NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Tisagenlecleucel (CTL019)

Trial Indication(s)

Relapsed and/or refractory diffuse large B-cell lymphoma

Protocol Number

CCTL019L12101C

Protocol Title

A phase Ib, multicenter study to determine the safety and tolerability of tisagenlecleucel in combination with ibrutinib in adult patients with relapsed and/or refractory diffuse large B-cell lymphoma

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 4

Study Start/End Dates

Study Start Date: June 2019 (Actual)
Primary Completion Date: November 2021 (Actual)
Study Completion Date: November 2021 (Actual)

Reason for Termination (If applicable)

This study was decided to be early terminated on 1-Nov-2021 by Novartis due to business reasons considering the changing competitive landscape. The decision was not related to any safety reason.

Study Design/Methodology

This was a multi-center, open label phase Ib study to evaluate the safety and tolerability of the administration of tisagenlecleucel in combination with ibrutinib in patients ≥ 18 years with relapsed or refractory diffuse large B cell lymphoma (r/r DLBCL) having received 2 or more lines of systemic therapy, including an anti CD20 and anthracyclin based chemotherapy, and who have progressed after or are ineligible for autologous hematopoietic stem cell transplant (ASCT).

The study enrolled patients into two arms in parallel:

- Ibrutinib lead-in arm (Tisagenlecleucel + Ibrutinib Pre-apheresis): patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis.
- Concomitant arm (Tisagenlecleucel + Ibrutinib Post-apheresis): patients were enrolled with the start of ibrutinib treatment after their leukapheresis product has been accepted for manufacture.

There was no formal randomization in this exploratory study. Assignment of patients to each arm was coordinated by Novartis with alternating assignment between the two arms.

The study was planned to have initial safety cohorts with approximately 3-6 patients enrolled into each of the two arms in parallel and afterwards enrichment cohorts with additional patients enrolled into both arms to further characterize the safety, tolerability, and preliminary efficacy of ibrutinib in combination with tisagenlecleucel. The enrichment cohorts were not enrolled in this study due to premature termination.

Centers

United States(2)

Objectives:

The primary objective of the trial was to assess the safety and tolerability of tisagenlecleucel in combination with ibrutinib.

The secondary objectives were:

- Evaluate the response rate (RR) as per Lugano criteria assessed by local investigator at 3 months and 6 months.
- Assess efficacy of tisagenlecleucel in combination with ibrutinib by evaluating overall response rate (ORR) as assessed by local investigator
- Evaluate duration of response (DOR) as per Lugano criteria assessed by local investigator
- Evaluate progression free survival (PFS) and overall survival (OS) as per Lugano criteria assessed by local investigator
- Characterize the cellular kinetics of tisagenlecleucel in peripheral blood, and tissues such as bone marrow, tumor tissue etc., if available, by quantitative polymerase chain reaction (qPCR)
- Characterize the impact of ibrutinib on the cellular kinetics of tisagenlecleucel
- Characterize the incidence and prevalence of CTL019 immunogenicity (humoral and cellular)
- Characterize the impact of pre-existing and treatment induced immunogenicity (cellular and humoral) on cellular kinetics and efficacy

Based on the primary and secondary objectives, the following endpoints were assessed:

Endpoint	Description
Primary: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)	Number of participants with AEs and SAEs, including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs.
Primary: Number of participants with ibrutinib dose reductions and dose interruptions after tisagenlecleucel infusion	Number of participants with at least one dose reduction of ibrutinib and number of participants with at least one dose interruption of ibrutinib after tisagenlecleucel infusion.
Secondary: Response Rate (RR) as per Lugano criteria assessed by local investigator at 3 months and 6 months	Response rates (RR) at months 3 and 6 from tisagenlecleucel infusion were determined from the local investigator assessment of overall response at the 3 and 6-month tumor assessment. RR was defined as the proportion of patients with a Complete Response(CR) or Partial Response (PR) per the Lugano classification 2014.
Secondary: Best Overall Response (BOR) as per Lugano criteria assessed by local investigator	BOR is defined as the best response recorded from tisagenlecleucel infusion until disease progression, based on local investigator assessment per the Lugano classification 2014.
Secondary: Overall Response Rate (ORR) as per Lugano criteria assessed by local investigator	ORR per Lugano criteria is defined as the percentage of participants with a best overall response of Complete Response (CR) or Partial Response (PR).
Secondary: Duration of Response (DOR) as per Lugano criteria assessed by local investigator	Duration of response (DOR) applies only to patients whose best overall disease response was CR or PR. It is defined as the time from the date of first documented disease response (CR or PR) after tisagenlecleucel infusion to the date of first documented progression or death due to diffuse large B-cell lymphoma (DLBCL). DOR was estimated using the Kaplan-Meier method.

