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Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

tisagenlecleucel

Trial Indication(s)

Adult patients with relapsed/refractory DLBCL

Protocol Number

CCTL019J2101

Protocol Title

Phase Ib study of tisagenlecleucel in combination with pembrolizumab in relapsed/refractory (r/r) Diffuse large B-cell Lymphoma (DLBCL) patients.

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase IV

Study Start/End Dates

Study Start Date: 9 October 2018 (Actual)
Primary Completion Date: 20 July 2021 (Actual)
Study Completion Date: 20 July 2021 (Actual)

Reason for Termination (If applicable)

Novartis decided not to proceed to the dose expansion part of the study (part 2) based on the careful evaluation of this study data and in consideration of the rapidly evolving landscape for treatment options with similar efficacies.

Study Design/Methodology

This was a multi-center, open-label, Phase Ib, single administration study to evaluate the safety and efficacy of the administration of tisagenlecleucel in combination with pembrolizumab in patients with r/r DLBCL who received 2 or more lines of systemic therapy, including an anti-CD20 and anthracycline
based chemotherapy and having failed or are not candidates for or not consenting to autologous stem cell transplant (ASCT). There were 2 parts planned for the study: dose timing selection part (part 1) and dose expansion part (part 2). In dose timing selection part, the patients received bridging therapy once enrolled, which was later followed by lymphodepleting chemotherapy. The date when the patients were administered a single dose of tisagenlecleucel infusion after completion of lymphodepleting chemotherapy was considered as Day 1 (D1). The main purpose of this study was to know the best time to initiate administration of pembrolizumab at different times in combination with tisagenlecleucel, in order to mitigate the potential risk of increased cytokine release syndrome (CRS) (both in frequency and grade) due to increased chimeric antigen receptor (CAR)-T cell expansion after programmed death-1 (PD-1) inhibition, in particular when pembrolizumab was started too close to the expected tisagenlecleucel expansion post-infusion. Therefore, pembrolizumab was administered in 3 cohorts on day prior to tisagenlecleucel infusion i.e., Day-1 (D-1), on Day 8 (D8) and on Day 15 (D15).

Novartis decided not to proceed to the dose expansion part based on the careful evaluation of this study data in the dose timing selection part, and in consideration of the rapidly evolving landscape for treatment options with similar efficacies. Enrollment of patients into the study was halted on 13-Apr-2021. Importantly, the decision to halt the study was not a consequence of any safety concerns. The global Last Patient Last Visit (LPLV) was reached on 20-July-2021 and therefore the early termination of trial was declared and notified to Health Authorities. The evaluation of the results and the overall benefit-risk assessments were not impacted by this early trial termination.

Centers

5 centers in 3 countries: United States(3), Austria(1), Canada(1)

Objectives:

Primary Objectives:

- Dose timing selection: Assess the feasibility, safety and tolerability of administration of pembrolizumab in combination with tisagenlecleucel infusion, and determine the optimal time to start pembrolizumab
- Expansion phase: Evaluate overall response rate (ORR) as per Lugano criteria assessed by local investigator

Secondary Objectives:

- Evaluate duration of response (DOR) as per Lugano criteria assessed by local investigator.
- Evaluate progression free survival (PFS) as per Lugano criteria assessed by local investigator.
- Evaluate overall survival (OS).
- Evaluate the safety and tolerability of tisagenlecleucel in combination with pembrolizumab.
- Characterize the in vivo cellular kinetics of tisagenlecleucel in blood, bone marrow, lymph nodes and other tissues if available by quantitative polymerase chain reaction (qPCR) and flow cytometry.
- Characterize the impact of pembrolizumab dosing strategy on the cellular kinetics of tisagenlecleucel.
- Characterize immunogenicity (cellular and humoral) of tisagenlecleucel and impact on cellular kinetics, efficacy and safety.

