A Study to Evaluate the Safety and Efficacy of JCAR017 in Pediatric Subjects With Relapsed/Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (B-ALL) and B-cell Non-Hodgkin Lymphoma (B-NHL)

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT03743246	RECRUITING	NOVEMBER 16, 2018	JULY 14, 2022

STUDY DESCRIPTION

Brief Summary

This is a Phase 1/2, open-label, single arm, multicohort study to evaluate the safety and efficacy of JCAR017 in pediatric subjects aged ≤ 25 years with CD19+ r/r B-ALL and B-NHL. Phase 1 will identify a recommended Phase 2 dose (RP2D). Phase 2 will evaluate the efficacy of JCAR017 RP2D in the following three disease cohorts: Cohort 1 (r/r B-ALL), Cohort 2 (MRD+ B-ALL) and Cohort 3 (r/r B-NHL, [DLBCL, BL, or PMBCL]). A Simon's Optimal two-stage study design will be applied to Cohort 1 and 2 in Phase 2.

Condition or Disease: Precursor Cell Lymphoblastic Leukemia-Lymphoma
Lymphoma, Non-Hodgkin

Intervention/treatment: Drug: JCAR017
Drug: Lymphodepleting
Drug: Fludarabine
Drug: Cyclophosphamide

Phase: Phase 1/Phase 2

DETAILED DESCRIPTION

This is a Phase 1/2, open-label, single arm, multicohort study incorporating Simon's Optimal two-stage design to evaluate the safety and efficacy of JCAR017 in pediatric subjects aged ≤ 25 years with CD19+ r/r B-ALL and B-NHL.
In the Phase 1, up to 5 dose levels will be of JCAR017 will be evaluated. Enrollment will commence in pediatric subjects with r/r B-ALL at Dose Level 1 (DL1) of 0.05x10^6 CAR+ T cells/kg (maximum DL1 of 5x10^6 JCAR017 CAR+ T cells [non-weight adjusted]). If this dose is confirmed to be safe and tolerable, additional subjects will be enrolled at higher dose(s) up to 0.75 x10^6 CAR+ T cells/kg (maximum of 75x10^6 JCAR017 CAR+ T cells [non-weight adjusted]) with the aim to identify the RP2D. Dose escalation/de-escalation will follow a modified toxicity probability interval (mTPI-2) algorithm. A Safety Review Committee (SRC) will recommend the Phase 2 dose (defined as RP2D) based on an integrated assessment of the safety, PK and preliminary efficacy information from at least 10 pediatric subjects treated at the RP2D.
In Phase 2, a minimum of 71 additional subjects (< 18 years of age) will be enrolled into one of the 3 cohorts listed below. The sample size for Cohorts 1 and 2 is calculated according to Simon's Optimal two-stage design. The 10 or more pediatric subjects treated at the RP2D in Phase 1 will form part of the sample size (ie, Cohort 1 and Cohort 2). Therefore, the protocol intends to treat 81 primary endpoint evaluable pediatric subjects in Phase 2, if warranted by the evaluation of results at the completion of the first stage of the study in each cohort. Cohort 1 (r/r B-ALL): 48 evaluable pediatric subjects (13 subjects in Stage 1 and 35 in Stage 2) Cohort 2 (MRD+ B-ALL): 23 evaluable pediatric subjects (9 subjects in Stage 1 and 14 subjects in Stage 2) Cohort 3 (r/r B-NHL [DLBCL, BL, or PMBCL]): 10 evaluable pediatric subjects. Due to the very low incidence rate and therefore expected low subject accrual, there is no formal sample size for this arm. Up to 20 additional B-ALL subjects between 18 and 25 years of age may be enrolled in Phase 2. Following treatment with JCAR017 subjects will then enter the post-treatment period for disease progression/relapse, safety, CAR T cell persistence, and survival up to 24 months after administration of JCAR017. Efficacy will be assessed both locally and by an Independent Review Committee. Response assessments will be based on bone marrow and blood morphologic criteria, physical examination findings, along with laboratory assessments of cerebral spinal fluid (CSF) and bone marrow MRD (B-ALL only) assessments. B-NHL subjects will also have radiographic disease assessment by CT/MRI scans and tumor biopsies, if accessible. Post-study follow-up for survival, relapse, long-term toxicity, and lentiviral vector safety will continue under a separate long-term follow-up protocol for up to 15 years after the JCAR017 infusion as per health authority regulatory guidelines. An Independent Data Monitoring Committee will monitor the study conduct.

