Tisagenlecleucel versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: A randomized, open label, phase III trial

Published: 19-12-2018
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This study has been transitioned to CTIS with ID 2023-508343-48-00 check the CTIS register for the current data. To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to delaying the composite event of disease...

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

Summary

ID

NL-OMON56315

Source
ToetsingOnline

Brief title
BELINDA - CCTL019H2301

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Lymphoma, Non-Hodgkin Lymphoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: CART-Cell therapy, Non-Hodgkin lymphoma, tisagenlecleucel

Outcome measures

Primary outcome

Event Free Survival, defined as time from date of randomization to the date of first documented disease progression or stable disease at or after the week 12 (±1 week) assessment, as assessed by blinded independent review committee (BIRC) per Lugano criteria, or death at any time.

Secondary outcome

- Event Free Survival as assessed by local investigator

- Overall Survival: defined as the time from randomization to date of death

- Overall Response Rate: overall response rate as per the Lugano criteria

- Duration of response: time from the date of first documented response of CR or PR to the date of first documented progression (SD or PD at or after the week 12 (±1w) assessment will be considered progression) or death due to aggressive B-cell NHL

- Time to response (TTR): time from the date of randomization to the date of a patient first achieved a response of CR or PR on or after the Week 12 assessment.

- Type, frequency and severity of serious and non-serious adverse events and laboratory abnormalities and discontinuations due to adverse events

- Time to definitive deterioration in SF-36v2, FACT-Lym, and EQ-VAS

- Evaluate efficacy and safety of both treatment arms in histological subgroups (DLBCL, NOS, FL3B, other) and molecular subgroups (e.g., GCB, ABC, other) by Event Free Survival, Overall Survival and AEs.

- To characterize the in vivo cellular kinetics of tisagenlecleucel transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid and other tissues if available), as measured by qPCR summarized by clinical response in patients receiving tisagenlecleucel therapy in
arm A or after crossover: Summary of qPCR detected tisagenlecleucel transgene concentrations in peripheral blood and bone marrow (and other tissue, if available), and cellular kinetic parameters from peripheral blood profile samples by time point and clinical response status

- To characterize the incidence and prevalence of tisagenlecleucel immunogenicity (humoral and cellular) and impact on cellular kinetics, efficacy, and safety in patients receiving tisagenlecleucel therapy in arm A or after crossover : Summary of pre-existing and treatment induced immunogenicity (cellular and humoral) of tisagenlecleucel. Levels of pre-existing and treatment induced immunogenicity. Cellular kinetic parameters, concentrationtime profile by immunogenicity category (positive/negative), and efficacy (Month 3 response)

- To assess presence of Replication Combinant Lentivirus (RCL) in patients receiving tisagenlecleucel in arm A or after corssover: RCL by VSV-qPCR

Study description

Background summary

Non-Hodgkin Lymphomas (NHL) comprise a heterogeneous group of malignancies. Estimated new cases are 72,240 and deaths are 20,140 in the United States (US) for 2017 (Siegel et al 2017). In Europe, for 2012, there were an estimated 93,500 new cases and 37,800 deaths due to NHL (Ferlay et al 2015).

Tisagenlecleucel (CART-19, CTL019) is a second generation CAR-T cell product that uses autologous peripheral blood T cells that have been genetically modified ex vivo to target CD19 on the surface of B cells.

Recent clinical trials of tisagenlecleucel in r/r CLL, r/r ALL, and r/r B-cell lymphomas have shown promising and durable anti-tumor efficacy (Porter et al 2011, Grupp et al 2013, Maude et al 2014, Schuster et al 2017). Consequently, tisagenlecleucel appears to be a therapeutic alternative for patients with B cell malignancies (including DLBCL) refractory to the current therapies.

Study objective

This study has been transitioned to CTIS with ID 2023-508343-48-00 check the CTIS register for the current data.

To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to delaying the composite event of disease progression / stable disease at or after the week 12 assessment; or death at any time.

Study design

This is a randomized, open label, multicenter phase III trial comparing the efficacy, safety, and tolerability of tisagenlecleucel treatment strategy to SOC treatment strategy in adult patients with aggressive B-cell NHL after failure of rituximab and anthracycline containing first line immunochemotherapy. Failure of frontline therapy is defined as refractoriness (lack of response or progression during therapy) or relapse/progression within 365 days of last dose of first line therapy (in patients who achieved CR on first line therapy). Screened patients may undergo non-mobilized leukapheresis for autologous T cell collection after obtaining informed consent (unless historical product is to be used). There is a cross-over possibillity to arm A for patients in arm B who have a Stable or Progressive disease response at or after week 12.

Intervention

Patients in Arm A receive tisagenlecleucel, and patients in Arm B are treated according to Standard of Care. The physicians can choose between the following treatments: R-ICE, R-DHAP, R-GDP, R-GemOx.

For patients randomized to Arm B (SOC therapy), a change in immunochemotherapy is required if the patient achieves a response which is not sufficientto allow HSCT, and change in treatment is in the best interest of the patient. Investigators should choose one of the four regimens above in an effort to achieve a response that allows the patient to proceed to transplant. Patients who are deemed no longer eligible for HSCT (e.g. adverse event, poor tolerance to immunochemotherapy, worsening of performance status) after two cycles of immunochemotherapy may proceed to treatment with ibrutinib or lenalidomide.