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

Patients received tisagenlecleucel as a single dose of 0.6 – 6.0 x 108 CAR-positive viable T cells via intravenous infusion. Pembrolizumab was administered at the approved single agent dose of 200 mg intravenously over 30 minutes every 3 weeks for up to 6 doses in 3 cohorts. The 3 cohorts are, Cohort 1: Four patients received the pembrolizumab dose one day prior to tisagenlecleucel infusion on D-1. Cohort 2: Four patients received the pembrolizumab dose on D8; and Cohort 3: Four patients received the pembrolizumab dose on D15 as shown:

- Cohort 1: Tisagenlecleucel + Pembrolizumab (Pemb D15, n=4)
- Cohort 2: Tisagenlecleucel + Pembrolizumab (Pemb D8, n=4)
- Cohort 3: Pembrolizumab + Tisagenlecleucel (Pemb D-1, n=4)

Statistical Methods

Dose timing selection part:
The primary objective of the dose timing selection part of the study was to characterize the safety and tolerability of tisagenlecleucel in combination with pembrolizumab and establish the optimal dose timing for the first pembrolizumab administration. The primary variable was the incidence of pembrolizumabinduced dose limiting toxicities (DLTs) observed between first pembrolizumab infusion to 21 days thereafter.

For patients who start with the pembrolizumab dose at D8 and D15 post tisagenlecleucel infusion, the optimal timing of the pembrolizumab administration was determined based upon the estimation of the probability of DLT. A 2-parameter Bayesian logistic regression model (BLRM) guided by the Escalation with Overdose Control (EWOC) principle was used to guide dose timing selection together with clinical review of accumulating safety and cellular kinetic data.

As the trial progresses, the BLRMs were updated using DLT data accumulated during the study to guide the selection of dose timing for the next cohort. Safety data for the Phase I part was summarized by cohorts as well as pooled groups.

For additional patients who started with the pembrolizumab dose one day prior to tisagenlecleucel infusion (D-1 cohort), all relevant safety, biomarker, laboratory and cellular kinetic data was summarized separately. The probability of excess toxicity in the D-1 cohort was assessed using Bayesian modelling, independent from the BLRM used for the other cohorts. Only if the posterior probability of excess toxicity is less than 25% the D-1 timing be considered as a possible timing for dose expansion.

The timing of the pembrolizumab administration for expansion was selected between the D-1 and the selected timing (i.e. D8 and D15) from the BLRM model based on clinical review of all relevant data available for comparison of the different cohorts.

Dose expansion part:
The primary objective of the dose expansion part was to evaluate the efficacy in terms of disease ORR as per Lugano criteria (assessed by local investigator) of tisagenlecleucel and pembrolizumab.

Due to early termination of the study, the expansion phase was not conducted and therefore, ORR was reported along with other secondary endpoints (BOR, DOR, PFS) and was summarized descriptively with 95% exact confidence interval.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Confirmed DLBCL per local histopathology assessment.
- Relapsed or refractory disease after having recieved 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 not candidates for or not consenting to ASCT.
- Measurable disease at time of enrollment
- ECOG performance status that is either 0 or 1 at screening.

Exclusion Criteria:
- Patients with Richter's transformation, and Burkitt lymphoma, and primary DLBCL of CNS.
- Prior treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy.
- Patients with active CNS involvement are excluded, except if the CNS involvement has been effectively treated and provided that local treatment was >4 weeks before enrollment.
- Prior allogeneic HSCT.
- Unstable angina and/or myocardial infarction and/or coronary artery bypass graft (CABG), or stroke within 6 months prior to screening, and/or impaired cardiac function or clinically significant cardiac disease
- Patients with a history of prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibodies, other immune checkpoint inhibitors.
- History of interstitial lung disease or (non-infectious) pneumonitis that required oral or intravenous steroids (other than COPD exacerbation) or current pneumonitis.

