Trial to Determine the Efficacy and Safety of JCAR017 in Adult Subjects With Aggressive B-Cell Non-Hodgkin Lymphoma

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT03484702	RECRUITING	APRIL 2, 2018	JUNE 22, 2020

STUDY DESCRIPTION

Brief Summary

This open-label Phase 2 study will evaluate the safety and efficacy of modified T cells (JCAR017) administered to adult patients with aggressive B-cell non-Hodgkin lymphoma (NHL). The study will also help determine how long the modified T cells stay in the patient's body. Furthermore, changes in the patient's quality of life will be described. Phase 2 (autologous T cells expressing anti-CD19 chimeric antigen receptor) (DLBCL NOS [de novo or tFL], follicular lymphoma Grade 3B [FL3B], high grade B-cell Lymphoma [HGBL] and primary central nervous system lymphoma [PCNSL]).

Condition or Disease: Lymphoma, Non-Hodgkin

Intervention/treatment: Drug: JCAR017

Phase: Phase 2

DETAILED DESCRIPTION

This is a single-arm, multi-cohort, multi-center, Phase 2 study to determine the efficacy and safety of JCAR017 in adult patients with aggressive B-cell NHL. The study will enroll patients in Europe and Japan with diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS; de novo or transformed follicular lymphoma [tFL]), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (HGBL), follicular lymphoma Grade 3B (FL3B), and primary central nervous system lymphoma (PCNSL). Patients with secondary central nervous system (CNS) involvement are allowed.
Once enrolled, patients will undergo leukapheresis to enable JCAR017 cell product generation. Upon successful JCAR017 cell product generation, patients will receive lymphodepleting chemotherapy followed by infusion of JCAR017. JCAR017 will be administered at a dose of 100 x 10^6 JCAR017-positive transfected viable T cells by intravenous infusion. Patients will be followed for approximately 2 years after their JCAR017 infusion for safety, disease status, survival and health-related quality of life.
Delayed adverse events following exposure to gene modified T cells will be assessed and long-term persistence of these modified T cells will continue to be monitored under a separate long-term follow-up protocol for up to 15 years after JCAR017 infusion as per competent authority guidelines.

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 116 participants

Intervention Model : Single Group Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: A Phase 2, Single-arm, Multi-center Trial to Determine the Efficacy and Safety of JCAR017 in Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma or With Other Aggressive B-Cell Malignancies

Actual Study Start Date: June 2018

Estimated Primary Completion Date: August 2021

Estimated Study Completion Date: June 2023

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: Administration of JCAR017 JCAR017 will be infused at a dose of 100 x 10^6 JCAR017-positive transfected viable T cells (50 × 10^6 CD8+ CAR+ T cells and 50 × 10^6 CD4+ CAR+ T cells), on Day 1 (2 to 7 days after completion of lymphodepleting chemotherapy (LD) chemotherapy)	Drug: JCAR017 JCAR017

OUTCOME MEASURES

Primary Outcome Measures: 1. Overall Response Rate (ORR) of JCAR017 in subjects with Non-Hodgkin Lymphoma (NHL; including secondary central nervous system (CNS) involvement) [Time Frame: Up to 2 years after JCAR017 infusion]
Proportion of subjects achieving a complete response (CR) or partial response (PR) based on the Lugano classification (Cheson, 2014)