Secondary: Progression-Free Survival (PFS) as per Lugano criteria assessed by local investigator	PFS is defined as the time from the date of tisagenlecleucel infusion to the date of event defined as the first documented progression or death due to any cause. PFS was estimated using the Kaplan-Meier Method.
Secondary: Overall Survival (OS)	OS is defined as the time from date of first tisagenlecleucel infusion to date of death due to any reason. If a death was not been observed by the date of analysis cutoff, OS was censored at the date of last contact. OS was estimated using the Kaplan-Meier Method.
Secondary: PK parameters (Cmax, Tmax, AUC0-28d, Clast, Tlast, T1/2) of tisagenlecleucel transgene in peripheral blood	Pharmacokinetic (PK) parameters were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by quantitative polymerase chain reaction (qPCR). PK parameters were calculated by using non-compartmental methods.
Secondary: Number of participants with anti-tisagenlecleucel antibodies	The humoral immunogenicity assay measured the antibody titers specific to the tisagenlecleucel molecule prior to and following infusion. The number of humoral immunogenicity positive and negative patients is reported in the results table. Baseline is defined as the last non-missing value prior to first tisagenlecleucel infusion date. In the summary of at any time post-baseline, patients are counted as positive if they have one or more positive samples post-baseline, otherwise negative if they have at least one negative sample post baseline and otherwise unknown.

Secondary: Activation of T-cells in peripheral blood mononuclear cells	Activation of T-cells in peripheral blood mononuclear cells collected from subjects in response to mCAR19-derived peptides was used to assess the cellular immunogenicity against tisagenlecleucel. T-cell activation was measured by the percentage of interferon gamma positive cells by flow cytometry. The response measured by the assay is referred to as net response (%) and calculated for 2 mCAR19 peptide pools (Pool 1 and Pool 2).

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

The study treatment included a single tisagenlecleucel (CTL019) infusion that was preceded and followed by a continuous daily oral administration of ibrutinib.

For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells. Ibrutinib dosage was 560 mg once daily administered as tablets or capsules for oral use.

In the arm “Tisagenlecleucel + Ibrutinib Pre-apheresis”, patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis.

In the arm “Tisagenlecleucel + Ibrutinib Post-apheresis”, patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture.

Statistical Methods

The primary objectives of the study was to characterize the safety and tolerability of tisagenlecleucel in combination with ibrutinib. Safety was primarily assessed through descriptive summaries of safety data collected after tisagenlecleucel infusion, including the incidence and severity of AEs and SAEs, and changes in laboratory parameters. Tolerability was primarily assessed through a descriptive summary of ibrutinib dose modifications following tisagenlecleucel infusion.

Anti-tumor activity was evaluated as post-tisagenlecleucel response from baseline defined as the last assessment prior to tisagenlecleucel infusion. The variables used to evaluate anti-tumor activity were RR, ORR, DOR, PFS, and OS.

Humoral and cellular immunogenicity data were reported as summary statistics of pre and post-dose levels of activated T lymphocytes using Safety Set. The proportion of humoral immunogenicity positive and negative patients were summarized by time points and BOR.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Confirmed DLBCL as per the local histopathological assessment.
2. Relapsed or refractory disease having received 2 or more lines of systemic therapy, including anti-CD20 and anthracycline based chemotherapy, and either having progressed after (or relapsed after) ASCT, or being ineligible for or not consenting to ASCT.
3. Measurable disease at time of enrollment.
4. Eastern Cooperative Oncology Group (ECOG) performance status that is either 0 or 1 at screening.
5. Adequate renal, liver, and bone marrow organ function, and minimum level of pulmonary reserve.

Exclusion Criteria:

1. Patients with Richter's transformation, Burkitt's lymphoma, and primary DLBCL of the CNS.
2. Prior anti-CD19 directed therapy.
3. Prior gene therapy.
4. Prior adoptive T cell therapy.
5. Prior ibrutinib therapy within the 30 days prior to screening.
6. Patients with active CNS involvement were excluded, except if the CNS involvement has been effectively treated and provided that local treatment was > 4 weeks before enrollment.
7. Prior allogeneic HSCT
8. Significant cardiac abnormality including history of myocardial infarction within 6 months prior to screening as detailed

in the study protocol.