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Overall Study

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D8	Tisagenlecleucel + Pemb D1	Total
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which,	Patients received a single dose of tisagenlecleucel infusion, of which,	Patients received a single dose of tisagenlecleucel infusion, of which,	

	pembrolizumab was administered on day 15 (D15)	pembrolizumab was administered on day 8 (D8)	pembrolizumab was administered on day 1 (D-1)	
Started	4	6	5	15
Completed	1	1	0	2
Not Completed	3	5	5	13
Death	1	4	2	7
Study terminated by sponsor	0	0	3	3
Adverse Event	0	1	0	1
Progressive disease	1	0	0	1
Subject decision	1	0	0	1

Baseline Characteristics

	Tisagenlecleucel + Pemb D 15	**Tisagenlecleucel + Pemb D 8**	**Tisagenlecleucel + Pemb D-1**	**Total**
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)	
Number of Participants [units: participants]	4	4	4	12

Age Continuous (units: years) Mean ± Standard Deviation				
	55.3±18.84	66.0±6.16	63.0±4.97	61.4±11.67
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)				
Female	1	3	4	8
Male	3	1	0	4
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)				
White	4	3	4	11
Black	0	1	0	1

Primary Outcome Result(s)

Percent of participants recieving pembrolizumab per protocol schedule

(Time Frame: 21 days after first pembrolizumab infusion)

	Tisagenlecleucel + Pemb D 15	**Tisagenlecleucel + Pemb D 8**	**Tisagenlecleucel + Pemb D-1**
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4

Percent of participants recieving pembrolizumab per protocol schedule (units: Participants) Count of Participants (Not Applicable)			
	4 (100%)	4 (100%)	4 (100%)

Dose Timing part: Incidence of dose limiting toxicities (DLTs)

(Time Frame: 21 days after first pembrolizumab infusion)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Dose Timing part: Incidence of dose limiting toxicities (DLTs) (units: participants) Count of Participants (Not Applicable)			
	0 (%)	0 (%)	0 (%)

Expansion part: Overall response rate (ORR)

(Time Frame: 3 month post tisagenlecleucel infusion)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Expansion part: Overall response rate (ORR) (units: Participants) Count of Participants (Not Applicable)			
	2 (50%)	1 (25%)	3 (75%)

Secondary Outcome Result(s)

Duration of Response (DOR)

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D-1)

Number of Participants Analyzed [units: participants]	4	4	4
Duration of Response (DOR) (units: days) Median (Full Range)			
	100.0 (92 to 108)	658.0 (658 to 658)	196.0 (163 to 345)

Progression Free Survival (PFS)

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	**Tisagenlecleucel + Pemb D 8**	**Tisagenlecleucel + Pemb D-1**
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Progression Free Survival (PFS) (units: days) Median (Full Range)			
	109.5 (28 to 193)	69.5 (56 to 722)	282.5 (29 to 378)

Overall Survival (OS)

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Overall Survival (OS) (units: days) Median (Full Range)			
	298.5 (44 to 743)	122.5 (94 to 752)	282.5 (53 to 378)

Quantitative polymerase chain reaction (qPCR) detected tisagenlecleucel transgene concentrations in peripheral blood, bone marrow and lymph nodes, and other tissues if available: AUC

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Quantitative polymerase chain reaction (qPCR) detected tisagenlecleucel transgene concentrations in peripheral blood, bone marrow and lymph nodes, and			

other tissues if available: AUC (units: Copies/ug×days) Geometric Mean (Geometric Coefficient of Variation)			
AUC 0-28d	109000 (274%)	42200 (153%)	359000 (1470%)
AUC 0-84d (n= 3, 2, 3)	107000 (329%)	113000 (3.30%)	45600 (624%)
AUC 0-180 (n = 2, 1, 3)	179000 (556%)	125000 (NA%)[1]	874000 (295%)

[1] NA = sample size is too small to calculate GEO CV%

Quantitative polymerase chain reaction (qPCR) detected tisagenlecleucel transgene concentrations in peripheral blood, bone marrow and lymph nodes, and other tissues if available: Cmax & Clast

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	**Tisagenlecleucel + Pemb D 8**	**Tisagenlecleucel + Pemb D-1**
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Quantitative polymerase chain reaction (qPCR) detected tisagenlecleucel transgene concentrations in peripheral blood, bone marrow and lymph nodes, and other tissues if available: Cmax & Clast (units: Copies/ug) Geometric Mean (Geometric Coefficient of Variation)			
Cmax	10600 (423%)	4840 (163%)	3400 (1120%)
Clast	212 (504%)	252 (28.9%)	693 (205%)