STUDY DESIGN

Study Type:	Interventional
Estimated Enrollment :	121 participants
Intervention Model :	Single Group Assignment
Masking:	None (Open Label) ()
Primary Purpose:	Treatment
Official Title:	A Study to Evaluate the Safety and Efficacy of JCAR017 in Pediatric Subjects With Relapsed/Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (B-ALL) and B-cell Non-Hodgkin Lymphoma (B-NHL)
Actual Study Start Date:	October 2018
Estimated Primary Completion Date:	December 2024
Estimated Study Completion Date:	December 2024

ARMS AND INTERVENTIONS

Arm	Intervention/treatment

Experimental: Administration of JCAR017 Subjects will receive Lymphodepleting 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 by JCAR017 cells infusion. Phase 1 will evaluate up to 5 JCAR017 cells dose levels and dose escalation/de-escalation will follow a modified toxicity probability interval (mTPI-2) algorithm. The declared RP2D in Phase 1 will be applied to the subjects enrolled in Phase 2	Drug: JCAR017 JCAR017 Drug: Lymphodepleting Lymphodepleting Drug: Fludarabine Fludarabine Drug: Cyclophosphamide Cyclophosphamide

OUTCOME MEASURES

Primary Outcome Measures:
1. Recommended Phase 2 Dose (RP2D) of JCAR017 [Time Frame: 28 days after JCAR017 infusion]
The dose recommended for use in phase 2 studies on the basis of dose limiting toxicities observed in phase 1 studies.
2. Overall response rate (ORR)- Cohort 1 [Time Frame: Up to day 56]
Total number of subjects achieving a Complete response (CR) or CR with incomplete blood count recovery (CRi) on Day 28 and confirmed on Day 56 as determined by IRC assessment.
3. Minimal residual disease (MRD) negative rate - Cohort 2 [Time Frame: Up to day 56]
Total number of subjects achieving a CR or CRi with an MRD negative bone marrow (<0.01% tumor cells) on Day 28 and confirmed on Day 56 as determined by IRC assessment.
4. Overall response rate (ORR)- Cohort 3 [Time Frame: On day 28]
Total number of subjects achieving a CR or PR on Day 28 as determined by IRC assessment.

