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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Tisagenlecleucel

Trial Indication(s)

Relapsed or refractory mature B-cell non-Hodgkin lymphoma

Protocol Number

CCTL019C2202

Protocol Title

A Phase II, single arm, multicenter open label trial to determine the safety and efficacy of tisagenlecleucel in pediatric subjects with relapsed or refractory mature B-cell non-Hodgkin lymphoma (NHL)

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase IV

Study Start/End Dates

Study Start Date: February 15, 2019 (Actual)
Primary Completion Date: July 27, 2021 (Actual)

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Study Completion Date: April 26, 2023 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This Phase II, single arm, multicenter, open-label study had the following sequential phases: Consent, Screening, Pre-treatment, Treatment and Follow-up. In the Pretreatmentm phase, the subject may have undergone optional bridging therapy or lymphodepleting chemotherapy. The Treatment and Follow-up Phase included tisagenlecleucel infusion, safety, and efficacy follow-up until all subjects completed 24 months on study or discontinued early.

The primary efficacy and safety analysis was conducted when all evaluable subjects had been infused and followed for at least 6 months from tisagenlecleucel infusion or discontinued early as well as at least 50% of those subjects having a follow-up of at least 9 months from tisagenlecleucel infusion or early discontinuation.

Centers

26 centers in 14 countries: United States(8), Spain(2), Austria(1), Canada(1), France(2), Japan(2), Netherlands(1), Australia(2), Italy(2), Denmark(1), Finland(1), Norway(1), United Kingdom(1), Germany(1)

Objectives:

The primary objective was to evaluate the efficacy of tisagenlecleucel therapy as measured by ORR and determined by local investigator assessments in subjects with aggressive r/r B-cell NHL.

Secondary objectives:

- To evaluate the efficacy of tisagenlecleucel as measured by additional efficacy measurements including DOR, EFS, RFS, PFS, and OS
- To evaluate the safety of tisagenlecleucel

- To characterize the in vivo cellular kinetics (levels, expansion, persistence) of tisagenlecleucel cells into target tissues (blood, bone marrow, lymph nodes, CSF, and other tissues if available) as measured by qPCR in relation to safety and efficacy
- To characterize the presence of pre-existing and treatment induced immunogenicity and impact on cellular kinetics and response
- To assess the proportion of subjects who proceeded to HSCT transplant following tisagenlecleucel infusion
- To retrospectively assess potential CRS predictive models considering data from other trials

Test Product (s), Dose(s), and Mode(s) of Administration

Test therapy was tisagenlecleucel, planned to be administered once as an intravenous infusion, at a dose of either 0.2 to 5 x 106 CAR-positive viable T cells per kg body weight for subjects ≤ 50 kg or 0.1 to 2.5 x 108 CARpositive viable T cells for subjects > 50 kg.

No reference therapy was administered.

Statistical Methods

- Screened set: all subjects who signed ICF and were screened
- Enrolled set: subject met all inclusion/exclusion criteria and leukapheresis material was received and accepted for manufacturing
- EAS: all subjects with aggressive r/r B-cell NHL who received an infusion of tisagenlecleucel and had measurable disease at baseline
- FAS and safety set: all subjects who received an infusion of tisagenlecleucel
- CKAS: subjects in the FAS who provided at least 1 valid cellular kinetic concentration
- TPAS: all subjects who took at least 1 dose of tocilizumab and provided at least 1 tocilizumab PK concentration

The primary efficacy endpoint analysis was conducted when all evaluable subjects with measurable disease at baseline had been infused and followed for at least 6 months from study Day 1 or discontinued early as well as at least 50% of those subjects having a follow-up of at least 9 months.

The final analysis was conducted after all subjects had completed the study. The ORR was summarized along with the 95% exact Clopper-Pearson CIs. Sensitivity analyses were performed for ORR on different analysis sets and exploratory supplemental analyses were performed on different subgroups.

While no formal hypothesis testing was planned for secondary endpoints, medians and probabilities at different time points are estimated by Kaplan-Meier methodology for DOR, EFS, RFS, PFS, and OS.

