A Phase II, single arm, multicenter open label trial to determine the safety and efficacy of tisagenlecleucel in pediatric patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma (NHL) (BIANCA)

Published: 29-01-2019
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Primary: To evaluate the efficacy of tisagenlecleucel therapy as measured by overall response rate by investigator assessment.Secondary: Duration of response, event free survival, relapse free survival, overall survival, safety, kinetics,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49158

Source
ToetsingOnline

Brief title
BIANCA - CCTL019C2202

Condition

- Other condition
- Lymphomas non-Hodgkin's B-cell

Synonym
lymphoma, Mature non-Hodgkin Lymphoma

Health condition

Burkitt Leukemie

Research involving

Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V.

Intervention

Keyword: CAR-T Cell therapy, Mature B-Cell Non-Hodgkin Lymphoma, Pediatric and young adults, tisagenlecleucel

Outcome measures

Primary outcome

Overall response rate.

Secondary outcome

Duration of response, event free survival, relapse free survival, overall

survival, adverse events, kinetics, immunogenicity, transplant, cytokine

release syndrome.

Study description

Background summary

Lymphomas most commonly occur during the second decade of life, with a median age at diagnosis of 10 years 8 months, and is rare in infants (*1 percent). The incidence increases with age as lymphomas account for approximately 4, 14, 22, and 25 percent of neoplasms in children 1 to 4, 5 to 9, 10 to 14, and 15 to 19 years of age, respectively.
Non-Hodgkin lymphoma (NHL), a heterogeneous group of lymphoid malignancies, is the fourth most common malignancy diagnosed in children.
In adults, NHL typically presents as a low or intermediate grade disease, however, childhood NHL is usually an aggressive, poorly differentiated,

disseminated disease, often invading extra nodal sites, the bone marrow, and central nervous system in advanced stages. Aggressive mature B-cell NHL consists mainly of Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), and primary mediastinal large B-cell lymphoma (PMBCL).
Newly diagnosed pediatric B-cell NHL patients are cured in the vast majority of cases, with rates approaching 80-90%, with standard available therapies. However, there remains a high unmet medical need for patients with relapsed or refractory mature B-cell NHL, as salvage therapies including hematopoietic stem cell transplant, rituximab-based therapies and intensive chemotherapy regimens, offer limited clinical benefit and no therapies are currently accepted as the standard of care. Outcomes for this patient population are generally poor, with 5 year survival rates approaching 10-30%.
Tisagenlecleucel, marketed as Kymriah in the US, is a treatment which uses the body's own T-cells to fight NHL. T-cells from a person with cancer are removed (leukapheresis), genetically engineered to make a specific T-cell receptor that reacts to the cancer, and transferred back to the person. The T-cells are engineered to target a protein called CD19 that is common on B-cells (both the malignant and the healthy B-cells).
It was invented and initially developed at the University of Pennsylvania. Novartis completed development and obtained FDA approval in 2017 for the indications inadequately responding or relapsed B-cell acute lymphoblastic leukemia in children and young adults and relapsed or refractory diffuse large B-cell lymphoma in adults. It became the first FDA-approved treatment that included a gene therapy step in the US. It is administered in a single treatment.

Study objective

Primary:
To evaluate the efficacy of tisagenlecleucel therapy as measured by overall response rate by investigator assessment.
Secondary: Duration of response, event free survival, relapse free survival, overall survival, safety, kinetics, immunogenicity, % subjects who proceed to transplant, potential predictive models for cytokine release syndrome.

Study design

Single arm, open-label, multi-center, phase II study to determine the efficacy and safety of tisagenlecleucel in pediatric subjects and young adults (up to 25 years) with CD19-positive relapsed or refractory mature B-cell NHL. The study will have the following sequential phases: screening phase, pre-treatment phase, treatment & follow-up phase.
Prior to planned infusion date: lymphodepleting chemotherapy (fludarabine, cyclophosphamide) (unless the subject has a significant cytopenia), see protocol section 6.1.5.2 for details.
Leukapheresis, genetic engineering of T-cells and transfer back to patient

(tisagenlecleucel infusion).
After tisagenlecleucel infusion, efficacy will be assessed at Day 29, then every 3 months for the first year, every 6 months for the second year, then yearly until the end of study.
The study will end when the last subjects has completed the 2nd study year.
A post-study long term follow-up for lentiviral vector safety is planned via a separate protocol.
Approx. 35 subjects enrolled.

Intervention

Treatment with 1 tisagenlecleucel infusion.

Study burden and risks

Risk: Adverse effects of study treatment.
Burden:
Screening 4 weeks, including leukapheresis
Lymphodepleting chemotherapy: fludarabine I.V. and cyclophosphamide I.V. or cytarabine I.V. and etoposide I.V.
Treatment: 1 tisagenlecleucel infusion (premedication: acetaminophen or paracetamol plus antihistaminic).
Study procedures (based on 2 years study duration):
Physical examination: 15.
Blood tests: 17 (5-30 ml).
Bone marrow aspirate: 1.
Lumbar puncture: 1.
Tumor biopsy: 1-2. (in case of Burkitt Leukemia 7)
Pregnancy test (if relevant): 8.
Pulse oximetry: 2.
ECG: 2.
Echocardiography/MUGA: 1.
CT/MRI scan(s): 9.
Tanner staging (up to 18 years of age, up to Tanner stage 5): 4.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

* Males or females 1 up to 25 years of age at the time of screening.
* Mature B-cell non-Hodgkin lymphoma and Burkitt leukemia, see protocol paragraph 5.1 item 2 for details.
* Relapse after one or more prior therapies or primary refractory, see protocol paragraph 5.1 item 3 for details.
* Measurable disease, see protocol Appendix 1 for details.
* Lansky (age < 16 years) or Karnofsky (age * 16 years) performance status * 60%.
* Adequate organ function. See protocol paragraph 5.1 item 7-8 for details

Exclusion criteria

* Any prior anti-CD19 therapy.
* Any prior gene or engineered T cell therapy.
* Allogeneic hematopoietic stem cell transplant (HSCT) <3 months prior to screening and *4 months prior to infusion.
* Presence of grade 2 to 4 acute or extensive chronic graft-versus-host disease in patients who received prior allogenic HSCT.

* Active or prior hepatitis B or C (positive test), positive HIV test. See protocol paragraph 5.2 item 7-8 for details.
* Active neurological autoimmune or inflammatory disorders.
* Active CNS involvement by malignancy.
* Pregnant or lactating women, females of childbearing potential and males not using adequate contraception. See protocol paragraph 5.2 item 16-18 for details.

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):	20-12-2019
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kymriah
Generic name:	tisagenlecleucel
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	RoActemra
Generic name:	tocilizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-01-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-06-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-07-2019
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:	15-10-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	26-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-04-2020
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:	22-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-07-2020
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:	26-01-2021
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:	02-07-2021
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)

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	EUCTR2017-005019-15-NL
ClinicalTrials.gov	NCT03610724
CCMO	NL66860.000.18