Quantitative polymerase chain reaction (qPCR) detected tisagenlecleucel transgene concentrations in peripheral blood, bone marrow and lymph nodes, and other tissues if available: Tmax, T1/2 & Tlast

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Quantitative polymerase chain reaction (qPCR) detected tisagenlecleucel transgene concentrations in peripheral blood, bone marrow and lymph nodes, and other tissues if available: Tmax, T1/2 & Tlast (units: days) Median (Full Range)			
Tmax	7.91 (5.85 to 15.0)	7.82 (5.74 to 11.1)	16.0 (12.9 to 29.8)
T1/2 (n = 3, 2, 1)	37.5 (4.33 to 81.2)	18.5 (15.7 to 21.4)	4.48 (4.48 to 4.48)
Tlast	135 (27.7 to 742)	68.9 (57.9 to 721)	276 (26.0 to 376)

CD3+ tisagenlecleucel cells concentration measure by flow cytometry in peripheral blood, bone marrow and other tissues if available: AUCs

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of	Patients received a single dose of	Patients received a single dose of

	tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
CD3+ tisagenlecleucel cells concentration measure by flow cytometry in peripheral blood, bone marrow and other tissues if available: AUCs (units: %×days) Geometric Mean (Geometric Coefficient of Variation)			
AUC 0-28d	38.7 (186%)	29.3 (152%)	17.8 (523%)
AUC 0-84d (n= 3, 3, 3)	62.8 (255%)	64.7 (145%)	23.4 (61.2%)
AUC 0-180 (n = 3, 1, 3)	96.9 (163%)	75.0 (NA%)[1]	52.8 (11.0%)

[1] NA = sample size is too small to calculate GEO CV%

CD3+ tisagenlecleucel cells concentration measure by flow cytometry in peripheral blood, bone marrow and other tissues if available: Cmax, Clast

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
CD3+ tisagenlecleucel cells concentration measure by flow cytometry in peripheral blood, bone marrow and other tissues if available: Cmax, Clast			

(units: percentage of participants) Geometric Mean (Geometric Coefficient of Variation)			
Cmax	4.89 (191%)	3.89 (227%)	1.77 (294%)
Clast	0.291 (103%)	0.366 (79.0%)	0.645 (170%)

CD3+ tisagenlecleucel cells concentration measure by flow cytometry in peripheral blood, bone marrow and other tissues if available: Tmax, T1/2 & Tlast

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
CD3+ tisagenlecleucel cells concentration measure by flow cytometry in peripheral blood, bone marrow and other tissues if available: Tmax, T1/2 & Tlast (units: days) Median (Full Range)			
Tmax	6.01 (2.84 to 10.7)	8.39 (1.04 to 12.8)	12.6 (0.187 to 75.8)
T1/2 (n = 2, 1, 1)	25.2 (7.05 to 43.3)	18.8 (18.8 to 18.8)	7.59 (7.59 to 7.59)
Tlast	266 (27.7 to 555)	82.8 (57.9 to 545)	189 (26.0 to 278)

Cellular kinetics of tisagenlecleucel transgene and CD3+ tisagenlecleucel cells (including CD4+/CD8+ subsets) in peripheral blood: AUCs

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Cellular kinetics of tisagenlecleucel transgene and CD3+ tisagenlecleucel cells (including CD4+/CD8+ subsets) in peripheral blood: AUCs (units: %×days) Geometric Mean (Geometric Coefficient of Variation)			
AUC 0-28d (n = 3, 4, 4)	16.3 (87.3%)	16.5 (182%)	9.84 (674%)
AUC 0-84d (n= 3, 3, 3)	28.5 (90.8%)	38.7 (149%)	9.90 (63.0%)
AUC 0-180 (n = 3, 1, 3)	45.7 (53.4%)	40.1 (NA%)[1]	31.2 (4.26%)

[1] NA = sample size is too small to calculate GEO CV%

Cellular kinetics of tisagenlecleucel transgene and CD3+ tisagenlecleucel cells (including CD4+/CD8+ subsets) in peripheral blood: Cmax, Clast

