25 January 2024
EMA/62477/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Kymriah

Tisagenlecleucel

Procedure no: EMEA/H/C/004090/P46/022

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 5-Oct-2023, the MAH submitted a completed paediatric study for tisagenlecleucel, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Primary results with cut-off date 10-Oct-2021 of the CCTL019C2202-study were submitted as a part of the Type II variation EMEA/H/C/004090/II/0056.

A short critical expert overview has also been provided.

Steps taken for the assessment	
Description	**Actual Date**
Start of procedure	27.11.2023
CAT Rapporteur Assessment Report	03.01.2024
CAT conclusion	19.01.2024
CHMP adoption of conclusions:	25.01.2024

Rapporteur: Rune Kjeken

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study CCTL019C2202 is a stand-alone study.

Primary results with cut-off date 10-Oct-2021 of the CCTL019C2202-study were submitted as a part of the Type II variation EMEA/H/C/004090/II/0056. The primary results of the study fulfilled the paediatric investigational plan (PIP) EMEA-001654-PIP02-17-M01, which do not support a paediatric indication.

The second of two opened PIPs for Kymriah, is EMEA-001654-PIP01-14-M03 with clinical measure still ongoing and completion date by Nov-2026.

2.2. Information on the pharmaceutical formulation used in the study

According to SmPC, the approved dose range for paediatric and young adult patients with B-cell ALL is 0.2 to 5 $\times$ 10^6 CAR-positive viable T cells/kg body weight for patients $\leq$ 50 kg and 0.1 to 2.5 $\times$ 10^8 CAR-positive viable T cells (non-weight based) for patients > 50 kg. The approved dose range (non-weight based) for adult patients with DLBCL and FL is 0.6 to 6 × 10^8 CAR-positive viable T cells.

2.3. Clinical aspects

2.3.1. Introduction

Kymriah (INN: tisagenlecleucel, product code CTL019) was approved in the Europe Union (EU) via the centralised procedure No. EMEA/H/C/004090 on 22-Aug-2018 and is indicated for the treatment of:

Paediatric and young adult patients up to and including 25 years of age with B cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

Adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Tisagenlecleucel is a second-generation chimeric antigen receptor (CAR)-based gene therapy product that contains autologous genetically modified T-cells. The product is manufactured from the patient's own peripheral blood T-cells, which are transduced ex vivo with a lentiviral vector that encodes a CAR directed against human CD19 on the surface of B-cells. The CAR is comprised of a murine single chain antibody fragment that recognises CD19 and is fused to intracellular signalling domains from the costimulatory receptor 4-1BB (CD137) and the T-cell receptor associated CD3 zeta complex. The CD3 zeta component is critical for initiating T-cell activation and anti-tumour activity, while 4-1BB enhances the activation, expansion, and persistence of tisagenlecleucel. Upon binding to CD19 expressing cells, the CAR transmits a signal promoting T-cell activation, expansion, and acquisition of effector functions of tisagenlecleucel, such as cytotoxicity and elimination of CD19 expressing target cells. This allows the genetically modified T-cells to specifically target and destroy CD19-positive malignant B-cells in an antigen dependent, but major histocompatibility complex (MHC) independent manner.

The MAH submitted a final report for:

- CCTL019C2202; BIANCA

The CCTL019C2202 (C2202) study is a phase II, single arm, multicenter open label trial to determine the safety and efficacy of tisagenlecleucel in paediatric patients with relapsed or refractory (r/r) mature B-cell non-Hodgkin lymphoma (NHL; Burkitt lymphoma, diffuse large B-cell lymphoma [DLBCL], primary mediastinal B-cell lymphoma [PMBCL] and gray zone lymphoma [GZL]).

The primary analysis of the C2202-study was assessed in the type II variation, category C.I.4 procedure EMEA/H/C/004090/II/0056 with CAT opinion in 09-Sep-2022. The aim was to update the SmPC sections 4.2 and 5.1 to include the primary analysis results from study C2202. The MAH considered that the submitted study results did not support a paediatric indication. The PDCO issued a positive outcome for the final compliance check of EMEA-001654-PIP02-17-M01 on 24-June-2022.

Since the analysis of the C2202-study is finalised, the MAH has submitted the completed paediatric study for tisagenlecleucel, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. No changes to the current tisagenlecleucel core data sheet and/or the approved Kymriah SmPC are proposed.