Tisagenlecleucel concentrations in peripheral blood were descriptively summarized by time points for the CAR transgene levels as assessed by qPCR and for CAR-positive T cells as measured by flow cytometry of CD3+, CD3+/CD4+, and CD3+/CD8+ viable cells. Descriptive statistics of cellular kinetic parameters (AUC0-28d, Cmax, Tmax, T1/2, Clast, Tlast) were summarized and reported by BOR, CRS grade, use of tocilizumab, and anti-tisagenlecleucel antibody status. Tocilizumab PK was summarized by time point and by maximum CRS grade for the TPAS.

Summary statistics for humoral immunogenicity were summarized by time point and BOR. Cellular immunogenicity was summarized by time points.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Histologically confirmed pediatric mature B-cell non-Hodgkin lymphoma (B-cell NHL) including the following subtypes; Burkitt lymphoma/ Burkitt leukemia (BL), diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), gray zone lymphoma (GZL), and follicular lymphoma (FL)
Note: Patients with B-cell NHL associated with Nijmegen breakage syndrome will be allowed.
- Patients <25 years of age and weighing at least 6 kg at the time of screening
- Patients who have relapsed after one or more prior therapies (can include allogeneic and autologous hematopoietic stem cell transplant) or are primary refractory (have not achieved a CR or PR after the first line of therapy)
- Measurable disease by radiological criteria in all patients at the time of screening. Patients with Burkitt leukemia who don’t meet radiological criteria
must have bone marrow involvement of >25% by local assessment of bone
marrow aspirate and/or biopsy.
- Karnofsky (age ≥16 years) or Lansky (age <16 years) performance status ≥60.
- Adequate bone marrow reserve without transfusions (transfusion >2 weeks prior to laboratory assessment is allowed) defined as:
a. Absolute neutrophil count (ANC) >1000/mm3

b. Platelets ≥50000//mm3
c. Hemoglobin ≥8.0 g/dl
- Adequate organ function defined as:
a. a serum creatinine (sCR) based on gender/age as follows:
Maximum Serum Creatinine (mg/dL)
Age Male Female
1 to <2 years 0.6 0.6
2 to <6 years 0.8 0.8
6 to <10 years 1.0 1.0
10 to <13 years 1.2 1.2
13 to <16 years 1.5 1.4
≥16 years 1.7 1.4
b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 times the upper limit of normal (ULN) for age
c. Total bilirubin <2 mg/dL (for Gilbert's Syndrome patients total bilirubin <4 mg/dL)
d. Adequate pulmonary function
i. Oxygen saturation of >91% on room air
ii. No or mild dyspnea (≤Grade 1)
- Must have a leukapheresis material of non-mobilized cells accepted for manufacturing.

Exclusion Criteria:
- Prior gene therapy or engineered T cell therapy.
- Prior treatment with any anti-CD19 therapy.
- Allogeneic hematopoietic stem cell transplant (HSCT) <3 months prior to screening and ≤4 months prior to infusion.
- Presence of grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD) in patients who received prior allogeneic HSCT.
- Prior diagnosis of malignancy other than study indication, and not disease free for 5 years.
- Clinically significant active infection confirmed by clinical evidence, imaging,
or positive laboratory tests (e.g., blood cultures, PCR for DNA/RNA, etc.)
- Presence of active hepatitis B or C as indicated by serology.
- Human Immunodeficiency Virus (HIV) positive test.
- Active neurological autoimmune or inflammatory disorders not related to B cell NHL (eg: Guillain-Barre syndrome, Amyotrophic Lateral Sclerosis)
- Active central nervous system (CNS) involvement by malignancy.

- Patients with B-cell NHL in the context of post-transplant lymphoproliferative disorders (PTLD) associated lymphomas.

