A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

Published: 10-12-2015
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to determine the safety and efficacy of CTL019 in adults with relapsed or refractory DLBCL and to monitor all patients exposed to CTL019 for 5 years following CTL019 infusion

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

Summary

ID

NL-OMON55408

Source
ToetsingOnline

Brief title
CCTL019C2201 (CART-DLBCL)

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
diffuse large B-cell lymphoma, Gene Therapy

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: NOVARTIS

Intervention

Keyword: DLBCL, Lentiviral, overall response rate, T-Cell Therapy

Outcome measures

Primary outcome

To evaluate the efficacy of CTL019 therapy, defined as overall response rate (ORR), which includes complete response (CR) and partial response (PR) based on Cheson 2007 response criteria modified by Novartis version 1 as determined by a central independent review committee. (Cheson et al 2007)

Secondary outcome

To evaluate the safety of CTL019, time to response (TTR), duration of overall response (DOR), event free survival (EFS), progression free survival (PFS), overall survival (OS), safety and efficacy in histological and molecular subtypes. Characterize the in vivo cellular PK profile (levels, persistence, trafficking) of CTL019 transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid and other tissue if available). Describe the incidence of immunogenicity to CTL019 and describe the presence of Replication competent lentivirus (RCL)

Study description

Background summary

DLBCL is the most frequent lymphoma subtype, representing 30-35% of all non-

Hodgkin lymphomas (NHL). Two-thirds of patients are cured by a combination of chemotherapy agents ± radiotherapy in addition to rituximab, but one-third of patients
have disease that is either refractory to initial therapy or relapses after standard
therapy. Relapsed and refractory patients have a poor prognosis, particularly those who do not respond to 2nd
line chemotherapy. The median survival of patients non-responding to 2nd line chemotherapy is 4 months and. For patients relapsing with
chemotherapy-sensitive disease, high-dose chemotherapy followed by autologous hematopoetic stem cell transplantation (HSCT) provides the best chance
of cure. However due to advanced age and comorbidities, only half of all patients are
eligible for such an intensive approach. Yet, only a modest minority of patients undergoing HSCT are cured. In summary treatment options for patients who do not respond to 2nd line chemotherapy or who relapse after autologous HSCT are generally considered palliative. Novel therapies are urgently needed for this patient
population.
CTL019 is a novel adoptive cancer immunotherapy whereby autologous T cells are genetically
modified/transduced by replication-deficient lentiviral vector (rdLVV) to express anti CD19
antibody based receptors on the surface of T cells (the GMO) to target CD19 antigens on the
surface of malignant B cells (i.e., tumour cells).

Study objective

to determine the safety and efficacy of CTL019 in adults with relapsed or refractory DLBCL and to monitor all patients exposed to CTL019 for 5 years following CTL019 infusion

Study design

Patients will be treated with chemotherapie: Fludarabine and Cyclophosphamide, during this phase autologous T-cells, from afaresis, will be genetically modified. After chemotherapie the modified T-cells are infused. The patient will be monitored for 5 years on regular basis and adverse events will be monitored for 15 years after infusion.

Intervention

Leucopheresis, 3 days chemotherapie (Fludarabine and Cyclophosphamide) and CTL019 infusion

Study burden and risks

Risk: adverse events of the CTL019 treatment after infusiion. Risk of assessments e.g. bone marrow aspirate/biopsy, tumor biopsy and blood draw.

Burden: CTL019 infusion 1 time, possible hospitalization after infusion (d1-d21) (dependant of medical condition), 8 controls in the first 28 days, 15 visites afterwards (m2-m60)

Physical examination: 6 times first 28 days after infusion, from there every month (till m6) and from there every 3 months (m9-m12 and everry 6 months (m18-m60)
Blood tests: every visit, maximal 50 ml per visit, depending on requierd tests: 2-6 tubes
Lymphodepleting chemo: 1 time (2-3 weeks for infusion)
Leukafresis (B2206 protocol): 1 time
CT/MRI: D28 and from there every 3 months
PET-CT: only M3
Beenmerg biopt en of aspiraat: SCR, M3 and when CR occurs
Pregnancy check: every 3 months, testing only at SCR and prior infusion
Tumor biopsy: SCR and M3
Questionaires: Scr, M3, M6, M12, M18 en M24
optional use of remaining blood, bone marrow and tissue for future research

