A pivotal Phase II randomised, multi-centre, open-label study to evaluate the efficacy and safety of MB-CART2019.1 compared to standard of care therapy in participants with relapsed/refractory diffuse large B-cell lymphoma (R-R DLBCL), who are not eligible for high-dose chemotherapy and autologous stem cell transplantation

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This study has been transitioned to CTIS with ID 2023-506270-13-00 check the CTIS register for the current data. The primary objective is to determine superiority of MB CART2019.1 treatment compared to standard-of-care (SoC) therapy with R GemOx (...

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

Summary

ID

NL-OMON54269

Source
ToetsingOnline

Brief title
M-2020-371 (3304/0008); DALY 2-EU

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Lymph node cancer; B-cell Non Hodgkin's lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Miltenyi Biomedicine GmbH
Source(s) of monetary or material Support: the study sponsor as listed in B6/7

Intervention

Keyword: B-Non Hodgkin's Lymphoma (B-NHL), CAR-T, Genetically Modified Organism (GMO)

Outcome measures

Primary outcome

Event-free survival (EFS), defined as the time between the date of

randomisation and the date of objective disease progression, failure to

achieve partial response (PR) or CR at or beyond Week 8 after randomisation

leading to a new anti-lymphoma therapy or death of any cause, whichever occurs

first, based on Independent Review Committee (IRC) assessment.

Secondary outcome

Secondary Endpoints:

Key Efficacy Endpoints:

1. Progression-free survival (PFS), defined as the time between the date of

randomisation and the date of objective disease progression or death of any

cause, whichever occurs first, based on IRC assessment.

2. Best complete response rate (BCRR), defined as the proportion of

participants with at least one complete response (CR) assessment until Week 24 in the MB-CART2019.1 arm and Week 26 in the comparator arm based on IRC assessment.

3. Duration of complete response (DOCR), defined as the time between the date of a first CR and the date of assessment of objective disease progression or the date of death of any cause, whichever occurs first, based on IRC assessment.

4. Overall survival (OS), defined as time between the date of randomisation and the date of death of any cause.

Other Secondary Endpoints:

• PFS rates at 6 and at 12 months based on investigator assessment and based on IRC assessment.

• PFS based on investigator assessment.

• EFS based on investigator assessment.

• EFS rates at 6 and at 12 months based on investigator assessment and based on IRC assessment.

• Time to new anti-lymphoma therapy defined as the time between the date of randomisation and the date of the event (start of new anti-lymphoma therapy or death of any cause).

• BCRR, defined as the proportion of participants with at least one CR assessment until Week 24 in the MB-CART2019.1 arm and Week 26 in the comparator arm based on investigator assessment.

• BCRR until Week 48 in the MB-CART2019.1 arm and Week 50 in the comparator arm based on investigator assessment and based on IRC assessment.

• Modified BCRR (mBCRR), defined as the proportion of participants with at

least one CR assessment without symptoms (B symptoms, symptomatic splenomegaly, symptomatic hepatomegaly, symptomatic lymphadenopathy and infections) at the time of this CR based on investigator assessment and based on IRC assessment.

• DOCR, defined as the time between the date of a first CR and the date of assessment of objective disease progression or the date of death of any cause, whichever occurs first, based on investigator assessment.

• Duration of response (DOR), defined as the time between the date of a first objective response (CR/partial response [PR]) and the date of assessment of objective disease progression or the date of death of any cause, whichever occurs first based on investigator assessment and based on IRC assessment.

• Time to objective response (TTR), defined as the time between the date of randomisation and the date of a first objective response (CR/PR) based on investigator assessment and based on IRC assessment.

• Time to complete response (TTCR), defined as the time between the date of randomisation and the date of a first objective CR based on investigator assessment and based on IRC assessment.

• Time to modified complete response (TTmCR), defined as the time between the date of randomisation and the date of a first objective CR without symptoms (B symptoms, symptomatic splenomegaly, symptomatic hepatomegaly, symptomatic lymphadenopathy and infections) at the time of this CR based on investigator assessment and based on IRC assessment.

• Objective response rate (ORR), defined as the proportion of participants with either a CR or PR based on investigator and based on IRC assessment.