Participant Flow Table

Overall Study

	Tisagenlecleucel	Total
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.	
Started	34	34
Met Eligibilty criteria and were infused	33	33
Met Eligibilty criteria but was not infused*	1	1
Completed treatment & primary follow-up phase	14	14
Discont. treatment & primary follow-up phase	19	19
Completed	14	14
Not Completed	20	20
Death	17	17
Lost to Follow-up	1	1
Physician Decision	1	1
Died prior to infusion	1	1

Baseline Characteristics

	Tisagenlecleucel	Total

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Arm/Group Description	These participants were infused once with CAR-positive viable T cells.	
Number of Participants [units: participants]	33	33
Baseline Analysis Population Description	FAS and safety set: all subjects who received an infusion of tisagenlecleucel	
Age Continuous (units: years) Analysis Population Type: Participants Median ± Standard Deviation		
	12.8±4.98	12.8±4.98
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)		
Female	10	10
Male	23	23
Race/Ethnicity, Customized (units: Participants) Analysis Population Type: Participants		
White	28	28
Black or African American	1	1
Asian	2	2
Missing	2	2
Study Specific Characteristic **Histology (type of lymphoma)** (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)		
Burkitt lymphoma	18	18
Large B-cell lymphoma	15	15

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Primary Outcome Result(s)

Overall response rate (ORR) as determined by local investigator

Description	The overall response rate (ORR) is defined as the percentage of subjects with a best overall disease response of complete response (CR) or partial response (PR), where the best overall disease response is defined as the best disease response recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever comes first.
Time Frame	6 months post-tisagenlecleucel infusion
Analysis Population Description	Efficacy Analysis Set (EAS): all subjects with aggressive r/r B-cell NHL who received an infusion of tisagenlecleucel and had measurable disease at baseline, i.e participants with complete or unknown response after bridging therapy were excluded from the efficacy analysis set.

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	28
Overall response rate (ORR) as determined by local investigator (units: Percentage of participants)	**Number (95% Confidence Interval)**
	32.1 (15.9 to 52.4)

Secondary Outcome Result(s)

Duration of response (DOR)

Description	Duration of response (DOR) is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented progression or death due to underlying cancer.

Time Frame	Post-infusion Day 28, Month 3, Month 6, Month 9, Month 12, Month 18, Month 24, and then annually until Month 48
Analysis Population Description	EAS: all subjects with aggressive r/r B-cell NHL who received an infusion of tisagenlecleucel and had measurable disease at baseline. Only participants with best response of CR/PR post-infusion were included in the DOR analysis.

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	9
Duration of response (DOR) (units: months)	**Median (95% Confidence Interval)**
	NA (1.0 to NA)[1]

[1] NA: Median and Upper limit of Confidence Interval (CI) not reached because there were not sufficient events during study follow-up

Event free survival (EFS)

Description	Event free survival (EFS) is defined as the time from date of first tisagenlecleucel infusion to the earliest date of death from any cause, disease progression as determined by local investigator assessments, or starting new anticancer therapy for underlying cancer, excluding hematopoietic stem cell transplant (HSCT).
Time Frame	Post-infusion Day 28, Month 3, Month 6, Month 9, Month 12, Month 18, Month 24, and then annually until Month 48
Analysis Population Description	EAS: all subjects with aggressive r/r B-cell NHL who received an infusion of tisagenlecleucel and had measurable disease at baseline, i.e participants with complete or unknown response after bridging therapy were excluded from the efficacy analysis set.

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	28

Event free survival (EFS) (units: months)	Median (95% Confidence Interval)
	2.1 (1.1 to 2.8)

Relapse free survival (RFS)

Description	Relapse free survival (RFS) is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented disease progression or death due to any cause.
Time Frame	Post-infusion Day 28, Month 3, Month 6, Month 9, Month 12, Month 18, Month 24, and then annually until Month 48
Analysis Population Description	EAS: all subjects with aggressive r/r B-cell NHL who received an infusion of tisagenlecleucel and had measurable disease at baseline. Only participants with best response of CR/PR post-infusion were included in the RFS analysis.