Participant Flow Table

Overall Study

	Tisagenlecleucel + Ibrutinib Pre-apheresis	Tisagenlecleucel + Ibrutinib Post-apheresis	Total
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	
Started	4	6	10
Completed	3	1	4
Not Completed	1	5	6
Death	1	4	5
Progressive Disease	0	1	1

Baseline Characteristics

	Tisagenlecleucel + Ibrutinib Pre-apheresis	Tisagenlecleucel + Ibrutinib Post-apheresis	Total
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	
Number of Participants [units: participants]	4	6	10
Age Continuous (units: years) Mean ± Standard Deviation			
	54.3±15.39	66.2±8.23	61.4±12.43
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)			
Female	0	2	2
Male	4	4	8
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)			
White	4	5	9
Missing	0	1	1

Primary Outcome Result(s)

Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

(Time Frame: From the day of tisagenlecleucel infusion up to the end of the study, with a maximum duration of 2.1 years)

	Tisagenlecleucel + Ibrutinib Pre-apheresis	Tisagenlecleucel + Ibrutinib Post-apheresis
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	4	6
Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) (units: participants) Count of Participants (Not Applicable)		
AEs	4 (100%)	6 (100%)
Treatment-related AEs	3 (75%)	6 (100%)
AEs with grade ≥ 3	3 (75%)	5 (83.33%)
Treatment-related AEs with grade ≥ 3	2 (50%)	3 (50%)
SAEs	2 (50%)	3 (50%)
Treatment-related SAEs	2 (50%)	0 (%)
Fatal SAEs	0 (%)	1 (16.67%)

AEs leading to discontinuation	1 (25%)	0 (%)
AEs leading to dose adjustment/interruption	0 (%)	1 (16.67%)
AEs requiring additional therapy	3 (75%)	6 (100%)

Number of participants with ibrutinib dose reductions and dose interruptions after tisagenlecleucel infusion

(Time Frame: From the day of tisagenlecleucel infusion up to the day of last dose of ibrutinib, with a maximum duration of 1.2 years)

	Tisagenlecleucel + Ibrutinib Pre-apheresis	**Tisagenlecleucel + Ibrutinib Post-apheresis**
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	4	6
Number of participants with ibrutinib dose reductions and dose interruptions after tisagenlecleucel infusion (units: participants) Count of Participants (Not Applicable)		
Ibrutinib, at least one dose reduction	1 (25%)	2 (33.33%)
Ibrutinib, at least one dose interruption	2 (50%)	2 (33.33%)

Secondary Outcome Result(s)

Response Rate (RR) as per Lugano criteria assessed by local investigator at 3 months and 6 months

(Time Frame: 3 months and 6 months)

	Tisagenlecleucel + Ibrutinib Pre-apheresis	Tisagenlecleucel + Ibrutinib Post-apheresis
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	4	6
Response Rate (RR) as per Lugano criteria assessed by local investigator at 3 months and 6 months (units: participants) Count of Participants (Not Applicable)		
3-month RR	3 (75%)	2 (33.33%)
6-month RR	3 (75%)	2 (33.33%)

Best Overall Response (BOR) as per Lugano criteria assessed by local investigator

(Time Frame: From the day of tisagenlecleucel infusion up to the end of the study, with a maximum duration of 2.1 years)

	Tisagenlecleucel + Ibrutinib Pre-apheresis	Tisagenlecleucel + Ibrutinib Post-apheresis
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose

	infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	4	6
Best Overall Response (BOR) as per Lugano criteria assessed by local investigator (units: participants) Count of Participants (Not Applicable)		
Complete Response (CR)	3 (75%)	2 (33.33%)
Partial Response (PR)	1 (25%)	1 (16.67%)
Progressive Disease (PD)	0 (%)	3 (50%)

Overall Response Rate (ORR) as per Lugano criteria assessed by local investigator

(Time Frame: From the day of tisagenlecleucel infusion up to the end of the study, with a maximum duration of 2.1 years)

	Tisagenlecleucel + Ibrutinib Pre-apheresis	**Tisagenlecleucel + Ibrutinib Post-apheresis**
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	4	6
Overall Response Rate (ORR) as per Lugano criteria assessed by local investigator (units: participants) Count of Participants (Not Applicable)		
	4 (100%)	3 (50%)

Duration of Response (DOR) as per Lugano criteria assessed by local investigator

(Time Frame: From first documented disease response to first documented progression or death due to DLBCL, assessed up to 2.1 years)

	Tisagenlecleucel + Ibrutinib Pre-apheresis	Tisagenlecleucel + Ibrutinib Post-apheresis
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	4	3
Median Duration of Response (DOR) as per Lugano criteria assessed by local investigator (units: months) Median	NA[1]	17.18

[1] Not estimable due to insufficient number of participants with events.