• Complete response rate (CRR), defined as the proportion of participants with

a CR based on investigator assessment and based on IRC assessment.

• Best objective response (BOR), defined as the best objective response in the time between the date of randomisation and the date of objective disease progression, the start of new anti-lymphoma therapy or the date of death from any cause, whichever occurs first based on investigator assessment and based on IRC assessment.

• Change in B symptoms (recurrent, unexplained fever > 38 °C without signs of infection, drenching night sweats without signs of infection and/or unintentional weight loss >= 10% within the preceding 6 months) defined as the proportion of participants with B symptoms at baseline and with changes in B symptoms from baseline at any time following randomisation.

• Changes in HRQoL.

• Changes in lymphoma symptoms.

Only for participants treated with MB-CART2019.1:

• Persistence of MB-CART2019.1 and phenotype and immune cell compositions based on flow cytometry analyses and real time quantitative polymerase chain reaction (qPCR).

• Types and levels of cytokines (including sIL-2R, IL 6, IL-10, IL-15, IFN and TNF).

• Anti-MB-CART2019.1 antibody.

Safety Endpoints:

• Type, frequency and severity of adverse events (AEs), serious adverse events

(SAEs) and adverse events of special interest (AESIs).

• Hospital days within 7 months after randomisation.

• Intensive care unit (ICU) admission days within 7 months after randomisation.

• Use of tocilizumab and/or high-dose steroids.

• Need for transfusions, prophylactic antimicrobial therapy and gamma globulin substitution within 12 months after randomisation.

FOR EXPLORATORY ENDPOINTS PLEASE REFER TO THE STUDY PROTOCOL

Study description

Background summary

MB CART2019.1 is designed to effectively target malignant B cells in patients suffering from late stage haematological B cell malignancies. MB CART2019.1 consists of autologous cluster of differentiation CD20/CD19 chimeric antigen receptor (CAR) transduced CD4/CD8 enriched T cells, derived from a leukapheresis and processed by using the CliniMACS Prodigy® device. The CliniMACS Prodigy® performs all manufacturing steps in a single automated and functionally closed system. The CD20/CD19 CAR transduced T cells (MB CART2019.1) are to be administered for the treatment of relapsed/refractory (R R) CD19 and CD20 expressing B cell non Hodgkin lymphoma (B NHL).
CARs have been generated against many cell surface molecules, including CD19, CD20, CD22, human epidermal growth factor receptor 2, GD2, prostate specific membrane antigen and mesothelin, and many of them are presently under evaluation in over 370 Phase I or II clinical studies (https://ClinicalTrials.gov/29.Sep.2020). To date, the most promising clinical outcomes of this technology have been reported in patients treated with autologous CAR transduced T cells targeting CD19. The first complete responses (CR) to CAR T cell therapy were seen in participants with chronic lymphocytic leukaemia (CLL). In pilot clinical studies, CAR T cells expressing second generation CARs against CD19 produced durable remissions even in participants with bulky lymphomas. Subsequent Phase I/II studies in children and adults with relapsed and highly refractory acute lymphoblastic leukaemia (ALL) resulted in high proportions of complete, mostly molecular remissions across 4 institutions, with follow up periods of up to 2 years reported. CAR-engineered autologous and allogeneic T cells expanded and persisted in vivo and had