	2. ORR of JCAR017 in subjects with relapsed/refractory (r/r) primary central nervous system lymphoma (PCNSL) [Time Frame: Up to 2 years after JCAR017 infusion] Proportion of subjects achieving a CR/complete response unconfirmed (CRu) or PR based on the International Workshop to Standardize Baseline Evaluation and Response Criteria in Primary CNS Lymphoma (Abrey, 2005) 3. Adverse Events (AEs) in subjects intended to be treated as outpatients [Time Frame: Up to 2 years after JCAR017 infusion] Type, frequency, and severity of all AEs, including serious adverse events (SAEs) and laboratory abnormalities
Secondary Outcome Measures:	1. Adverse Events (AEs) [Time Frame: Up to 2 years after JCAR017 infusion] Type, frequency, and severity of AEs, including serious adverse events (SAEs) and laboratory abnormalities 2. Overall Response Rate (ORR) in subjects intended to be treated as outpatients [Time Frame: Up to 2 years after JCAR017 infusion] Proportion of subjects achieving a complete response (CR) or partial response (PR) based on the Lugano classification (Cheson, 2014) 3. Complete response rate (CRR) [Time Frame: Up to 2 years after JCAR017 infusion] Proportion of subjects achieving a CR (or CR and CRu for subjects with PCNSL) following JCAR017 infusion 4. Event-free survival (EFS) [Time Frame: Up to 2 years after JCAR017 infusion] Time from JCAR017 infusion to death from any cause, progressive disease (PD), or starting a new anticancer therapy, whichever occurs first 5. Progression-free survival (PFS) [Time Frame: Up to 2 years after JCAR017 infusion] Time from JCAR017 infusion to the first documentation of PD, or death due to any cause, whichever occurs first 6. Overall survival (OS) [Time Frame: Up to 2 years after last patient's JCAR017 infusion] Time from JCAR017 infusion to time of death due to any cause 7. Duration of response (DOR) [Time Frame: Up to 2 years after JCAR017 infusion] Time from first response to progressive disease or death from any cause, whichever occurs first 8. Pharmacokinetics by quantitative polymerase chain reaction (qPCR) - Cmax [Time Frame: Up to 2 years after JCAR017 infusion] Maximum concentration 9. Pharmacokinetics by qPCR - Tmax [Time Frame: Up to 2 years after JCAR017 infusion] Time to peak concentration 10. Pharmacokinetics by qPCR - AUC [Time Frame: Up to 2 years after JCAR017 infusion] Area under the curve 11. Patient-Reported Outcomes - EORTC QLQ-C30 [Time Frame: Up to 2 years after JCAR017 infusion] The European Organization for Research and Treatment of Cancer - Quality of Life C30 questionnaire will be used as a measure of health-related quality of life 12. Patient-Reported Outcomes - FACT-LymS [Time Frame: Up to 2 years after JCAR017 infusion] Functional Assessment of Cancer Therapy-Lymphoma "Additional concerns" subscale: Only the LYM subscale will be administered in this study. This scale addresses symptoms and functional limitations (15 item) that are important to lymphoma patients. 13. Adverse Events (AEs) in subjects treated as outpatients [Time Frame: Up to 2 years after JCAR017 infusion] Type, frequency, and severity of AEs, including serious adverse events (SAEs) and laboratory abnormalities