Progression-Free Survival (PFS) as per Lugano criteria assessed by local investigator

(Time Frame: From the day of tisagenlecleucel infusion until first documented progression or death due to any cause, assessed up to 2.1 years)

	Tisagenlecleucel + Ibrutinib Pre-apheresis	Tisagenlecleucel + Ibrutinib Post-apheresis
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.

Number of Participants Analyzed [units: participants]	4	6
Median Progression-Free Survival (PFS) as per Lugano criteria assessed by local investigator (units: months) Median		
	NA[1]	1.40

[1] Not estimable due to insufficient number of participants with events.

Overall Survival (OS)

(Time Frame: From the day of tisagenlecleucel infusion until death due to any cause, assessed up to 2.1 years)

	Tisagenlecleucel + Ibrutinib Pre-apheresis	Tisagenlecleucel + Ibrutinib Post-apheresis
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.
Number of Participants Analyzed [units: participants]	4	6
Median Overall Survival (OS) (units: months) Median		
	NA[1]	8.41

[1] Not estimable due to insufficient number of participants with events.

Maximum observed concentration (Cmax) of tisagenlecleucel transgene in peripheral blood

(Time Frame: Day 1 (pre-dose, 10 minutes post-infusion), Days 2, 4, 7, 11, 14, 17, 21 and 28 and Months 3, 6, 9, 12, 18 and 24)

Tisagenlecleucel + Ibrutinib Pre-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Pre-apheresis – SD/PD	Tisagenlecleucel + Ibrutinib Post-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Post-apheresis – SD/PD

Arm/Group Description	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).
Number of Participants Analyzed [units: participants]	3	0	3	2
Maximum observed concentration (Cmax) of tisagenlecleucel transgene in peripheral blood (units: copies/µg) Geometric Mean (Geometric Coefficient of Variation)				
	590 (117.8%)		3980 (160.2%)	1350 (278.1%)

Time to reach maximum concentration (Tmax) of tisagenlecleucel transgene in peripheral blood

(Time Frame: Day 1 (pre-dose, 10 minutes post-infusion), Days 2, 4, 7, 11, 14, 17, 21 and 28 and Months 3, 6, 9, 12, 18 and 24)

	Tisagenlecleucel + Ibrutinib Pre-apheresis – CR/PR	**Tisagenlecleucel + Ibrutinib Pre-apheresis – SD/PD**	**Tisagenlecleucel + Ibrutinib Post-apheresis – CR/PR**	**Tisagenlecleucel + Ibrutinib Post-apheresis – SD/PD**
Arm/Group Description	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).
Number of Participants Analyzed [units: participants]	3	0	3	2
Time to reach maximum concentration (Tmax) of tisagenlecleucel transgene in peripheral blood (units: days) Median (Full Range)				
	10.1 (5.51 to 16.1)		6.17 (2.72 to 9.76)	9.88 (9.85 to 9.91)

Area under the concentration-time curve from time zero to Day 28 (AUC 0-28d) of tisagenlecleucel transgene in peripheral blood

(Time Frame: Day 1 (pre-dose, 10 minutes post-infusion), Days 2, 4, 7, 11, 14, 17, 21 and 28 and Months 3, 6, 9, 12, 18 and 24)

	Tisagenlecleucel + Ibrutinib Pre-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Pre-apheresis – SD/PD	Tisagenlecleucel + Ibrutinib Post-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Post-apheresis – SD/PD
Arm/Group Description	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).
Number of Participants Analyzed [units: participants]	2	0	3	2
Area under the concentration-time curve from time zero to Day 28 (AUC 0-28d) of tisagenlecleucel transgene in peripheral blood (units: copies/µg*days) Geometric Mean (Geometric Coefficient of Variation)				
	10100 (97.8%)		39300 (76.2%)	13300 (256.1%)

Last observed quantifiable concentration (Clast) of tisagenlecleucel transgene in peripheral blood

(Time Frame: Day 1 (pre-dose, 10 minutes post-infusion), Days 2, 4, 7, 11, 14, 17, 21 and 28 and Months 3, 6, 9, 12, 18 and 24)

	Tisagenlecleucel + Ibrutinib Pre-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Pre-apheresis – SD/PD	Tisagenlecleucel + Ibrutinib Post-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Post-apheresis – SD/PD
Arm/Group Description	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).
Number of Participants Analyzed [units: participants]	3	0	3	2