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	9
Relapse free survival (RFS) (units: months)	**Median** **(95% Confidence Interval)**
	NA (1.0 to NA)[1]

[1] NA: Median and Upper limit of Confidence Interval (CI) not reached because there were not sufficient events during study follow-up

Progression free survival (PFS)

Description	Progression free survival (PFS) is defined as the time from the date of first tisagenlecleucel infusion to the date of first documented disease progression as determined by local investigator assessments or death due to any cause. Progression is defined using the International non-Hodgkin Lymphoma Response Criteria. For a PET-based response, progressive disease is defined as a 4 or 5 on the 5 point scale with increased uptake compared to the nadir or new FDG-avid foci consistent with lymphoma. For a CT/MRI based response progressive disease is defined as a 25% increase in the SPD (sum of the products of two largest perpendicular diameters) of index lesions, or unequivocal progression in either non-index lesions or the spleen. Any new disease attributable to lymphoma would also constitute progressive disease.

Time Frame	Post-infusion Day 28, Month 3, Month 6, Month 9, Month 12, Month 18, Month 24, and then annually until Month 48
Analysis Population Description	EAS: all subjects with aggressive r/r B-cell NHL who received an infusion of tisagenlecleucel and had measurable disease at baseline, i.e participants with complete or unknown response after bridging therapy were excluded from the efficacy analysis set.

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	28
Progression free survival (PFS) (units: months)	**Median (95% Confidence Interval)**
	2.5 (1.1 to 2.9)

Overall survival (OS)

Description	Overall survival (OS) is defined as the time from date of first tisagenlecleucel infusion to the date of death due to any cause.
Time Frame	Post-infusion Day 28, Month 3, Month 6, Month 9, Month 12, Month 18, Month 24, and then annually until Month 48
Analysis Population Description	EAS: all subjects with aggressive r/r B-cell NHL who received an infusion of tisagenlecleucel and had measurable disease at baseline, i.e participants with complete or unknown response after bridging therapy were excluded from the efficacy analysis set.

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	28
Overall survival (OS) (units: months)	**Median (95% Confidence Interval)**

10.4
(3.4 to NA)[1]

[1] NA: Upper limit of Confidence Interval (CI) not reached because there were not sufficient events during study follow-up

Cellular kinetics parameter: Cmax

Description	The maximum (peak) transgene level (copies/µg) observed in peripheral blood or other body fluid after single dose administration as measured by qPCR. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.
Time Frame	Post-infusion day 4, day 7, day 11, day 14, day 21, day 28, month 3, month 6, month 9, month 12, month 18, month 24, and then annually until Month 48
Analysis Population Description	Cellular kinetic analysis set (CKAS): subjects in the FAS who provided at least 1 valid cellular kinetic concentration for tisagenlecleucel. Certain PK parameters were not estimable for all subjects due to insufficient samples.

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells
Number of Participants Analyzed [units: participants]	31
Cellular kinetics parameter: Cmax (units: copies/µg)	**Geometric Mean (Geometric Coefficient of Variation)**
	5140 (238.9%)

Cellular kinetics parameter: Tmax

Description	The time to reach maximum (peak) transgene level (days) in peripheral blood or other body fluid after single dose administration. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.
Time Frame	Post-infusion day 4, day 7, day 11, day 14, day 21, day 28, month 3, month 6, month 9, month 12, month 18, month 24, and then annually until Month 48

Analysis Population Description	CKAS: subjects in the FAS who provided at least 1 valid cellular kinetic concentration for tisagenlecleucel. Certain PK parameters were not estimable for all subjects due to insufficient samples.

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	31
Cellular kinetics parameter: Tmax (units: days)	**Median (Full Range)**
	12.7 (1.90 to 21.9)

Cellular kinetics parameter: AUC0-28d

Description	Area Under the Concentration-time Curve (AUCs) from the time course of transgene levels in peripheral blood following tisagenlecleucel infusion (days*copies/µg), from day of infusion to day 28. D28 refers to the timepoint for definition of responder populations. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.
Time Frame	0 to 28 days
Analysis Population Description	CKAS: subjects in the FAS who provided at least 1 valid cellular kinetic concentration for tisagenlecleucel. Certain PK parameters were not estimable for all subjects due to insufficient samples.