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ELIGIBILITY CRITERIA

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No
Criteria	

Inclusion Criteria:
Subjects must satisfy the following criteria to be enrolled in the study:
1. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF)
2. Subject must understand and voluntarily sign an ICF prior to any study-related ssessments/procedures being conducted
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements
4. Investigator considers the subject is appropriate for adoptive T cell therapy
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Subjects not eligible for transplant (TNE) in Cohorts 2 and 3 and subjects in Cohort 5 may be enrolled with ECOG of 2 only if they meet all other inclusion/exclusion criteria.
6. Subjects with one of the following:
Cohort 1: Subjects with DLBCL NOS (de novo or tFL), HGBL and FL3B per WHO 2016 classification (Swerdlow, 2016), after ≥ 2 lines of therapy*, including an anthracycline and rituximab (or other CD20-targeted agent) Cohort 2: Transplant not eligible subjects with DLBCL NOS (de novo or tFL), HGBL and FL3B per WHO 2016 classification (Swerdlow, 2016), who failed first line therapy*, including an anthracycline and rituximab (or other CD20-targeted agent)
- Transplant not eligible subjects will include those who are deemed ineligible for high-dose chemotherapy and HSCT due to age, performance status or comorbidity, while also having adequate organ function for CAR T cell treatment. At the very least, subjects have to meet one of the following criteria:
1. Age ≥ 70 years
2. ECOG performance status ≥ 2
3. Impaired pulmonary function (DLCO ≤ 60%, adjusted for hemoglobin concentration using the Dinakara equation)
4. Impaired cardiac function (LVEF < 50%) 5. Impaired renal function (CrCl 2 x ULN, bilirubin ≥ 2 mg/dL or cirrhosis Child-Pugh B or C)
- Subjects must fulfil all other in- and exclusion criteria Cohort 3 (Japan only): Subjects meeting eligibility criteria for either Cohort 1 or 2 Cohort 4: Subjects with newly diagnosed HGBL. Subjects must be eligible for anthracycline and rituximab (or other CD20-targeted agent) containing regimen as induction prior to consolidation with JCAR017** Cohort 5: Subjects with PCNSL who failed first line therapy with HDCT and ASCT Cohort 6: (REMOVED) Cohort 7: Subjects meeting eligibility criteria for Cohort 1 and suitable for outpatient treatment***
- For subjects with transformed disease, the subject should have had at least 2 lines of systemic therapy for his/her transformed disease (ie, DLBCL) for Cohort 1 and 1 line for Cohort 2 to be eligible. Lines of therapy do not include those given for a previously indolent condition (ie, follicular lymphoma). Subjects do NOT have to have anthracycline for their DLBCL if received for indolent disease.
- For subjects already undergoing anthracycline and rituximab containing regimen, eligibility is to be discussed with Medical Monitor. Subjects with complete metabolic response after 2 cycles of induction will proceed with JCAR017 infusion only at time of relapse, if applicable.
- Subjects must meet the conditions for outpatient treatment and monitoring as outlined in the Outpatient Administration and Monitoring Guidance for Lisocabtagene Maraleucel.
Note: Subjects with secondary CNS lymphoma involvement may enroll in Cohorts 1 to 4 and 7; subjects with PCNSL are eligible for Cohort 5. Subject selection must consider clinical risk factors for severe adverse events (AEs) and alternative treatment options. Subjects should only be enrolled if the Investigator considers the potential benefit outweighs the risk for the subject. For Cohort 5 and to not compromise safety, subject selection has been restricted to those fit enough to HDCT and ASCT as their prior therapy.
7. Histological confirmation of diagnosis at last relapse. Enough tumor material must be available for central confirmation of diagnosis, otherwise a new tumor biopsy is mandated.
Note: If the subject did not experience CR since last biopsy, the most recent biopsy will be considered adequate to participate in the trial. For subjects with PCNSL, at a minimum, corresponding pathology report is required if archival tumor material is not available and repeated biopsy not feasible.
8. (REMOVED) For subjects with NHL and Richter's transformed CLL
9. For subjects with PCNSL: Subjects must have disease that is objectively measurable by International Workshop to Standardize Baseline Evaluation and Response Criteria in Primary Central Nervous System (CNS) Lymphoma (Abrey, 2005), cerebrospinal fluid (CSF) cytology (in case of leptomeningeal only disease), or vitreal aspiration cytology and/or retinal photographs (in case of ocular lymphoma if clinically indicated)
10. Adequate organ function, defined as:
- Adequate bone marrow function to receive LD chemotherapy as assessed by the Investigator
- Serum creatinine 30 mL/min (estimated glomerular filtration rate [eGFR] by Cockroft Gault)
- Alanine aminotransferase (ALT) ≤ 5 x ULN and total bilirubin < 2.0 mg/dL (or 20 mg/day prednisone or equivalent) within 7 days prior to leukapheresis or 72 hours prior to JCAR017 infusion. Physiologic replacement, topical, and inhaled steroids are permitted.
- Low-dose chemotherapy (eg, vincristine, rituximab, cyclophosphamide ≤ 300 mg/m2) given after leukapheresis to maintain disease control must be stopped ≥ 7 days prior to LD chemotherapy
- Cytotoxic chemotherapeutic agents that are not considered lymphotoxic within 1 week prior to leukapheresis. Oral anticancer agents, including lenalidomide and ibrutinib, are allowed if at least 3 half-lives have elapsed prior to leukapheresis
- Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide > 300 mg/m2, ifosfamide, bendamustine) within 2 weeks prior to leukapheresis
- Experimental agents within 4 weeks prior to leukapheresis unless no response or progressive disease (PD) is documented on the experimental therapy and at least 3 half-lives have elapsed prior to leukapheresis
- Immunosuppressive therapies within 4 weeks prior to leukapheresis and JCAR017 infusion (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-tumor necrosis factor [TNF], anti-IL-6, or anti-IL-6R)
- Donor lymphocyte infusions (DLI) within 6 weeks prior to JCAR017 infusion
- Radiation within 6 weeks prior to leukapheresis. Subjects must have progressive disease in irradiated lesions or have additional non-irradiated, PET-positive lesions to be eligible. Radiation to a single lesion, if additional non-irradiated, measurable PET-positive lesions are present, is allowed up to 2 weeks prior to leukapheresis. Prior WBRT for subjects enrolled in Cohort 5 is not allowed
- Allogeneic HSCT within 90 days prior to leukapheresis
- Prior hematopoietic stem cell transplant (only applicable to Cohort 2) Systemic immunostimulatory agents (including but not limited to interferon and IL-2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to JCAR017 infusion
17. Progressive vascular tumor invasion, thrombosis, or embolism
18. Venous thrombosis or embolism not managed on a stable regimen of anticoagulation
19. Known severe hypersensitivity to DMSO or Dextran