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab

	was administered on day 15 (D15)	was administered on day 8 (D8)	was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Cellular kinetics of tisagenlecleucel transgene and CD3+ tisagenlecleucel cells (including CD4+/CD8+ subsets) in peripheral blood: Cmax, Clast (units: percentage of participants) Geometric Mean (Geometric Coefficient of Variation)			
Cmax	0.911 (297%)	2.55 (301%)	1.23 (381%)
Clast	0.141 (41.7%)	0.168 (74.4%)	0.524 (137%)

Cellular kinetics of tisagenlecleucel transgene and CD3+ tisagenlecleucel cells (including CD4+/CD8+ subsets) in peripheral blood: Tmax, T1/2 & Tlast

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	**Tisagenlecleucel + Pemb D 8**	**Tisagenlecleucel + Pemb D-1**
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Cellular kinetics of tisagenlecleucel transgene and CD3+ tisagenlecleucel cells (including CD4+/CD8+ subsets) in peripheral blood: Tmax, T1/2 & Tlast (units: days) Median (Full Range)			
Tmax	6.27 (2.86 to 18.9)	6.89 (1.04 to 12.8)	5.40 (0.187 to 19.2)

T1/2 (n = 0, 2, 1)		38.0 (17.4 to 58.6)	7.62 (7.62 to 7.62)
Tlast	266 (27.7 to 555)	82.8 (57.9 to 545)	189 (26.0 to 278)

Summary of peripheral blood cellular kinetic parameter for tisagenlecleucel by flow cytometry, by cohort - D3+/CTL019+/CD8+: AUCs

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Summary of peripheral blood cellular kinetic parameter for tisagenlecleucel by flow cytometry, by cohort - D3+/CTL019+/CD8+: AUCs (units: %×days) Geometric Mean (Geometric Coefficient of Variation)			
AUC 0-28d (n = 3, 4, 4)	13.4 (819%)	10.3 (185%)	3.89 (1190%)
AUC 0-84d (n= 3, 3, 2)	16.3 (1500%)	22.8 (155%)	6.16 (8.92%)
AUC 0-180 (n = 2, 1, 2)	49.4 (1880%)	24.8 (NA%)[1]	9.97 (0.327%)

[1] NA = sample size is too small to calculate GEO CV%

Summary of peripheral blood cellular kinetic parameter for tisagenlecleucel by flow cytometry, by cohort - CD3+/CTL019+/CD8+: Cmax, Clast

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Summary of peripheral blood cellular kinetic parameter for tisagenlecleucel by flow cytometry, by cohort - CD3+/CTL019+/CD8+: Cmax, Clast (units: percentage of participants) Geometric Mean (Geometric Coefficient of Variation)			
Cmax	1.68 (1080%)	1.31 (245%)	0.645 (199%)
Clast	0.157 (111%)	0.178 (88.8%)	0.245 (150%)

Summary of peripheral blood cellular kinetic parameter for tisagenlecleucel by flow cytometry, by cohort - CD3+/CTL019+/CD8+: Tmax, T1/2 & Tlast

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4

Summary of peripheral blood cellular kinetic parameter for tisagenlecleucel by flow cytometry, by cohort - CD3+/CTL019+/CD8+: Tmax, T1/2 & Tlast
(units: days)
Median (Full Range)

Tmax	6.27 (2.86 to 18.9)	6.89 (1.04 to 12.8)	5.40 (0.187 to 19.2)
T1/2 (n = 0, 2, 1)		38.0 (17.4 to 58.6)	7.62 (7.62 to 7.62)
Tlast	266 (27.7 to 555)	82.8 (57.9 to 545)	189 (26.0 to 278)

Summary of Pembrolizumab pharmacokinetic parameters in peripheral blood by cohort: AUC

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	**Tisagenlecleucel + Pemb D 8**	**Tisagenlecleucel + Pemb D-1**
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Summary of Pembrolizumab pharmacokinetic parameters in peripheral blood by cohort: AUC (units: h×ug/mL) Geometric Mean (Geometric Coefficient of Variation)			
AUC (n = 3, 4, 2)	10100 (16.0%)	11800 (18.5%)	12200 (1190%)