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	27

Cellular kinetics parameter: AUC0-28d (units: copies/µg*days)	Geometric Mean (Geometric Coefficient of Variation)
	53500 (154.9%)

Cellular kinetics parameter: Clast

Description	The last observed quantifiable transgene level in peripheral blood. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.
Time Frame	Post-infusion day 4, day 7, day 11, day 14, day 21, day 28, month 3, month 6, month 9, month 12, month 18, month 24, and then annually until Month 48
Analysis Population Description	CKAS: subjects in the FAS who provided at least 1 valid cellular kinetic concentration for tisagenlecleucel. Certain PK parameters were not estimable for all subjects due to insufficient samples.

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	30
Cellular kinetics parameter: Clast (units: copies/µg)	**Geometric Mean** **(Geometric Coefficient of Variation)**
	344 (350.4%)

Cellular kinetics parameter: Tlast

Description	The time of last observed quantifiable transgene level in peripheral blood. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.
Time Frame	Post-infusion day 4, day 7, day 11, day 14, day 21, day 28, month 3, month 6, month 9, month 12, month 18, month 24, and then annually until Month 48
Analysis Population Description	CKAS: subjects in the FAS who provided at least 1 valid cellular kinetic concentration for tisagenlecleucel. Certain PK parameters were not estimable for all subjects due to insufficient samples.

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	30
Cellular kinetics parameter: Tlast (units: days)	**Median (Full Range)**
	40.0 (13.0 to 1090)

Levels of pre-existing and treatment induced humoral immunogenicity and cellular immunogenicity against tisagenlecleucel cellular kinetics, safety and efficacy

Description	The humoral immunogenicity assay measures the antibody titers specific to tisagenlecleucel prior to and following infusion by flow cytometry. A subject was only defined as positive for tisagenlecleucel treatment-induced or -boosted anti-mCAR19 antibodies when the anti-mCAR19 antibody median fluorescence intensity at any time post-infusion was at least 2.28-fold higher (for samples analyzed on or prior to 05-May-2021) or 2.38-fold higher (for samples analyzed on or after 06-May-2021) than pre-infusion levels for participants whose baseline status was positive (boosted) or if the baseline status was negative but any post-baseline interpretation was positive (induced).
Time Frame	Until disease progression or through study completion, up to 4 years
Analysis Population Description	Safety set: All participants who received an infusion of tisagenlecleucel

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	33

Levels of pre-existing and treatment induced humoral immunogenicity and cellular immunogenicity against tisagenlecleucel cellular kinetics, safety and efficacy (units: Percentage of participants)	
anti-tisagenlecleucel antibodies (positive) at baseline (BL)	87.9
anti-tisagenlecleucel antibodies (positive) anytime post-BL	97.0

Percentage of participants who proceeded to stem cell transplant (SCT) after tisagenlecleucel infusion

Description	These participants proceeded to transplant any time post-tisagenlecleucel therapy until end of study (EOS).
Time Frame	Through study completion, up to 4 years
Analysis Population Description	Safety set: All participants who received an infusion of tisagenlecleucel

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	33
Percentage of participants who proceeded to stem cell transplant (SCT) after tisagenlecleucel infusion (units: Percentage of participants)	
	21.2

Maximum Positive Predictive Value (PPV)

Description	Retrospective assessment of potential cytokine release syndrome (CRS) predictive models considering also data from other CTL019 trials. The Positive Predictive Value (PVV) is the percentage of participants who actually had severe CRS out of all the cases where the prediction model predicts that severe CRS will occur. The maximum PPV is the highest value attained across all potential CRS predictive models.
Time Frame	Through study completion, up to 4 years

Analysis Population Description	Safety set: All participants who received an infusion of tisagenlecleucel

	Tisagenlecleucel
Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	33
Maximum Positive Predictive Value (PPV) (units: Percentage of participants)	
	36.0

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

All Collected Deaths

Description	On-treatment deaths were collected during the post-infusion period starting at the day of first infusion until the end of the study, up to 48 months. All deaths is the sum of pre-infusion and post-infusion deaths.
Time Frame	Pre-treatment deaths: from enrollment to pre-infusion; On-treatment deaths: post-infusion up to 48 months
Analysis Population Description	Clinical Database Population: All infused and non-infused participants who met the criteria to be enrolled in the study