Last observed quantifiable concentration (Clast) of tisagenlecleucel transgene in peripheral blood (units: copies/µg) Geometric Mean (Geometric Coefficient of Variation)			
67.4 (19.4%)	208 (98.9%)	101 (110.6%)

Time of last observed quantifiable concentration (Tlast) of tisagenlecleucel transgene in peripheral blood

(Time Frame: Day 1 (pre-dose, 10 minutes post-infusion), Days 2, 4, 7, 11, 14, 17, 21 and 28 and Months 3, 6, 9, 12, 18 and 24)

	Tisagenlecleucel + Ibrutinib Pre-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Pre-apheresis – SD/PD	Tisagenlecleucel + Ibrutinib Post-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Post-apheresis – SD/PD
Arm/Group Description	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).
Number of Participants Analyzed [units: participants]	3	0	3	2
Time of last observed quantifiable concentration (Tlast) of tisagenlecleucel transgene in peripheral blood (units: days) Median (Full Range)				
	26.2 (12.8 to 658)		282 (27.4 to 752)	37.9 (27.0 to 48.9)

Terminal elimination half-life (T1/2) of tisagenlecleucel transgene in peripheral blood

(Time Frame: Day 1 (pre-dose, 10 minutes post-infusion), Days 2, 4, 7, 11, 14, 17, 21 and 28 and Months 3, 6, 9, 12, 18 and 24)

	Tisagenlecleucel + Ibrutinib Pre-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Pre-apheresis – SD/PD	Tisagenlecleucel + Ibrutinib Post-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Post-apheresis – SD/PD
Arm/Group Description	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of

	Complete Response (CR) or Partial Response (PR).	Stable Disease (SD) or Progressive Disease (PD).	Complete Response (CR) or Partial Response (PR).	Stable Disease (SD) or Progressive Disease (PD).
Number of Participants Analyzed [units: participants]	1	0	2	0
Terminal elimination half-life (T1/2) of tisagenlecleucel transgene in peripheral blood (units: days) Geometric Mean (Geometric Coefficient of Variation)				
	116		65.0 (1182.0%)	

Number of participants with anti-tisagenlecleucel antibodies

(Time Frame: Pre-dose (Screening and Day -1), Post-Dose (Days 14 and 28 and Months 3, 6, 12, 18 and 24))

	Tisagenlecleucel + Ibrutinib Pre-apheresis – CR/PR	**Tisagenlecleucel + Ibrutinib Pre-apheresis – SD/PD**	**Tisagenlecleucel + Ibrutinib Post-apheresis – CR/PR**	**Tisagenlecleucel + Ibrutinib Post-apheresis – SD/PD**
Arm/Group Description	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).
Number of Participants Analyzed [units: participants]	4	0	3	3
Number of participants with anti-tisagenlecleucel antibodies (units: participants) Count of Participants (Not Applicable)				
Baseline (pre-dose): Positive	3 (75%)	(NaN%)	3 (100%)	2 (66.67%)
Baseline (pre-dose): Negative	1 (25%)	(NaN%)	0 (%)	1 (33.33%)
At any time post-baseline: Positive	4 (100%)	(NaN%)	3 (100%)	2 (66.67%)

At any time post-baseline: Negative	0 (%)	(NaN%)	0 (%)	1 (33.33%)

Activation of T-cells in peripheral blood mononuclear cells

(Time Frame: Baseline (Screening), Maximum post-Baseline (one of the following: Days 1, 14 and 28 and Months 3, 6, 12 and 18))

	Tisagenlecleucel + Ibrutinib Pre-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Pre-apheresis – SD/PD	Tisagenlecleucel + Ibrutinib Post-apheresis – CR/PR	Tisagenlecleucel + Ibrutinib Post-apheresis – SD/PD
Arm/Group Description	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Pre-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Complete Response (CR) or Partial Response (PR).	Participants in the Tisagenlecleucel + Ibrutinib Post-apheresis arm who had a Best Overall Response of Stable Disease (SD) or Progressive Disease (PD).
Number of Participants Analyzed [units: participants]	4	0	3	3
Activation of T-cells in peripheral blood mononuclear cells (units: net response (%)) Median (Full Range)				
Baseline, CTL019 Pool 1 CD3+ CD4+ IFNg+ (n=4,0,3,3)	0.00 (0.0 to 0.0)		0.03 (0.0 to 0.1)	0.03 (0.0 to 0.0)
Maximum post-baseline, CTL019 Pool 1 CD3+ CD4+ IFNg+ (n=3,0,3,2)	0.69 (0.2 to 1.2)		0.06 (0.0 to 0.9)	0.00 (0.0 to 0.0)
Baseline, CTL019 Pool 2 CD3+ CD4+ IFNg+ (n=4,0,3,3)	0.01 (0.0 to 0.9)		0.02 (0.0 to 3.5)	0.00 (0.0 to 0.0)
Maximum post-baseline, CTL019 Pool 2 CD3+ CD4+ IFNg+ (n=3,0,3,3)	1.65 (0.0 to 4.8)		0.03 (0.0 to 0.0)	0.00 (0.0 to 33.3)
Baseline, CTL019 Pool 1 CD3+ CD8+ IFNg+ (n=4,0,3,3)	0.00 (0.0 to 0.0)		0.00 (0.0 to 0.0)	0.00 (0.0 to 0.1)