Summary of peripheral blood cellular kinetic parameter for tisagenlecleucel by flow cytometry, by cohort - CD3+/CTL019+/CD8+: Cmax

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Summary of peripheral blood cellular kinetic parameter for tisagenlecleucel by flow cytometry, by cohort - CD3+/CTL019+/CD8+: Cmax (units: ug/ml) Geometric Mean (Geometric Coefficient of Variation)			
Cmax (n =4, 4, 3)	47.6 (9.46%)	57.7 (35.4%)	66.8 (27.5%)

Summary of peripheral blood cellular kinetic parameter for tisagenlecleucel by flow cytometry, by cohort - CD3+/CTL019+/CD8+: Tmax

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1

Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Summary of peripheral blood cellular kinetic parameter for tisagenlecleucel by flow cytometry, by cohort - CD3+/CTL019+/CD8+: Tmax (units: days) Median (Full Range)			
Tmax	1.56 (1.42 to 1.58)	1.77 (1.68 to 1.78)	1.50 (1.50 to 1.53)

Pre-existing and treatment induced immunogenicity (cellular and humoral) of tisagenlecleucel

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4

Pre-existing and treatment induced immunogenicity (cellular and humoral) of tisagenlecleucel (units: participants) Count of Participants (Not Applicable)			
Positive	0 (%)	0 (%)	1 (25%)
Negative	4 (100%)	4 (100%)	3 (75%)

Cellular kinetic parameter: CRS grades

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	**Tisagenlecleucel + Pemb D 8**	**Tisagenlecleucel + Pemb D-1**
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Cellular kinetic parameter: CRS grades (units: participants) Count of Participants (Not Applicable)			
CRS - No	3 (75%)	0 (%)	2 (50%)

CRS -Yes	1 (25%)	4 (100%)	2 (50%)

Cellular kinetic parameter: AUC 0 - 84d

(Time Frame: 24 months)

	Tisagenlecleucel+ Pemb D15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Cellular kinetic parameter: AUC 0 - 84d (units: Copies/ug*days) Median (Full Range)			
Anti-mCAR19 antibody post infusion positive (n =1, 0, 0)	52000 (52000 to 52000)		
Anti-mCAR19 antibody post infusion negative (n =2, 2, 3)	344000 (36600 to 652000)	113000 (110000 to 116000)	23400 (12200 to 398000)

Cellular kinetic parameter: Cmax

(Time Frame: 24 months)

	Tisagenlecleucel + Pemb D 15	Tisagenlecleucel + Pemb D 8	Tisagenlecleucel + Pemb D-1

Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)
Number of Participants Analyzed [units: participants]	4	4	4
Cellular kinetic parameter: Cmax (units: Copies/ug) Median (Full Range)			
Anti-mCAR19 antibody post infusion positive (n = 1, 0, 0)	3340 (3340 to 3340)		
Anti-mCAR19 antibody post infusion negative (n = 3, 4, 4)	24900 (1980 to 77200)	7090 (981 to 12400)	10600 (270 to 22800)

Safety Results

All-Cause Mortality

	Tisagenlecleucel + Pemb D 15 N = 4	Tisagenlecleucel + Pemb D 8Edit N = 4	Tisagenlecleucel + Pemb D-1 N = 4	All patients N = 12
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab	All patients enrolled in the study

	was administered on day 15 (D15)	was administered on day 8 (D8)	was administered on day 1 (D-1)	
Total participants affected	1 (25.00%)	3 (75.00%)	1 (25.00%)	5 (41.67%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events were reported from first dose of study treatment until Month 12, with a maximum duration of exposure of 66 days for tisagenlecleucel maximum duration of 126 days for pembrolizumab.
Additional Description	Adverse Event (AE): Any sign or symptom that occurs during treatment.
Source Vocabulary for Table Default	MedDRA (24.0)
Assessment Type for Table Default	Systematic Assessment