	Tisagenlecleucel

Arm/Group Description	These participants were infused once with CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	34
All Collected Deaths (units: Participants)	
On-treatment deaths include post-treatment survival follow-up deaths	17
Deaths prior to infusion	1
All Deaths	18

Safety Results

Time Frame	Adverse Event (AE) timeframe: AEs were collected during the post-infusion period (starting at the day of 1st infusion until the end of the study), up to maximum duration of 48 months for each patient. Deaths were collected at all points: pre-infusion period and post-infusion period until the patient completed the study duration (48 months) or further safety follow-up under the study protocol. Therefore on-treatment deaths include post-infusion deaths until Last patient Last Visit (LPLV)
Additional Description	AE description: Any sign or symptom that occurs during the post-infusion period (starting at the day of first infusion of CTL019 until the end of the study) and safety follow-up. Deaths in the post treatment survival follow-up are not considered Adverse Events while still included in the All-Cause Mortality table.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

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All-Cause Mortality

	Tisagenlecleucel - Post-infusion N = 33	Tisagenlecleucel - Pre-infusion deaths N = 34
Arm/Group Description	AEs/deaths collected during and post-infusion until patient completed study.	Deaths collected prior to infusion. No AEs were collected during this period.
Total Number Affected	17	1
Total Number At Risk	33	34

Serious Adverse Events

Time Frame	Adverse Event (AE) timeframe: AEs were collected during the post-infusion period (starting at the day of 1st infusion until the end of the study), up to maximum duration of 48 months for each patient. Deaths were collected at all points: pre-infusion period and post-infusion period until the patient completed the study duration (48 months) or further safety follow-up under the study protocol. Therefore on-treatment deaths include post-infusion deaths until Last patient Last Visit (LPLV)
Additional Description	AE description: Any sign or symptom that occurs during the post-infusion period (starting at the day of first infusion of CTL019 until the end of the study) and safety follow-up. Deaths in the post treatment survival follow-up are not considered Adverse Events while still included in the All-Cause Mortality table.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

	Tisagenlecleucel - Post-infusion N = 33	Tisagenlecleucel - Pre-infusion deaths N = 0
Arm/Group Description	AEs/deaths collected during and post-infusion until patient completed study.	Deaths collected prior to infusion. No AEs were collected during this period.

Total # Affected by any Serious Adverse Event	24	0
Total # at Risk by any Serious Adverse Event	33	0
Blood and lymphatic system disorders		
Febrile neutropenia	2 (6.06%)	
Cardiac disorders		
Cardiac arrest	1 (3.03%)	
Tachycardia	1 (3.03%)	
Eye disorders		
Vision blurred	1 (3.03%)	
Gastrointestinal disorders		
Abdominal pain	2 (6.06%)	
Dental caries	1 (3.03%)	
Large intestinal obstruction	1 (3.03%)	
Pancreatitis	1 (3.03%)	
Proctitis	1 (3.03%)	
General disorders and administration site conditions		
Chest pain	1 (3.03%)	
Condition aggravated	1 (3.03%)	
Disease progression	1 (3.03%)	
Pyrexia	7 (21.21%)	
Immune system disorders		

Cytokine release syndrome	8 (24.24%)
Haemophagocytic lymphohistiocytosis	1 (3.03%)
Infections and infestations	
Aspergillus infection	1 (3.03%)
Candida infection	1 (3.03%)
Pseudomonas infection	1 (3.03%)
Sepsis	1 (3.03%)
Urinary tract infection	1 (3.03%)
Vascular device infection	1 (3.03%)
Investigations	
Ejection fraction decreased	1 (3.03%)
Neutrophil count decreased	1 (3.03%)
Musculoskeletal and connective tissue disorders	
Back pain	1 (3.03%)
Nervous system disorders	
Aphasia	1 (3.03%)
Depressed level of consciousness	2 (6.06%)
Disturbance in attention	1 (3.03%)
Hemiparesis	1 (3.03%)
Memory impairment	1 (3.03%)
Motor dysfunction	1 (3.03%)