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Written informed consent must be obtained prior to any screening procedures
2) Histologically confirmed DLBCL at last relapse (by central pathology review before enrolment)
3) Relapsed or refractory disease after *2 lines of chemotherapy, including rituximab and anthracycline, and
either having failed autologous HSCT, or being ineligible for or not consenting to autologous HSCT
4) Measurable disease at time of enrollment
5) Life expectancy *12 weeks
6) ECOG performance status that is either 0 or 1 at screening
7) Adequate organ function:
- Renal function defined as: A serum creatinine of *1.5 x ULN OR eGFR * 60 mL/min/1.73 m2
- Liver function defined as:
* ALT * 5 times the ULN for age
* Bilirubin * 2.0 mg/dl with the exception of patients with Gilbert* Meulengracht syndrome; patients with Gilbert-Meulengracht syndrome may be included if their total bilirubin is * 3.0 x ULN and direct bilirubin * 1.5 x ULN . Must have a minimum level of pulmonary reserve defined as * Grade 1 dyspnea and pulse oxygenation > 91% on room air . Hemodynamically stable and LVEF * 45% confirmed by echocardiogram or MUGA .
- Adequate bone marrow reserve without transfusions defined as:
* Absolute neutrophil count (ANC) > 1.000/mm3
* Absolute lymphocyte count (ALC) * 300/mm3
* Platelets * 50.000//mm3
* Hemoglobin > 8.0 mg/dl .
8) Must have an apheresis product of non-mobilized cells accepted for manufacturing .
9) Women of child-bearing potential (defined as all women

physiologically capable of becoming pregnant) and all male participants must agree to use highly effective methods of contraception for at least 12 months
following CD19 CART infusion and untill CAR-T cells are no longer present by PCR on two consecutive tests.

Exclusion criteria

1) Prior treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy
2) Treatment with any prior gene therapy product
3) Active CNS involvement by malignancy
4) Prior allogeneic HSCT
5) Eligible for and concenting to autologus HSCT
6) Chemotherapy other than lymphodepleting chemotherapy within 2 weeks of infusion.
7) Investigational medicinal product within the last 30 days prior to screening
Note: Investigational therapies must not be used at any time while on study until the first
progression following CTL019 infusion.
8) The following medications are excluded:
* Steroids: Therapeutic doses of steroids must be stopped > 72 hours prior to prior to leukapheresis and > 72 hours CTL019 infusion. However, the following physiological
replacement doses of steroids are allowed: <6 * 12 mg/m2/day hydrocortisone or equivalent
* Immunosuppression: Any immunosuppressive medication must be stopped * 2 weeks prior to leukapheresis and * 2 weeks prior to CTL019 infusion.
* Antiproliferative therapies other than lymphodepleting chemotherapy within 2 weeks of leukapheresis and 2 weeks prior to infusion
* Antibody use including anti-CD20 therapy within 4 weeks prior to enrollment or 5 halflives of the respected antibody, whichever is longer
* CNS disease prophylaxis must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate)
9) Prior radiation therapy within 2 weeks of enrollment
10) Active replication of or prior infection with latent hepatitis B or active hepatitis C
11) HIV positive patients
12) Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive * 72 hours prior to infusion)
13) Unstable angina and/or myocardial infarction within 6 months prior to screening
14) Previous or concurrent malignancy with the following exceptions:
* Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to study entry)

* In situ carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to the study
* A primary malignancy which has been completely resected and in complete remission more than 5 years

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):	26-07-2016
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	10-12-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	07-03-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-06-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-06-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-07-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-09-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-10-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-10-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-10-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	14-12-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-01-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-08-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-09-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-04-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-05-2018

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-01-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-05-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	26-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-04-2021
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	23-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2014-003060-20-NL
ClinicalTrials.gov	NCT02445248
CCMO	NL54154.000.15