A global randomized multicenter Phase 3 trial to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell non-Hodgkin lymphomas (TRANSFORM)

Published: 09-05-2018
Last updated: 10-01-2025

Primary Objective:To compare the efficacy in subjects treated with JCAR017 versus subjects treated according to standard of care (SOC) defined as event-free survival (EFS) Key Secondary Objectives:To compare additional parameters of efficacy in...

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

Summary

ID

NL-OMON52699

Source
ToetsingOnline

Brief title
0451-0311
JCAR017-BCM-003
Transform

Condition

- Lymphomas non-Hodgkin's B-cell
- Lymphomas non-Hodgkin's unspecified histology

Synonym
Aggressive Non-Hodgkin B-Cell Lymphoma, fast growing B-cell cancer of the lymph nodes

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: The study sponsor as listed in question B6/B7

Intervention

Keyword: B-Cell Non-Hodgkin Lymphoma, CAR-T, Phase 3

Outcome measures

Primary outcome

Efficacy

* Event-free survival (EFS)

The time from randomization to death from any cause, progressive disease (PD),

failure to achieve complete response (CR) or partial response (PR) by 9 weeks

post-randomization, or start of new antineoplastic therapy due to efficacy

concerns, whichever occurs first.

Secondary outcome

Key secondary endpoints:

Efficacy

• Complete response rate (CRR), defined as the proportion of subjects achieving

a CR from randomization up to 3 years post-randomization. Subjects with unknown

or missing response will be counted as non-responders in the analysis. Any

responses after a start of a new antineoplastic therapy will not be considered.

Responses after cross over will be analyzed descriptively;

• Progression-free survival (PFS), defined as the time from randomization to PD

or death from any cause, whichever occurs first;

• Overall survival (OS), defined as the time from randomization to death due to

any cause.

For the other Secondary and Exploratory endpoints please refer to the section 2

from the protocol.

Study description

Background summary

Disease Background
Non-Hodgkin lymphomas (NHLs) comprise a heterogeneous group of malignancies. Within Europe, the incidence of NHL is approximately 49,533 new cases annually with 20,347 deaths per year.

In the United States (US), it is estimated that approximately 72,580 new cases of NHL will be diagnosed and approximately 20,150 subjects will die of their disease per year.

Diffuse large B-cell lymphoma is the most frequent lymphoma subtype, representing approximately 30% of all NHL.
Diffuse large B-cell lymphoma is a heterogeneous disease with several histological and molecular subtypes. The largest subgroup is DLBCL.
Despite follicular lymphoma being an indolent lymphoma type, follicular lymphoma Grade 3B is regarded as an aggressive lymphoma. Clinical behavior is very similar to DLBCL, and follicular lymphoma frequently undergoes histological transformation into DLBCL.
Despite overall improvement in outcomes of DLBCL, approximately one-third of

subjects do not respond to initial therapy or will relapse (relapsed/refractory [R/R] disease) that remains a major cause of mortality.

Compound Background: CD19 as a Therapeutic Target
CD19 is a 95-kDa glycoprotein present on B-cells from early development until differentiation into plasma cells. It is a member of the immunoglobulin superfamily and a component of a B-cell surface signal transduction complex that positively regulates signal transduction through the B-cell receptor.

CD19 is an attractive therapeutic target because it is expressed by most B-cell malignancies, including B-cell NHL. Importantly, the CD19 antigen is not expressed on hematopoietic stem cells or on any normal tissue apart from those of the B-cell lineage.

JCAR017 Investigational Drug Product
The final JCAR017 investigational drug product (also known as lisocabtagene maraleucel or liso-cel) includes two individually formulated CD4+CAR+ and CD8+ CAR+ frozen T cell suspensions in media containing dimethyl sulfoxide (DMSO) that are thawed and infused separately. JCAR017 is administered by intravenous (IV) infusion.

The CD19-specific CAR and truncated human epidermal growth factor receptor (EGFRt) are introduced into autologous CD8+ and CD4+ T cells ex vivo using a replication-incompetent, self inactivating lentiviral vector. The CD19-specific CAR includes an scFv binding domain derived from a murine CD19-specific monoclonal antibody (mAb; FMC63) and 4-1BB and CD3* chain signaling domains. The EGFRt protein is expressed as a separate cell surface protein for purposes of cell tracking.