Peripheral sensorimotor neuropathy	2 (6.06%)
Seizure	2 (6.06%)
Renal and urinary disorders	
Acute kidney injury	2 (6.06%)
Respiratory, thoracic and mediastinal disorders	
Pleural effusion	3 (9.09%)
Pneumothorax	1 (3.03%)
Respiratory distress	1 (3.03%)
Respiratory failure	1 (3.03%)
Vascular disorders	
Hypertension	1 (3.03%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse Event (AE) timeframe: AEs were collected during the post-infusion period (starting at the day of 1st infusion until the end of the study), up to maximum duration of 48 months for each patient. Deaths were collected at all points: pre-infusion period and post-infusion period until the patient completed the study duration (48 months) or further safety follow-up under the study protocol. Therefore on-treatment deaths include post-infusion deaths until Last patient Last Visit (LPLV)
Additional Description	AE description: Any sign or symptom that occurs during the post-infusion period (starting at the day of first infusion of CTL019 until the end of the study) and safety follow-up. Deaths in the post treatment survival follow-up are not considered Adverse Events while still included in the All-Cause Mortality table.
Source Vocabulary for Table Default	MedDRA (26.0)

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Collection Approach for Table Default Systematic Assessment

Frequent Event Reporting Threshold 5%

	Tisagenlecleucel - Post-infusion N = 33	Tisagenlecleucel - Pre-infusion deaths N = 0
Arm/Group Description	AEs/deaths collected during and post-infusion until patient completed study.	Deaths collected prior to infusion. No AEs were collected during this period.
Total # Affected by any Other Adverse Event	33	0
Total # at Risk by any Other Adverse Event	33	0
Blood and lymphatic system disorders		
Anaemia	11 (33.33%)	
Bone marrow failure	2 (6.06%)	
Coagulopathy	2 (6.06%)	
Febrile neutropenia	2 (6.06%)	
Leukopenia	5 (15.15%)	
Lymphopenia	2 (6.06%)	
Neutropenia	7 (21.21%)	
Thrombocytopenia	4 (12.12%)	
Cardiac disorders		

Sinus tachycardia	3 (9.09%)
Tachycardia	4 (12.12%)
Eye disorders	
Vision blurred	2 (6.06%)
Gastrointestinal disorders	
Abdominal pain	6 (18.18%)
Abdominal pain upper	2 (6.06%)
Constipation	3 (9.09%)
Diarrhoea	3 (9.09%)
Gastrooesophageal reflux disease	2 (6.06%)
Lower gastrointestinal haemorrhage	2 (6.06%)
Nausea	9 (27.27%)
Small intestinal obstruction	2 (6.06%)
Stomatitis	5 (15.15%)
Vomiting	13 (39.39%)
General disorders and administration site conditions	
Catheter site pain	3 (9.09%)
Chills	4 (12.12%)
Fatigue	5 (15.15%)
Generalised oedema	2 (6.06%)
Oedema peripheral	2 (6.06%)
Pain	2 (6.06%)

Pyrexia	14 (42.42%)
Hepatobiliary disorders	
Cholelithiasis	2 (6.06%)
Immune system disorders	
Cytokine release syndrome	16 (48.48%)
Drug hypersensitivity	2 (6.06%)
Hypogammaglobulinaemia	3 (9.09%)
Infections and infestations	
Myelitis	2 (6.06%)
Injury, poisoning and procedural complications	
Infusion related reaction	3 (9.09%)
Investigations	
Alanine aminotransferase increased	5 (15.15%)
Aspartate aminotransferase increased	2 (6.06%)
Blood bilirubin increased	2 (6.06%)
Blood creatinine increased	5 (15.15%)
Blood lactate dehydrogenase increased	3 (9.09%)
Lymphocyte count decreased	3 (9.09%)
Neutrophil count decreased	10 (30.30%)
Platelet count decreased	9 (27.27%)
SARS-CoV-2 test positive	2 (6.06%)

