= 2.0 mg/dL or measured creatinine clearance >= 50 mL/min

Exclusion criteria

Prior use of any monoclonal antibody, radioimmunoconjugate or antibodydrug conjugate within 4 weeks before Cycle 1, Day 1
• Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational anti-cancer agent within 2 weeks prior to Cycle 1, Day 1
Adverse events except for sensory neuropathy from any previous treatments must be resolved or stabilized to Grade <= 2 prior to Cycle 1, Day 1
• Completion of autologous stem cell transplant within 100 days prior to

Cycle 1, Day 1
• Prior allogeneic stem cell transplant
• Eligibility for autologous SCT (patients with relapsed or refractory DLBCL)
• History of transformation of indolent disease to DLBCL
• History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
• History of other malignancy that could affect compliance with the protocol or interpretation of results
Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma, e.g. of the cervix or breast, are allowed. Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for >= 2 years prior to Cycle 1, Day 1.
• Current or past history of CNS lymphoma
• Current Grade > 1 peripheral neuropathy
Evidence of significant, uncontrolled concomitant diseases which could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
• Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
• Recent major surgery within 6 weeks prior to Cycle 1, Day 1, other than for diagnosis
• Presence of positive test results for Hepatitis B (HBsAg and/or total Hepatitis B core antibody [anti-HBc]) or Hepatitis C (HCV antibody)
Patients who are positive for anti-HBc are eligible only if PCR is negative for HBV DNA and it is believed by both the investigator and Medical Monitor to be in the patient*s best interest to participate.
Patients who are positive for HCV antibody must be negative by for HCV by PCR to be eligible for study participation
• Known history of HIV seropositive status
• Women who are pregnant or lactating
• Ongoing corticosteroid use > 30 mg/day prednisone or equivalent
Patients receiving corticosteroid treatment <= 30 mg/day prednisone or equivalent must be documented to be on a stable dose prior to study enrollment and initiation of therapy
• For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use one highly effective form of non-hormonal contraception or two effective forms of non-hormonal contraception through the course of study treatment and for at least 3 months after the last dose of DCDT2980S or DCDS4501A or rituximab (whichever is later) in women and at least 5 months after the last dose of DCDT2980S or

DCDS4501A or rituximab (whichever is later) in men.
A woman is considered not to be of childbearing potential if she is postmenopausal, defined by amenorrhea of >= 12 months duration and age >= 45 years, or has undergone hysterectomy and/or bilateral oophorectomy.
The following are considered highly effective forms of contraception:
1) true abstinence; 2) male sterilization (with post-procedure documentation of absence of sperm in the ejaculate). For female patients, the sterilized male partner should be the sole partner.
The following are considered effective forms of contraception:
1) intrauterine device (copper IUD or hormonal IUDs only) or intrauterine system; 2) condom with spermicidal foam/gel/film/cream/suppository;
3) occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.
Males must agree to abstain from sperm donation for at least 5 months after the last dose of DCDT2980S or DCDS4501A or rituximab (whichever is later).

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-06-2013
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mabthera
Generic name:	Rituximab

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nvt
Generic name:	na

Ethics review

Approved WMO Date:	03-01-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	04-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2011-004377-84-NL
CCMO	NL42705.018.12