Subjects with Complete Response (CR) or Partial Response (PR) after the 2 cycles (SOC 1) of salvage therapy and adequate stem cell collection may receive an optional 3rd cycle of salvage therapy before transplant, or may proceed directly to transplant after 2 cycles. At the investigator*s discretion, patients in PR may change to one of the other 4 regimens. Every effort should be attempted to have SOC patients proceed to transplant, if deemed in the best interest of the patient. Patients should receive high dose chemotherapy approximately 4-6 weeks after the last cycle of salvage therapy.

Study burden and risks

Risks: Side effects may occur after tisagenlecleucel infusion, after the leukapheresis procedure, chemotherapy, autologues stemcell therapy, chemotherapy to reduce lymphocytes, and after examination procedures such as bone marrow puncture, PET-CT scan, MUGA, blood collection, tumor biopsy, and lumbar puncture.

Burden Arm A: Leukapheresis, possible bridging chemotherapy, chemotherapy to increase lymphocytes, single infusion of tisagenlecleucel, possible hospitalization D1 - D21 (depending on medical condition), 8 controls in the first 28 days after tisagenlecleucel infusion, and 12 visits thereafter.
Physical examination: 12x
Blood test: average blooddraw of 45ml, maximum 67.5 ml per visit.
Chemo to reduce lymphocytes in the patient: 1 time (3 to 7 days prior to infusion tisagenlecleucel)
CT / MRI: month 9, month 12, month 18, month 24, month 36, month 48, month 60.
CT / MRI brain: if clinically indicated
PET-CT: screening, week 6, week 12 and month 6
MUGA / Echo: screening and and if clinically indicated
ECG: screening, day of tisagenlecleucel infusion and if clinically indicated
Bone marrow biopsy: randomization, week 8, month 4 and afterwards if a complete response is achieved and the disease is in the bone marrow
Lumbar puncture: screening and then if clinically indicated
Tumor biopsy: screening, week 12 and afterwards if clinically indicated

Questionnaires: 13x
Optional use of body material (blood and tissues) and anonymous data for future research.

Burden Arm B: Leukapheresis, standard of care chemotherapy, patients who respond receive a high dose of chemotherapy, followed by a stem cell transplant (if this is in the best interest of the patient), 16 hospital visits in total.
Physical examination: 20x
Blood test: average 45 ml, maximum 67.5 ml per visit.
CT / MRI: month 9, month 12, month 18, month 24, month 36, month 48, month 60.
CT / MRI brain: if clinically indicated
PET-CT: screening, week 6 week 12 and month 6
MUGA / Echo: screening, thereafter as clinically indicated and at crossover visit
ECG: screening, thereafter as clinically indicated and at crossover visit
Bone marrow biopsy: screening and afterwards if a complete response is achieved and the disease is in the bone marrow
Lumbar puncture: screening and then if clinically indicated
Tumor biopsy: screening
Questionnaires: 12x
Optional use of body material (blood and tissues) and anonymous data for future research.

Contacts

Public
Novartis

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Scientific
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Histologically confirmed (by local histopathological assessment), aggressive B-cell NHL at relapse/progression or PR after front line therapy.
2. Relapse or progression within 365 days from last dose of anti-CD20 antibody and anthracycline containing first line immunochemotherapy or refractory (have not achieved a CR).
3. Patient is considered eligible for autologous stem cell transplant (HSCT) as per local investigator assessment.
4. Disease that is both active on PET scan (defined as Deauville score of 4 or 5) and measurable on CT scan, defined as:
a. Nodal lesions: >15 mm in the long axis, regardless of the length of the short axis, and/or
b. Extranodal lesions: >10 mm in long AND short axis
5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
6. Adequate organ functions
7. Must have a leukapheresis material of non-mobilized cells available for manufacturing of tisagenlecleucel.

Exclusion criteria

1. Prior treatment with anti-CD19 therapy, adoptive T cell therapy or any prior gene therapy product
2. Treatment with any systemic lymphoma-directed second line anticancer therapy prior to randomization. Only steroids and local irradiation are permitted for disease control.
3. Active central nervous system (CNS) involvement by disease under study are excluded, except if the CNS involvement has been effectively treated and local treatment was >4 weeks before randomization
4. Prior allogeneic HSCT
5. Clinically significant active infection
6. Any cardiovascular conditions (see page 31 of the protocol for specifications)
7. Patients with active neurological autoimmune or inflammatory disorders (e.g.,

Guillain-Barré Syndrome (GBS), Amyotrophic Lateral Sclerosis (ALS)) and clinically significant
active cerebrovascular disorders (e.g., cerebral edema, posterior reversible encephalopathy
syndrome (PRES))

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-11-2019
Enrollment:	12
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:	19-12-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-08-2019
Application type:	First submission
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:	20-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-03-2020
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:	16-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-05-2020
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:	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:	10-02-2021
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:	01-03-2021
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)
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)
Approved WMO Date:	08-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	13-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-10-2023
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
EU-CTR	CTIS2023-508343-48-00
EudraCT	EUCTR2016-002966-29-NL
CCMO	NL66861.000.18