	Tisagenlecleucel + Pemb D 15 N = 4	**Tisagenlecleucel + Pemb D 8Edit N = 4**	**Tisagenlecleucel + Pemb D-1 N = 4**	**All patients N = 12**
Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)	All patients enrolled in the study
Total participants affected	2 (50.00%)	4 (100.00%)	2 (50.00%)	8 (66.67%)
Blood and lymphatic system disorders				
Febrile neutropenia	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)

Gastrointestinal disorders				
Abdominal pain	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Colitis	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Diarrhoea	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Melaena	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Pancreatitis	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
General disorders and administration site conditions				
Pyrexia	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Hepatobiliary disorders				
Hepatitis	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Immune system disorders				
Cytokine release syndrome	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Infections and infestations				
Anal abscess	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Metabolism and nutrition disorders				
Failure to thrive	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal chest pain	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Metastases to meninges	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Nervous system disorders				
Syncope	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Pleural effusion	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Pleuritic pain	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events were reported from first dose of study treatment until Month 12, with a maximum duration of exposure of 66 days for tisagenlecleucel maximum duration of 126 days for pembrolizumab.
Additional Description	Adverse Event (AE): Any sign or symptom that occurs during treatment.
Source Vocabulary for Table Default	MedDRA (24.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Tisagenlecleucel + Pemb D 15 N = 4	**Tisagenlecleucel + Pemb D 8Edit N = 4**	**Tisagenlecleucel + Pemb D-1 N = 4**	**All patients N = 12**

Arm/Group Description	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 15 (D15)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 8 (D8)	Patients received a single dose of tisagenlecleucel infusion, of which, pembrolizumab was administered on day 1 (D-1)	All patients enrolled in the study
Total participants affected	4 (100.00%)	4 (100.00%)	4 (100.00%)	12 (100.00%)
Blood and lymphatic system disorders				
Anaemia	2 (50.00%)	2 (50.00%)	3 (75.00%)	7 (58.33%)
Leukopenia	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Neutropenia	1 (25.00%)	2 (50.00%)	3 (75.00%)	6 (50.00%)
Thrombocytopenia	1 (25.00%)	1 (25.00%)	0 (0.00%)	2 (16.67%)
Cardiac disorders				
Sinus tachycardia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Ear and labyrinth disorders				
Vertigo	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Endocrine disorders				
Hypoparathyroidism	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Eye disorders				
Dry eye	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Gastrointestinal disorders				
Abdominal pain	0 (0.00%)	2 (50.00%)	0 (0.00%)	2 (16.67%)
Cheilitis	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Constipation	2 (50.00%)	2 (50.00%)	0 (0.00%)	4 (33.33%)

Diarrhoea	3 (75.00%)	0 (0.00%)	0 (0.00%)	3 (25.00%)
Diverticulum intestinal	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Dry mouth	1 (25.00%)	1 (25.00%)	0 (0.00%)	2 (16.67%)
Dysphagia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Epigastric discomfort	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Haematochezia	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Haemorrhoids	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Lip dry	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Mesenteric vein thrombosis	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Nausea	2 (50.00%)	2 (50.00%)	2 (50.00%)	6 (50.00%)
Stomatitis	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Vomiting	0 (0.00%)	1 (25.00%)	2 (50.00%)	3 (25.00%)
General disorders and administration site conditions				
Asthenia	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Fatigue	2 (50.00%)	1 (25.00%)	0 (0.00%)	3 (25.00%)
Granuloma	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Oedema peripheral	1 (25.00%)	1 (25.00%)	0 (0.00%)	2 (16.67%)
Pyrexia	0 (0.00%)	2 (50.00%)	0 (0.00%)	2 (16.67%)
Systemic inflammatory response syndrome	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Hepatobiliary disorders				
Cholecystitis	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Immune system disorders				

Cytokine release syndrome	1 (25.00%)	4 (100.00%)	1 (25.00%)	6 (50.00%)
Hypogammaglobulinaemia	0 (0.00%)	1 (25.00%)	1 (25.00%)	2 (16.67%)
Infections and infestations				
Anal abscess	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Bronchitis	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Campylobacter gastroenteritis	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Conjunctivitis	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Eye infection	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Folliculitis	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Gastroenteritis rotavirus	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Rash pustular	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Rhinitis	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Upper respiratory tract infection	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Urinary tract infection	0 (0.00%)	2 (50.00%)	0 (0.00%)	2 (16.67%)
Injury, poisoning and procedural complications				
Chest injury	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Fall	0 (0.00%)	1 (25.00%)	1 (25.00%)	2 (16.67%)
Investigations				
Alanine aminotransferase increased	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)