CONTACTS AND LOCATIONS

Contacts

Contact:

Locations

Austria	Allgemeinen Krankenhaus (AKH) Wien - Medizinische Universitaet Wien	Wien
Belgium	Universitair Ziekenhuis Gent	Gent

Finland	Helsinki University	Helsinki
France	CHRU-Hopital Claude Huriez	Lille
France	Hopital Saint Louis	Paris Cedex 10
France	Centre Hospitalier Lyon Sud	Pierre Benite cedex
Germany	Medizinische Kinik und Poliklinik I	Dresden
Germany	Universitaetsklinikum Heidelberg	Heidelberg
Germany	Universitat zu Koln	Köln
Germany	LMU Klinikum der Universität	München
Germany	Universitatsklinikum Ulm	Ulm
Italy	Fondazione IRCCS Istituto Nazionale dei Tumori	Milan
Italy	Azienda Ospedaliera Citta della Salute e della Scienza di Torino	Torino
Japan	National Cancer Center Hospital	Chuo-ku
Japan	Toranomon Hospital	Minato-ku
Netherlands	Erasmus Medisch Centrum	Rotterdam
Spain	Hospital Val d'Hebron	Barcelona
Switzerland	Universitatsspital Bern	Bern
United Kingdom	UCL Cancer Institute	London
United Kingdom	The Christie NHS Foundation Trust	Manchester

Sponsors and Collaborators

Celgene

Investigator

Study Director : Claudia Schusterbauer, MD Celgene Corporation

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MORE INFORMATION

Responsible Party :	Celgene
ClinicalTrials.gov Identifier :	NCT03484702
Other Study ID Numbers :	JCAR017-BCM-001, U1111-1209-4055, 2017-000106-38
First Posted :	April 2, 2018
Last Update Posted :	June 22, 2020
Last Verified :	June 2020
Studies a U.S. FDA-regulated Drug Product:	Yes
Studies a U.S. FDA-regulated Device Product:	No
Product Manufactured in and Exported from the U.S.:	Yes
Keywords provided by Celgene:	*Non-Hodgkin lymphoma* *Aggressive B-cell non-Hodgkin lymphoma* *Diffuse large B-cell lymphoma* *Relapse / refractory lymphoma* *Transplant not eligible* *High-grade B-cell lymphoma Primary central nervous system lymphoma* *Transformed follicular lymphoma* *Follicular lymphoma Grade 3B* *JCAR017* *Liso-Cel*
Additional relevant MeSH terms :	*Lymphoma* *Aggression* *Lymphoma, Non-Hodgkin*