Maximum post-baseline, CTL019 Pool 1 CD3+ CD8+ IFNg+ (n=4,0,3,2)	0.19 (0.0 to 3.8)	0.11 (0.0 to 1.3)	0.00 (0.0 to 0.0)
Baseline, CTL019 Pool 2 CD3+ CD8+ IFNg+ (n=4,0,3,3)	0.00 (0.0 to 0.0)	0.00 (0.0 to 0.0)	0.02 (0.0 to 0.0)
Maximum post-baseline, CTL019 Pool 2 CD3+ CD8+ IFNg+ (n=4,0,3,3)	0.10 (0.0 to 1.7)	0.07 (0.0 to 0.1)	0.00 (0.0 to 0.0)

Safety Results

All-Cause Mortality

	Tisagenlecleucel + Ibrutinib Pre-apheresis N = 4	Tisagenlecleucel + Ibrutinib Post-apheresis N = 6	All Patients N = 10
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	All Patients
Total participants affected	1 (25.00%)	4 (66.67%)	5 (50.00%)

Serious Adverse Events by System Organ Class

Time Frame	From the day of tisagenlecleucel infusion up to the end of the study, with a maximum duration of 2.1 years.
Additional Description	Adverse events that started or worsened after the start of tisagenlecleucel infusion.
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment

	Tisagenlecleucel + Ibrutinib Pre-apheresis N = 4	**Tisagenlecleucel + Ibrutinib Post-apheresis N = 6**	**All Patients N = 10**
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	All Patients
Total participants affected	2 (50.00%)	3 (50.00%)	5 (50.00%)
Cardiac disorders			
Sinus tachycardia	0 (0.00%)	1 (16.67%)	1 (10.00%)
General disorders and administration site conditions			
Chills	0 (0.00%)	1 (16.67%)	1 (10.00%)

Pain	0 (0.00%)	1 (16.67%)	1 (10.00%)
Immune system disorders			
Cytokine release syndrome	1 (25.00%)	0 (0.00%)	1 (10.00%)
Musculoskeletal and connective tissue disorders			
Back pain	0 (0.00%)	2 (33.33%)	2 (20.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma	0 (0.00%)	1 (16.67%)	1 (10.00%)
Tumour pain	0 (0.00%)	1 (16.67%)	1 (10.00%)
Nervous system disorders			
Syncope	1 (25.00%)	0 (0.00%)	1 (10.00%)
Renal and urinary disorders			
Haematuria	0 (0.00%)	1 (16.67%)	1 (10.00%)
Urinary retention	0 (0.00%)	1 (16.67%)	1 (10.00%)

Other Adverse Events by System Organ Class

Time Frame	From the day of tisagenlecleucel infusion up to the end of the study, with a maximum duration of 2.1 years.
Additional Description	Adverse events that started or worsened after the start of tisagenlecleucel infusion.
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Tisagenlecleucel + Ibrutinib Pre-apheresis N = 4	Tisagenlecleucel + Ibrutinib Post-apheresis N = 6	All Patients N = 10
Arm/Group Description	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment 28 days before undergoing leukapheresis. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	Single tisagenlecleucel (CTL019) infusion in combination with a continuous once daily administration of ibrutinib 560 mg. Patients were enrolled with the start of ibrutinib treatment after their leukapheresis product had been accepted for manufacture. For tisagenlecleucel, the recommended dose consisted of a single i.v. infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.	All Patients
Total participants affected	4 (100.00%)	6 (100.00%)	10 (100.00%)
Blood and lymphatic system disorders			
Anaemia	1 (25.00%)	5 (83.33%)	6 (60.00%)
Febrile neutropenia	0 (0.00%)	1 (16.67%)	1 (10.00%)
Neutropenia	1 (25.00%)	0 (0.00%)	1 (10.00%)
Cardiac disorders			
Atrioventricular block first degree	0 (0.00%)	1 (16.67%)	1 (10.00%)
Bradycardia	1 (25.00%)	0 (0.00%)	1 (10.00%)
Sinus bradycardia	0 (0.00%)	1 (16.67%)	1 (10.00%)
Sinus tachycardia	0 (0.00%)	1 (16.67%)	1 (10.00%)
Supraventricular tachycardia	0 (0.00%)	1 (16.67%)	1 (10.00%)
Ear and labyrinth disorders			