anti-leukaemic efficacy even in participants with large refractory leukaemia burdens. Recently published results of Phase I/II studies in participants with large B-cell lymphoma demonstrate best objective response (BOR) rates ranging between 52% and 82% with a median progression free survival (PFS) ranging between 3 and 5.9 months for all participants, whereas PFS for complete responders was not reached. Grade 3 or worse cytokine release syndrome (CRS) occurred in 11% to 22% and Grade 3 or worse neurologic events in 12% to 32% of participants.
T cells transduced with a CAR directed against CD20 have also been used for treatment of individuals with B-cell malignancies. In one Phase I study, 3 of 4 participants received CD20 CAR T cell infusions: 2 participants had no evaluable disease after the treatment and remained progression free for 12 and 24 months, respectively; the third participant had an objective partial remission at 6 months and relapsed at 12 months after infusions. CD20 CAR T cells were detected by real time quantitative polymerase chain reaction (qPCR) at tumour sites and up to 1 year in peripheral blood, albeit at low levels. No evidence of host immune responses against infused cells was detected.
In another clinical study programme, CD20 CAR T cells were administered to participants with resistant or chemotherapy refractory advanced diffuse large B cell lymphoma (DLBCL) in a Phase I study and subsequently in a Phase IIa study. The overall objective response rate (ORR) after 4 to 6 weeks in the latter study was 9/11 (81.8%) participants with a median PFS of 6 months; no severe toxicity was observed.
There was one ongoing study with a product consisting of CD20/19 CAR T cells, conducted at the Medical College of Wisconsin, using the same lentiviral vector and a nearly identical manufacturing process as used in all Miltenyi sponsored studies (ClinicalTrials.gov Identifier: NCT03019055). First data have already been published showing that 13/19 (68%) participants had a CR on Day 28. Participants receiving fresh CAR T cells showed a numerical higher clinical response rate (79%) than participants receiving cryopreserved CAR T cells (40%). A Phase I/II safety, dose-finding and feasibility study of MB CART2019.1 in participants with R R B-NHL clinical study is currently ongoing.

Indication
Haematological malignancies include a diverse group of lymphomas and leukaemia that arise in cells of the immune and lymphatic systems. Aggressive B NHL are rare diseases sharing a cell origin from the B cell lineage expressing B lineage markers such as CD19, CD20 and CD22. According to the World Health Organization (WHO) classification 2008 and its revision 2016, B NHL include among others DLBCL, Burkitt lymphoma, mantle cell lymphoma and follicular lymphoma, as well as CLL/SLL (chronic lymphocytic leukaemia/ small lymphocytic lymphoma). Despite a high cure rate, a small subset of patients does not respond to first line chemotherapy or relapse. Among patients with DLBCL - the most common aggressive B NHL in adults - which are refractory to second line chemotherapy, current salvage therapies are mostly ineffective; in patients progressing after autologous stem cell transplantation (ASCT) or allogeneic SCT, median overall survival (OS) is < 10%. Thus, there is a strong need for

alternative treatment options for patients with chemotherapy refractory and relapsed aggressive B-NHL, not eligible for high-dose therapy/ASCT. Although there has been a decline in the national trends in cancer death rates in lymphoma and leukaemia from 2011 to 2015, an estimated 74,200 new cases of NHL occurred in 2019, with 19,970 deaths due to this disease. Patients failing first line therapy or relapsing post first line therapy who are not eligible to receive a high dose chemotherapy (HDC) followed by an ASCT have a dismal prognosis due to lack of effective treatments. This study is specifically designed to address this unmet medical need.

Study objective

This study has been transitioned to CTIS with ID 2023-506270-13-00 check the CTIS register for the current data.

The primary objective is to determine superiority of MB CART2019.1 treatment compared to standard-of-care (SoC) therapy with R GemOx (rituximab, gemcitabine and oxaliplatin) with respect to event-free survival in second line therapy in participants with R R DLBCL, who are non eligible for high dose chemotherapy and autologous stem cell transplantation (ASCT).

Secondary Objectives:
• To evaluate the efficacy of MB CART2019.1 compared to SoC therapy.
• To evaluate the safety and toxicity of MB CART2019.1 compared to SoC therapy.
• To evaluate changes in health-related quality of life (HRQoL) and lymphoma symptoms of participants receiving MB CART2019.1 compared to SoC therapy.
• To evaluate the humoral immunogenicity against MB CART2019.1.

FOR EXPLORATORY OBEJCTIVES PLEASE REFER TO THE STUDY PROTOCOL

Study design

This is a pivotal Phase II randomised, open label, multi-centre study evaluating the efficacy and safety of MB CART2019.1 versus SoC therapy in participants with R R DLBCL, who are non eligible for high dose chemotherapy (HDC) and ASCT. Adult participants with R R DLBCL after first line therapy will be randomised in a 1:1 ratio to receive MB CART2019.1 or SoC therapy as comparator. The comparator treatment is either a combination of rituximab, gemcitabine and oxaliplatin (R GemOx) or a combination of bendamustine and rituximab (BR) plus polatuzumab vedotin (Polivy®), with the latter accounting for up to 10% of participants in the comparator arm.