Aspartate aminotransferase increased	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Fibrin D dimer increased	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Immunoglobulins decreased	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Influenza A virus test positive	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Liver function test increased	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Lymphocyte count decreased	0 (0.00%)	1 (25.00%)	1 (25.00%)	2 (16.67%)
Neutrophil count decreased	0 (0.00%)	1 (25.00%)	1 (25.00%)	2 (16.67%)
N-terminal prohormone brain natriuretic peptide increased	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Platelet count decreased	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
White blood cell count decreased	1 (25.00%)	1 (25.00%)	2 (50.00%)	4 (33.33%)
Metabolism and nutrition disorders				
Decreased appetite	1 (25.00%)	1 (25.00%)	1 (25.00%)	3 (25.00%)
Folate deficiency	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Hypokalaemia	1 (25.00%)	3 (75.00%)	1 (25.00%)	5 (41.67%)
Hypomagnesaemia	0 (0.00%)	2 (50.00%)	0 (0.00%)	2 (16.67%)
Hypophosphataemia	1 (25.00%)	2 (50.00%)	0 (0.00%)	3 (25.00%)
Iron deficiency	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Malnutrition	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)

Musculoskeletal and connective tissue disorders				
Arthralgia	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Back pain	0 (0.00%)	2 (50.00%)	0 (0.00%)	2 (16.67%)
Bone pain	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Neck pain	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Nervous system disorders				
Amnesia	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Dizziness	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Dysgeusia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Dysgraphia	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Encephalopathy	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Headache	0 (0.00%)	2 (50.00%)	0 (0.00%)	2 (16.67%)
IIIrd nerve paralysis	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Immune effector cell-associated neurotoxicity syndrome	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Tremor	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Trigeminal neuralgia	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Psychiatric disorders				
Depression	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Disorientation	0 (0.00%)	2 (50.00%)	0 (0.00%)	2 (16.67%)
Renal and urinary disorders				
Pollakiuria	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)

Urinary incontinence	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Reproductive system and breast disorders				
Benign prostatic hyperplasia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Vaginal discharge	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Respiratory, thoracic and mediastinal disorders				
Cough	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Dyspnoea	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Nasal congestion	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Oropharyngeal pain	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Pleural effusion	1 (25.00%)	1 (25.00%)	0 (0.00%)	2 (16.67%)
Skin and subcutaneous tissue disorders				
Erythema	1 (25.00%)	1 (25.00%)	0 (0.00%)	2 (16.67%)
Pruritus	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (8.33%)
Rash	0 (0.00%)	1 (25.00%)	1 (25.00%)	2 (16.67%)
Skin exfoliation	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Vascular disorders				
Hot flush	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (8.33%)
Hypotension	0 (0.00%)	0 (0.00%)	2 (50.00%)	2 (16.67%)
Orthostatic hypotension	0 (0.00%)	2 (50.00%)	0 (0.00%)	2 (16.67%)
Vascular compression	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)

Conclusion:

In this study, a single dose of tisagenlecleucel in combination with pembrolizumab was generally tolerated, with no significant safety findings observed within the 3 dose timing cohorts explored prior to study termination, given the rapidly evolving landscape for treatment options with similar efficacies. The efficacy data showed clinical responses comparable to the earlier CTL019C2201 pivotal study in a comparable Diffuse large B-cell lymphoma (DLBCL) patient population. However, due to both the constrained sample size and the early termination of this study prior to dose expansion cohort, only limited conclusions can be drawn.

Nevertheless, this study constitutes a proof of concept that combination of tisagenlecleucel and immunotherapies is feasible from the safety and efficacy clinical point of view and may pave the way for the design of future research efforts.

Date of Clinical Trial Report

10 February 2022