Tinnitus	1 (25.00%)	0 (0.00%)	1 (10.00%)
Endocrine disorders			
Hypothyroidism	1 (25.00%)	1 (16.67%)	2 (20.00%)
Gastrointestinal disorders			
Abdominal pain	0 (0.00%)	1 (16.67%)	1 (10.00%)
Constipation	1 (25.00%)	0 (0.00%)	1 (10.00%)
Diarrhoea	1 (25.00%)	1 (16.67%)	2 (20.00%)
Flatulence	0 (0.00%)	1 (16.67%)	1 (10.00%)
Gastrooesophageal reflux disease	1 (25.00%)	1 (16.67%)	2 (20.00%)
Nausea	0 (0.00%)	2 (33.33%)	2 (20.00%)
Toothache	1 (25.00%)	0 (0.00%)	1 (10.00%)
Vomiting	0 (0.00%)	1 (16.67%)	1 (10.00%)
General disorders and administration site conditions			
Catheter site pain	0 (0.00%)	1 (16.67%)	1 (10.00%)
Chills	0 (0.00%)	2 (33.33%)	2 (20.00%)
Face oedema	1 (25.00%)	0 (0.00%)	1 (10.00%)
Fatigue	1 (25.00%)	1 (16.67%)	2 (20.00%)
Influenza like illness	1 (25.00%)	0 (0.00%)	1 (10.00%)
Malaise	0 (0.00%)	1 (16.67%)	1 (10.00%)
Non-cardiac chest pain	1 (25.00%)	0 (0.00%)	1 (10.00%)
Oedema peripheral	0 (0.00%)	1 (16.67%)	1 (10.00%)
Pain	0 (0.00%)	1 (16.67%)	1 (10.00%)
Pyrexia	0 (0.00%)	4 (66.67%)	4 (40.00%)

Immune system disorders			
Cytokine release syndrome	0 (0.00%)	5 (83.33%)	5 (50.00%)
Hypogammaglobulinaemia	1 (25.00%)	0 (0.00%)	1 (10.00%)
Infections and infestations			
Bronchitis	0 (0.00%)	1 (16.67%)	1 (10.00%)
Escherichia infection	0 (0.00%)	1 (16.67%)	1 (10.00%)
Fungal infection	0 (0.00%)	1 (16.67%)	1 (10.00%)
Sinusitis	1 (25.00%)	0 (0.00%)	1 (10.00%)
Upper respiratory tract infection	2 (50.00%)	0 (0.00%)	2 (20.00%)
Injury, poisoning and procedural complications			
Wound	0 (0.00%)	1 (16.67%)	1 (10.00%)
Investigations			
Alanine aminotransferase increased	0 (0.00%)	2 (33.33%)	2 (20.00%)
Blood alkaline phosphatase increased	1 (25.00%)	1 (16.67%)	2 (20.00%)
Blood bilirubin increased	0 (0.00%)	2 (33.33%)	2 (20.00%)
Blood lactate dehydrogenase increased	1 (25.00%)	0 (0.00%)	1 (10.00%)
Glycosylated haemoglobin increased	1 (25.00%)	0 (0.00%)	1 (10.00%)
International normalised ratio increased	1 (25.00%)	0 (0.00%)	1 (10.00%)
Lipase increased	0 (0.00%)	1 (16.67%)	1 (10.00%)
Lymphocyte count decreased	1 (25.00%)	4 (66.67%)	5 (50.00%)