Intervention

Single infusion of 2.5 × 106 CAR transduced autologous T cells per kg/body

weight (BW) (with a maximum dose equivalent to 100 kg for participants with a body weight > 100 kg). The Investigational medicinal product (IMP) will be administered over a period of approx. 15 minutes (slow intravenous [i.v.] infusion via a large peripheral vein or central line). The IMP is only to be administered after a lymphodepleting chemotherapy with fludarabine and cyclophosphamide.

Comparators:
The participants will receive 8 cycles of 14 days each of R GemOx per i.v. administration.
The participants will receive 6 cycles of 21 days each of BR plus polatuzumab vedotin per i.v. administration.

Study burden and risks

Clinical results for the use of CD19 and CD20 CAR-transduced T cells have been published. Therefore, all risks and benefits are estimated based on those data and extrapolated to the use of this new CD20/CD19 CAR construct where only limited data, mainly related to preclinical work, is available. CAR T-cell administration carries substantial well-known risks that have to be weighed against the risk of the malignancy as well as the consideration of other treatment options. Based on the evaluations of risks and potential benefits and bearing in mind that the participant population eligible for these studies has already received approved and available treatment without success, the benefit-risk ratio outweighs the above-mentioned potential risks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Histologically proven DLBCL and associated subtypes, according to the World Health Organisation (WHO) 2016 classification.
2. Relapsed or refractory disease after first line chemoimmunotherapy.
3. Participants must have received adequate first-line therapy containing at least the combination of an anthracycline based regimen and rituximab (anti CD20 monoclonal antibody). Local therapies (e.g. radiotherapies) will not be considered as line of therapy if performed during the same line of treatment.
4. Archival paraffin-embedded tumour tissue acquired <= 2 years (preferred: <= 2 months) prior to screening for the central pathology review to confirm DLBCL diagnosis must be made available for participation in this study. If archival paraffin-embedded tumour tissue is not available, fresh tumour tissue sample (preferred) or core-needle biopsy must be made available for the central pathology review.
5. Participants deemed ineligible to receive HDC followed by ASCT
6. Age >= 18 years.
7. Measurable disease according to Lugano criteria. The lesion must be measurable (nodes > 1.5 cm in the long axis; extranodal lesions > 1 cm in the long axis) and positive on a positron emission tomography scan.
8. Estimated life expectancy of > 3 months for other reasons than the primary disease.
9. Women of childbearing potential (WOCBP) must agree to use highly effective contraceptive measures.
Men with non-pregnant WOCBP partners must agree to use highly effective contraceptive measures
10. In the opinion of the investigator, the participant must be able to comply with all study-related procedures, medication use and evaluations.
11. Mental capacity and legal ability to consent to participation in the clinical study.

FOR FULL LIST OF INCLUSION CRITERIA PLEASE REFER TO THE STUDY PROTOCOL

Exclusion criteria

1. Contraindications for R-GemOx, BR plus polatuzumab vedotin, cyclophosphamide and fludarabine as judged by the treating physician.
2. Prior chimeric antigen receptor therapy or other genetically modified T-cell therapy.
3. Participants who have received more than one line of treatment for DLBCL or associated subtypes.
4. Prior haematopoietic stem cell transplantation (HSCT; as first-line consolidation) < 3 months at the time of leukapheresis.
5. ECOG performance status > 2.
6. Absolute neutrophil count < 1,000/µL (unless secondary to bone marrow involvement by DLBCL as demonstrated by bone marrow biopsy).
7. Platelet count < 50,000/µL (unless secondary to bone marrow involvement by DLBCL as demonstrated by bone marrow biopsy).
8. Absolute lymphocyte count < 100/µL.
9. Participants who have central nervous system (CNS) lymphoma involvement in present or past medical history.
10. Participants with the requirement for urgent therapy due to tumour mass effects.

FOR FULL LIST OF EXCLUSION CRITERIA PLEASE REFER TO THE STUDY PROTOCOL

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-07-2021
Enrollment:	30
Type:	Anticipated

Ethics review

Approved WMO Date:	04-03-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-10-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	08-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-07-2023
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	CTIS2023-506270-13-00
EudraCT	EUCTR2020-003908-14-NL
CCMO	NL76282.000.21