Serum ferritin increased	2 (6.06%)
Weight decreased	3 (9.09%)
White blood cell count decreased	8 (24.24%)
Metabolism and nutrition disorders	
Decreased appetite	5 (15.15%)
Hyperphosphataemia	3 (9.09%)
Hypokalaemia	5 (15.15%)
Hypomagnesaemia	4 (12.12%)
Hyponatraemia	2 (6.06%)
Hypophosphataemia	2 (6.06%)
Musculoskeletal and connective tissue disorders	
Arthralgia	2 (6.06%)
Neck pain	2 (6.06%)
Pain in extremity	2 (6.06%)
Nervous system disorders	
Depressed level of consciousness	2 (6.06%)
Dizziness	2 (6.06%)
Headache	8 (24.24%)
Neuralgia	2 (6.06%)
Neuropathy peripheral	2 (6.06%)
Paraesthesia	3 (9.09%)

Psychiatric disorders	
Anxiety	2 (6.06%)
Depression	2 (6.06%)
Insomnia	2 (6.06%)
Respiratory, thoracic and mediastinal disorders	
Cough	5 (15.15%)
Epistaxis	4 (12.12%)
Pleural effusion	2 (6.06%)
Tachypnoea	2 (6.06%)
Skin and subcutaneous tissue disorders	
Alopecia	2 (6.06%)
Dry skin	2 (6.06%)
Pruritus	3 (9.09%)
Rash	2 (6.06%)
Vascular disorders	
Haematoma	2 (6.06%)
Hypertension	3 (9.09%)
Hypotension	2 (6.06%)

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Other Relevant Findings

Not Applicable

Conclusion:

Although the sample size is small, overall, this study in pediatric and young adult patients with CD19+ r/r mature B-cell NHL, including Burkitt lymphoma, demonstrated efficacy of tisagenlecleucel in some subjects, with greater response observed in large B-cell lymphoma (LBCL). Of note, in this study, the dose range of infused CAR-positive viable T cells received for subjects 18 to 25 years of age was 0.7-2.10x108. The dose range for this trial for patients over 50 kg was 0.3-2.38x108, which is an upper dose limit less than half of what is within specification for commercial product (0.6-6x108 infused viable T cells) for the approved indications of adults with relapsed or refractory aggressive B cell NHL, including diffuse large B-cell lymphoma (DLBCL).

The overall response rate (ORR) was 32.1% (9/28 subjects) (95% confidence interval (CI): 15.9, 52.4) with subgroup analyses suggesting a trend for higher overall response rate ORR in subjects with histologies other than Burkitt lymphoma (BL): 3/8 subjects with DLCBL or 3/5 subjects with a histology of other vs 3/15 subjects with BL. Of the responders, 3 subjects (10.7%) achieved complete response (CR) as best overall response (BOR) (all in the LBCL subgroup) and 6 subjects (21.4%) achieved partial response (PR) as BOR (3 each in BL and LBCL). Median event-free survival was 2.1 months (95% CI: 1.1, 2.8) and median progression free survival was 2.5 months (95% CI: 1.1, 2.9). Overall median OS was 10.4 months (95% CI: 3.4, NE), and was 6.1 months (95% CI: 1.9, NE) and not estimable for BL and LBCL subgroups, respectively. After infusion with tisagenlecleucel, 16 subjects (48.5%) received anti-neoplastic therapies.

Additional subgroup analyses suggested a trend for a higher ORR in subjects with pre-tisagenlecleucel infusion serum LDH ≤ upper normal limit than > upper normal limit (50% vs 26.3%). Geometric mean CAR T cell exposure was similar between responders and non-responders and persistence of CAR T cells was observed for up to 1090 days.

The overall safety profile in pediatric and young adult patients with CD19+ r/r mature B-cell NHL infused with tisagenlecleucel was consistent with existing knowledge and safety profile of tisagenlecleucel. No new safety signals were observed in Study C2202.

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In conclusion, in pediatric and young adult patients with CD19+ r/r mature B-cell NHL, predominantly including high-risk aggressive Burkitt and large cell lymphoma, treatment with tisagenlecleucel may offer clinical benefit to some of these patients where beneficial treatment options are limited.

Date of Clinical Trial Report

Definition: *e-signature date*

Commented [AP1]: What is the publication date for the final CSR?