Neutrophil count decreased	1 (25.00%)	6 (100.00%)	7 (70.00%)
Platelet count decreased	1 (25.00%)	2 (33.33%)	3 (30.00%)
Staphylococcus test positive	0 (0.00%)	1 (16.67%)	1 (10.00%)
White blood cell count decreased	2 (50.00%)	6 (100.00%)	8 (80.00%)
Metabolism and nutrition disorders			
Decreased appetite	0 (0.00%)	1 (16.67%)	1 (10.00%)
Hyperglycaemia	1 (25.00%)	5 (83.33%)	6 (60.00%)
Hyperkalaemia	0 (0.00%)	3 (50.00%)	3 (30.00%)
Hypermagnesaemia	1 (25.00%)	1 (16.67%)	2 (20.00%)
Hypoalbuminaemia	1 (25.00%)	5 (83.33%)	6 (60.00%)
Hypocalcaemia	1 (25.00%)	4 (66.67%)	5 (50.00%)
Hypoferritinaemia	1 (25.00%)	0 (0.00%)	1 (10.00%)
Hypokalaemia	1 (25.00%)	3 (50.00%)	4 (40.00%)
Hypomagnesaemia	1 (25.00%)	2 (33.33%)	3 (30.00%)
Hyponatraemia	1 (25.00%)	4 (66.67%)	5 (50.00%)
Hypophosphataemia	1 (25.00%)	3 (50.00%)	4 (40.00%)
Vitamin B12 deficiency	1 (25.00%)	0 (0.00%)	1 (10.00%)
Vitamin D deficiency	1 (25.00%)	0 (0.00%)	1 (10.00%)
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (25.00%)	0 (0.00%)	1 (10.00%)
Back pain	0 (0.00%)	2 (33.33%)	2 (20.00%)
Muscle spasms	1 (25.00%)	2 (33.33%)	3 (30.00%)
Muscular weakness	0 (0.00%)	1 (16.67%)	1 (10.00%)
Nervous system disorders			

Aphasia	0 (0.00%)	1 (16.67%)	1 (10.00%)
Dizziness	0 (0.00%)	1 (16.67%)	1 (10.00%)
Encephalopathy	0 (0.00%)	1 (16.67%)	1 (10.00%)
Headache	2 (50.00%)	2 (33.33%)	4 (40.00%)
Neurotoxicity	0 (0.00%)	2 (33.33%)	2 (20.00%)
Paraesthesia	1 (25.00%)	0 (0.00%)	1 (10.00%)
Peripheral sensory neuropathy	0 (0.00%)	1 (16.67%)	1 (10.00%)
Tremor	1 (25.00%)	3 (50.00%)	4 (40.00%)
Psychiatric disorders			
Anxiety	0 (0.00%)	1 (16.67%)	1 (10.00%)
Hallucination	0 (0.00%)	1 (16.67%)	1 (10.00%)
Renal and urinary disorders			
Acute kidney injury	0 (0.00%)	1 (16.67%)	1 (10.00%)
Dysuria	0 (0.00%)	1 (16.67%)	1 (10.00%)
Haematuria	0 (0.00%)	2 (33.33%)	2 (20.00%)
Nocturia	1 (25.00%)	0 (0.00%)	1 (10.00%)
Pollakiuria	1 (25.00%)	2 (33.33%)	3 (30.00%)
Urinary retention	1 (25.00%)	1 (16.67%)	2 (20.00%)
Reproductive system and breast disorders			
Prostatic pain	1 (25.00%)	0 (0.00%)	1 (10.00%)
Testicular pain	1 (25.00%)	0 (0.00%)	1 (10.00%)
Respiratory, thoracic and mediastinal disorders			
Cough	0 (0.00%)	1 (16.67%)	1 (10.00%)

Dyspnoea	0 (0.00%)	2 (33.33%)	2 (20.00%)
Hypoxia	0 (0.00%)	2 (33.33%)	2 (20.00%)
Oropharyngeal pain	1 (25.00%)	1 (16.67%)	2 (20.00%)
Wheezing	1 (25.00%)	0 (0.00%)	1 (10.00%)
Skin and subcutaneous tissue disorders			
Petechiae	1 (25.00%)	0 (0.00%)	1 (10.00%)
Pruritus	0 (0.00%)	1 (16.67%)	1 (10.00%)
Rash maculo-papular	0 (0.00%)	2 (33.33%)	2 (20.00%)
Skin mass	1 (25.00%)	0 (0.00%)	1 (10.00%)
Vascular disorders			
Hypertension	1 (25.00%)	0 (0.00%)	1 (10.00%)
Hypotension	1 (25.00%)	1 (16.67%)	2 (20.00%)

Conclusion:

- Overall, treatment with tisagenlecleucel in combination with ibrutinib before undergoing leukapheresis (pre-apheresis) showed a better efficacy response in terms of ORR, DOR, PFS and OS as compared to tisagenlecleucel in combination with ibrutinib after undergoing leukapheresis (post-apheresis). However results must be interpreted with caution given the limited number of patients and the different patient population between the two arms.
- Overall, the treatment was well tolerated and the occurrence of serious cytokine release syndrome (CRS) events and neurological events remained low in both the arms.

Date of Clinical Trial Report

8-Jul-2022