2.3.2. Clinical study C2202

Description

Study C2202 is a phase II, single arm, multi-centre open-label trial to determine the safety and efficacy of tisagenlecleucel in paediatric patients with r/r mature B-cell NHL.

Methods

Study participants

Subjects recruited to Study C2202 were representative of the broader clinical population of paediatric and young adult patients with CD19+ mature B-cell NHL, who had relapsed after 1 or more prior

therapies or were primary refractory, defined as not achieved a CR or PR after first line of therapy. Subjects that achieved a CR prior to CTL019-infusion were excluded from the efficacy analysis set.

For inclusion/exclusion criteria and prior therapies, see documentation for procedure EMEA/H/C/004090/II/0056.

No additional subjects were enrolled or treated since the primary analysis of 2021.

Treatments

The approved dose range for paediatric and young adult patients with B-cell ALL is 0.2 to 5 $\times$ 10^6 CAR-positive viable T cells/kg body weight for patients $\leq$ 50 kg and 0.1 to 2.5 $\times$ 10^8 CAR-positive viable T cells (non-weight based) for patients > 50 kg. The approved dose range (non-weight based) for adult patients with DLBCL and FL is 0.6 to 6 × 10^8 CAR-positive viable T cells.

For given doses, bridging therapies and lymphodepleting therapies, see documentation for procedure EMEA/H/C/004090/II/0056.

Primary objective

The primary objective is 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.

Outcomes/endpoints

The primary endpoint is ORR, which includes CR and PR as determined by local investigator assessments.

Secondary endpoint included among others:

- DOR - 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
- EFS - 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 HSCT
- PFS - 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
- OS - defined as the time from date of first tisagenlecleucel infusion to the date of death due to any cause
- Evaluate the safety of tisagenlecleucel therapy with physical examination, vital signs, adverse events, laboratory abnormalities, performance status and as applicable physical development
- Characterize the presence of pre-existing and treatment induced immunogenicity and impact on cellular kinetics and response

Sample size, randomisation and blinding

The single arm, open-label study design and the sample size of the trial were justified, according to the MAH by the rarity of r/r B-cell NHL subject population, poor prognosis, lack of approved effective

standard therapies in this setting and limited recruitment to selected and specially trained tisagenlecleucel infusion centres.

Results

Primary analysis - data cutoff date 10-Oct-2021

A short description of the primary analysis is given here. For further details, the primary analysis of the C2202-study was assessed in the type II variation, category C.I.4 procedure EMEA/H/C/004090/II/0056 with CAT opinion in 09-Sep-2022.

The primary analysis covered 33 patients infused with tisagenlecleucel. The data cutoff date (DCO) for the analysis was 10-Oct-2021, and the median time between tisagenlecleucel infusion and DCO was 16.1 months. The efficacy analysis set (EAS) consisted of 24 patients <18 years of age, and four patients ≥18 and <25 years of age.

Of the 33 subjects, 55% had Burkitt lymphoma and 46% had LBCL (30% had DLBCL, 9% had PMBCL, and 3% each had GZL and high-grade B-cell lymphoma). No subject with FL was enrolled.

Subjects were classified as relapsed or progression (55%), refractory (30%), or primary refractory (15%). The patients enrolled had relatively advanced disease, with 88% at stage III/IV at baseline, a median of 2 lines of prior therapy, 18% with prior haematopoietic stem cell transplant (HSCT).

At the time of the DCO, the primary endpoint, ORR, was 32% (9/28 subjects) (95% CI: 15.9, 52.4), with 7% achieving complete response (CR) and 25% achieving partial response (PR) as best overall response (BOR). Subgroup analysis suggested a trend towards lower ORR in subjects with Burkitt lymphoma (20%) versus other histologies (46%). ORR in the DLBCL subgroup was 38%, and the two patients achieving CR in the EAS had DLBCL.

At DCO, median DOR in subjects who achieved a BOR of CR/PR was not reached due to short follow up (2.4 months). Of 9 responders, 3 subjects had an event prior to DCO, 3 subjects were censored due to new antineoplastic therapy or HSCT, and 3 subjects were censored due to ongoing without event. As of the DCO date, median PFS was 2.5 months (95% CI: 1.1, 2.9) while median OS was 11.4 months (95% CI: 3.4, NE). Fourteen subjects, including three subjects with a BOR of PR in the EAS, had died at the time of the DCO.

Final analysis – data cutoff date 26-Apr-2023

No additional subjects were enrolled or treated since the primary analysis data cut-off. At the time of the final analysis, there was 1 additional death since the primary analysis.