Secondary Outcome Measures:
1. Adverse Events (AEs) [Time Frame: Up to 2 years after JCAR017 infusion]
Type, frequency and severity of adverse events (AEs), serious adverse events (SAE), and laboratory abnormalities (overall and in clinical, histological and molecular subgroups)
2. Overall response rate (ORR) in the non-selected dose levels from Phase 1 [Time Frame: On day 28 and day 56]
Percentage of r/r B-ALL subjects achieving a best overall response (BOR) of CR or CRi on Day 28, confirmed on Day 56 as determined by IRC assessment
3. Duration of response (DOR) [Time Frame: Up to 2 years after JCAR017 infusion]
Time from first response until progressive disease (PD), disease relapse, or death from any cause, whichever occurs first
4. Relapse-free survival (RFS) [Time Frame: Up to 2 years after JCAR017 infusion]
Time from JCAR017 infusion to documentation of PD, disease relapse, or death due to any cause, whichever occurs first
5. Event-free survival (EFS) [Time Frame: Up to 2 years after JCAR017 infusion]
Time from JCAR017 infusion to PD, disease relapse, start of a new anticancer therapy, or death from any cause, whichever occurs first
6. Overall survival (OS) [Time Frame: Up to 2 years after JCAR017 infusion]
Time from JCAR017 infusion to time of death due to any cause
7. MRD negative response rate [Time Frame: Up to 2 years after JCAR017 infusion]
Number of B-ALL subjects achieving CR or CRi and a negative MRD bone marrow.
8. Rate of hematopoietic stem cell transplant (HSCT) after response to JCAR017 infusion [Time Frame: Up to 2 years after JCAR017 infusion]
Percentage of subjects who achieve a response after JCAR017 infusion and then proceed to HSCT
9. Pharmacokinetics - Cmax [Time Frame: Up to 2 years after JCAR017 infusion]
Maximum concentration
10. Pharmacokinetics - Tmax [Time Frame: Up to 2 years after JCAR017 infusion]
Time to peak concentration
11. Pharmacokinetics - AUC [Time Frame: Up to 2 years after JCAR017 infusion]
Area under the curve
12. Best Overall Response (BOR) [Time Frame: Up to 2 years after JCAR017 infusion]
Number of r/r B-NHL subjects achieving BOR of CR/PR

ELIGIBILITY CRITERIA

Ages Eligible for Study: up to 25 / (18 to 64 years)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
Subjects must satisfy the following criteria to be enrolled in the study:
Phase 1: Subject < 18 years of age and weighs ≥ 6 kg at the time of signing the informed consent form (ICF)/informed assent form (IAF). Phase 2: Subject ≤ 25 years of age and weighs ≥ 6 kg at the time of signing the ICF/IAF. Subject (when applicable, parental/legal representative) must understand and voluntarily provide permission to the ICF/IAF prior to conducting any study-related assessments/procedures. Subject is willing and able to adhere to the study visit schedule and other protocol requirements. Investigator considers the subject is appropriate for adoptive T cell therapy. Evidence of CD19 expression via flow cytometry (peripheral blood or bone marrow) or immunohistochemistry (bone marrow biopsy) Subject has a Karnofsky score of ≥ 50 (subjects ≥ 16 years of age) or a Lansky score ≥ 50 (subjects < 16 years of age). Diagnosis of B-cell ALL or B-cell NHL as defined below: Phase 1: Subjects with r/r B-ALL, defined as morphological evidence of disease in BM (5% or greater lymphoblast by morphology) and either of the following: First or greater marrow relapse, or Any marrow relapse after allogeneic HSCT, or Primary refractory defined as not achieving a CR or a CRi after 2 or more separate induction regimens (or chemo-refractory as not achieving CR/CRi after 1 cycle of standard chemotherapy for relapsed leukemia), or Ineligible for allogeneic HSCT Note: Subjects will be included regardless of MRD status. Phase 2: Subjects with one of the following: Cohort 1: r/r B-ALL, defined as morphological evidence of disease in BM (5% or greater lymphoblast by morphology) and either: First or greater marrow relapse, or Any marrow relapse after allogeneic HSCT, or Primary refractory defined as not achieving a CR or a CRi after 2 or more separate induction regimens (or chemo-refractory as not achieving CR/CRi after 1 cycle of standard chemotherapy for relapsed leukemia), or Ineligible for allogeneic HSCT. Cohort 2: MRD+ B-ALL, defined as: < 5% lymphoblasts by morphology with, MRD detected by a validated assay at a frequency of 1 x10-4 or greater in BM cells. Subjects eligible for enrollment in Cohort 2 are those with MRD positive morphologic CR2 after re-induction when these subjects had previously experienced an early relapse (70 mL/min/1.73 m2 are eligible.• Alanine aminotransferase (ALT) ≤ 5 x upper limit of normal (ULN) and total bilirubin < 2.0 mg/dL (or 0.4 mg/kg maximum 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 are allowed if at least 3 half-lives have elapsed prior to leukapheresis. Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide, ifosfamide, bendamustine) within 2 weeks prior to leukapheresis. Experimental agents within 4 weeks prior to leukapheresis unless no response or 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 antitumor 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 PD in irradiated lesions or have additional non-irradiated lesions to be eligible. Radiation to a single lesion, if additional non-irradiated, measurable lesions are present, is allowed up to 2 weeks prior to leukapheresis. Allogeneic HSCT within 90 days prior to leukapheresis. Tumor invasion of venous or arterial vessels (B-NHL subjects only). Deep Venous Thrombosis (DVT) or Pulmonary Embolism (PE) within 3 months prior to leukapheresis. Subjects with DVT or PE that occurred longer than 3 months prior to leukapheresis, who still require ongoing therapeutic levels of anti-coagulation therapy, are also excluded. Existence of CD19-negative clone(s) of leukemia cells