Please refer to the Investigator*s Brochure for detailed information concerning the available pharmacology, toxicology, clinical studies, and adverse event profile of the investigational product (IP).

Study objective

Primary Objective:
To compare the efficacy in subjects treated with JCAR017 versus subjects treated according to standard of care (SOC) defined as event-free survival (EFS)

Key Secondary Objectives:
To compare additional parameters of efficacy in subjects treated with JCAR017 versus subjects treated according to SOC defined as complete response rate (CRR), progression-free survival (PFS), and overall survival (OS)

Secondary Objectives:
• To compare other parameters of efficacy, defined as duration of response

(DoR), overall response rate (ORR), and PFS on next line of treatment (PFS-2)
• To compare efficacy rates (EFS, PFS, OS) at 6, 12, 24 and 36 months after randomization
• To compare safety defined as type and frequency of adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities
• To compare the safety and efficacy in clinical, histological and molecular subgroups
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For other secondary objectives please refer to the protocol.

Study design

This is a randomized, open-label, parallel-group, multi-center, Phase 3 study to demonstrate the efficacy and safety of JCAR017 (also known as lisocabtagene maraleucel or liso-cel) versus SOC salvage therapies in subjects with aggressive B-cell NHL (defined as diffuse large B-cell lymphoma [DLBCL] not otherwise specified [NOS], de novo or transformed indolent NHL), high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double-hit lymphoma/ triple-hit lymphoma [DHL/THL]), primary mediastinal (thymic) large B-cell lymphoma [PMBCL], T cell/histiocyte-rich large B-cell lymphoma [THRBCL] or follicular lymphoma Grade 3B [FL3B]) who are refractory to front-line immunochemotherapy or have relapsed within 12 months and are eligible for HDCT and HSCT. The time of relapse is calculated from the date of the first disease assessment confirming a complete response (CR) obtained with first-line treatment for disease under study, to the date of first assessment demonstrating a relapse.

During screening, a tumor biopsy will be collected for central confirmation of diagnosis.

During screening, all subjects will undergo an unstimulated leukapheresis to enable JCAR017 product generation.

Subjects will be randomized to receive either:
• Arm A (SOC): three cycles of SOC salvage therapy. Responding subjects are expected to proceed to HDCT and HSCT
• Arm B (JCAR017): lymphodepleting (LD) chemotherapy followed by JCAR017 infusion

Subjects in Arm B may receive bridging therapy with a protocol-defined SOC regimen to stabilize their disease during JCAR017 manufacturing. Investigational therapies are not allowed.

Subjects will be followed for safety and efficacy for up to 3 years under this protocol.

If requested by the investigator, subjects in Arm A may be allowed to receive JCAR017 upon central confirmation of one of the following criteria:
• Failure to achieve CR or PR by 9 weeks post-randomization (after 3 cycles of SOC)
• Progression at any time
• Need to start a new antineoplastic therapy due to efficacy concerns after 18 weeks post-randomization

Subjects who cross over to JCAR017 will be followed in the study for up to 1 year after the JCAR017 infusion. All subjects who received JCAR017 will continue to be monitored for long-term safety and efficacy after exposure to gene-modified T cells under a separate long-term follow-up (LTFU) protocol for up to 15 years after JCAR017 infusion, as per competent authority guidelines.

The conduct of the study will be overseen by a scientific steering committee (SSC).

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Intervention

Standard of care chemotherapy (Arm A) or experimental therapy (Arm B)

Arm B:

LD chemotherapy with intravenous (IV) fludarabine (30 mg/m2/day for 3 days) plus cyclophosphamide IV (300 mg/m2/day for 3 days) (flu/cy) concurrently followed at least 2 days later by JCAR017 infusion (100 x 10(to 6) chimeric antigen receptor [CAR]+ T cells)

Study burden and risks

Participation in the study will involve risks from the study procedures, from treatment with lymphodepleting chemotherapy and from treatment with JCAR017. The two most significant side effects that have been observed to occur with genetically modified T cells in previous studies are cytokine release syndrome (CRS) and neurologic toxicity.
Participation in the study also means additional time from participants (up to 24 hospital visits), additional or longer hospital stays up to 14 days, additional tests and instructions to be followed.

Although, the risks are significant for the participating subjects, they are acceptable when balanced against the anticipated efficacy of JCAR017 in this disease population provided that there is meticulous clinical management.