---

CONTACTS AND LOCATIONS

Contacts

Contact: BMS Study Connect Contact Center www.BMSStudyConnect.com 855-907-3286 Clinical.Trials@bms.com
Contact: First line of the email MUST contain NCT # and Site #.

Locations

United States, New York	Memorial Sloan Kettering Cancer Center	New York
United States, Pennsylvania	The Children's Hospital of Philadelphia	Philadelphia
United States, Washington	Seattle Children's Hospital	Seattle
Belgium	UZ Gent	Gent
France	Institute for Pediatric Hematology - Oncology, Leon Berard Cancer Center	Lyon
France	Hopital d'Enfants de la Timone	Marseille Cedex 01
France	Hopital Robert Debre	Paris
Germany	Charite Campus Virchow	Berlin
Germany	Local Institution - 501	Berlin
Germany	Klinikum der Johann Wolfgang Goethe-Universitaet Frankfurt	Frankfurt am Main
Italy	Fondazione MBBM	Monza
Italy	Local Institution - 301	Monza
Italy	Local Institution - 300	Roma
Italy	Ospedale Bambin Gesu	Roma
Netherlands	Local Institution - 400	Utrecht
Netherlands	Princess Maxima Center for Pediatric Oncology	Utrecht
Spain	Hospital San Joan de Deu Barcelona	Esplugues de Llobregat
Spain	Local Institution - 251	Esplugues de Llobregat
Spain	Hospital Infantil Universitario Nino Jesus	Madrid
Spain	Local Institution - 250	Madrid

Sponsors and Collaborators

Celgene

Investigator

Study Director :	Bristol-Myers Squibb	Bristol-Myers Squibb

MORE INFORMATION

Responsible Party :	Celgene
ClinicalTrials.gov Identifier :	NCT03743246
Other Study ID Numbers :	JCAR017-BCM-004, U1111-1220-3324, 2018-001246-34
First Posted :	November 16, 2018
Last Update Posted :	July 14, 2022
Last Verified :	July 2022
Studies a U.S. FDA-regulated Drug Product:	Yes
Studies a U.S. FDA-regulated Device Product:	No
Keywords provided by Celgene:	*Pediatric* *JCAR017* *CAR-T* *CART* *CD19* *ALL* *NHL* *DLBCL* *BL PMBCL* *Cell Therapy* *LisoCell* *Young Adults* *Lymphoproliferative disorders* *Immune system diseases* *Leukemia* *Lymphoma* *lymphatic diseases*

Additional relevant MeSH terms :

Lymphoma	*Neoplasms by Histologic Type*
Leukemia	*Neoplasms*
Lymphoma, Non-Hodgkin	*Lymphoproliferative Disorders*
Precursor Cell Lymphoblastic Leukemia-Lymphoma	*Lymphatic Diseases*
Leukemia, Lymphoid	*Immunoproliferative Disorders*
Lymphoma, B-Cell	*Immune System Diseases*