JCAR017 offers substantial potential clinical activity to patients with relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL). Current clinical data demonstrated that the remission rate for relapsed DLBCL subjects treated with JCAR017 is significantly improved compared to historical data. Therefore, JCAR017 may provide an opportunity to increase the rates and duration of remissions thereby potentially extending survival for a population with historically dismal clinical outcomes. Currently available treatments for relapsed or refractory DLBCL have limited activity. The prognosis is poor, especially for subjects having relapsed after multi-agent salvage chemotherapy and ASCT, or are ineligible to transplant.

Despite recent advances in the treatment of B-cell malignancies, many patients relapse or have refractory disease and remain incurable with current treatment options. Novel therapies are therefore urgently needed.

In conclusion, the current benefit-risk profile for JCAR017 after administration of the lymphodepleting chemotherapy is considered acceptable in the proposed clinical study given the potential for a durable remission, the overall manageable safety profile, and the plan for risk mitigation of potential safety concerns associated with JCAR017 administration, including routine trial safety surveillance practices.

Contacts

Public
Celgene Corporation

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US
Scientific
Celgene Corporation

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects must satisfy the following criteria to be enrolled in the study:
1. Subject is >= 18 years and <= 75 years of age at the time of signing the informed consent form (ICF).
2. ECOG performance status <= 1.
3. Histologically proven diffuse large B-cell lymphoma (DLBCL) NOS (de novo or transformed indolent NHL), high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple-hit lymphoma [DHL/THL]), primary mediastinal (thymic) large B-cell lymphoma (PMBCL), T cell/histiocyte-rich large B-cell lymphoma (THRBCL) or follicular lymphoma grade 3B (FL3B). Enough tumor material must be available for confirmation by central pathology.
4. Refractory (SD, PD, PR or CR with relapse before 3 months) or relapsed (CR with relapse on or after 3 months) within 12 months from CD20 antibody and anthracycline containing first-line therapy.
5. [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET) positive lesion per Lugano criteria at screening (Deauville score 4 or 5_
6. Adequate organ function
7. Participants must agree to use effective contraception

Please refer to protocol for full inclusion criteria.

Exclusion criteria

1. Subjects not eligible for hematopoietic stem cell transplantation (HSCT).
2. Subjects planned to undergo allogeneic stem cell transplantation.
3. Subjects with primary cutaneous large B-cell lymphoma, EBV (Epstein-Barr virus) positive DLBCL of the elderly and Burkitt lymphoma or transformation from chronic lymphocytic leukemia/small lymphocytic lymphoma (Richter transformation)..
4. Subjects with prior history of malignancies, other than aggressive R/R NHL, unless the subject has been free of the disease for >= 2 years with the exception of the following non-invasive malignancies:
=Basal cell carcinoma of the skin
=Squamous cell carcinoma of the skin
=Carcinoma in situ of the cervix

=Carcinoma in situ of the breast
=Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative.
=Other completely resected stage 1 solid tumor with low risk for recurrence
5. Treatment with any prior gene therapy product.
6. Subjects who have received previous CD19-targeted therapy.
7. Subjects with active hepatitis B, or active hepatitis C are excluded. Subjects with negative polymerase chain reaction (PCR) assay for viral load for hepatitis B or C are permitted. Subjects positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody with negative viral load are eligible and should be considered for prophylactic antiviral therapy. Subjects with a history of or active human immunodeficiency virus (HIV) are excluded.
8. Subjects with uncontrolled systemic fungal, bacterial, viral or other infection (including tuberculosis) despite appropriate antibiotics or other treatment.
9. Active autoimmune disease requiring immunosuppressive therapy.
10. History of any one of the following cardiovascular conditions within the past 6 months prior to signing the ICF: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease.
11. History or presence of clinically relevant central nervous system (CNS) pathology
12. Pregnant or nursing (lactating) women.

Please refer to protocol for full exclusion criteria.

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:	Completed
Start date (anticipated):	22-06-2020
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	09-05-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-01-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-08-2019

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	25-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-01-2022
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-04-2022
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:	05-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	15-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-12-2023
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
EudraCT	EUCTR2018-000929-32-NL
ClinicalTrials.gov	NCT03575351
CCMO	NL65765.000.18

Study results

Date completed:	23-10-2023

Results posted:	06-11-2024
Actual enrolment:	6

First publication
01-01-1900