Efficacy results

As seen in table 1, the ORR per local investigator assessment was 32% and complete response was observed in 3 subjects (11%), an increase from 2 subjects (7%) at the primary analysis. Median event-free survival was 2.1 months, median progression-free survival 2.5 months, and median overall survival was 10.4 months. The latter was 11.4 months in the primary analysis.

Median duration of response and relapse-free survival data were not estimable as of study completion, in accordance with the primary analysis. Of the 9 subjects (included in the EAS) with a BOR of CR/PR, 3 subjects reported relapse or died due to underlying disease prior to study completion, 3 subjects were censored due to new anticancer therapy (± HSCT), and 3 subjects had ongoing response at the end of study.

In BL, the ORR was 20% (3/15 subjects) (95% CI: 4.3, 48.1), with 0 subjects achieving CR as BOR and 3 subjects (20.0%) achieving PR as BOR. In subjects with LBCL, the ORR was 46% (6/13 subjects) (95% CI: 19.2, 74.9), with 3 subjects (23%) each achieving CR or PR as BOR.

There was a trend for higher ORR with higher age as young adults who were ≥ 18 years of age had a higher ORR (2 of 4 subjects, 50%) compared to subjects < 18 years of age (7 of 24 subjects, 29%).

The median observation time increased from 16.1 months at the primary analysis to 34.6 months at the final analysis. One subject changed from PR to CR as BOR, with an unchanged ORR of 32%. A trend for higher ORR was observed in subjects with histologies other than BL and in young adult subjects.

Table 1 Comparison of the results from the primary and final analysis

CCTL019C2202 – C2202 - BIANCA	**Primary analysis**	**Final analysis**
Data cutoff date	10-Oct-2021	26-Apr-2023
Subjects enrolled (FAS)	33	33
Age <18 years	29	29
Age ≥18 years	4	4
Median observation time, tisagenlecleucel infusion – LPLV date, months (range)	16.1 (6.1 – 29.6)	34.6 (24.6 – 48.1)
Efficacy analysis set (EAS), n=28		
ORR, n subjects, (95% CI)	32.1%, 9/28 (15.9, 52.4)	32.1% 9/28 (15.9, 52.4)
CR as BOR, n subjects	7.1%, 2/28	10.7%, 3/28
PR as BOR	25%, 7/28	21.4%, 6/28
Median DOR	Not estimable	Not estimable
Median relapse-free survival, months (95% CI)	Not estimable	Not estimable
Estimated relapse-free probability (95% CI)	62.5 (22.9, 86.1) at month 9	62.5 (22.9, 86.1) at month 12, 24, 36
Median EFS, months (95% CI)	2.1 (1.1, 2.8)	2.1 (1.1, 2.8)
Estimated event-free probability (95% CI)	13.4% (3.8, 29.0) at month 12	13.4% (3.8, 29.0) at month 39
Median OS, months (95% CI)	11.4 (3.4, NE)	10.4 (3.4, NE)
Median OS, sensitivity analysis censoring for HSCT (95% CI)	11.4 (3.4, NE)	6.1 (1.9, NE)
Median PFS, months (95% CI)	2.5 (1.1, 2.9)	2.5 (1.1, 2.9)
Estimated PFS probability (95% CI)	22.7% (8.9, 40.3) at month 12	22.7% (8.9, 40.3) at month 12, 24, 36, 39

FAS: Full analysis set, LPLV: Last patient, last visit, ORR: Objective Response Rate, 95% CI: 95% Confidence Interval, CR: Complete response, BOR: Best overall response, PR: partial response.

Endpoints

Selected endpoints presented in a table and as Kaplan-Meier plots, as background for the findings in Table 1.

Table 2 Best overall response and overall response (Efficacy analysis set)

	Burkitt lymphoma N=15 n (%) 95% CI	Large B-cell lymphoma N=13 n (%) 95% CI	All subjects N=28 n (%) 95% CI
Best overall response (BOR)			
Complete response (CR)	0	3 (23.1)	3 (10.7)
Partial response (PR)	3 (20.0)	3 (23.1)	6 (21.4)
Minor response (MR)	1 (6.7)	1 (7.7)	2 (7.1)
No response (NR)	1 (6.7)	0	1 (3.6)
Progressive disease (PD)	9 (60.0)	6 (46.2)	15 (53.6)
Unknown	1 (6.7)	0	1 (3.6)
Overall response rate (ORR: CR+PR)	3 (20.0) (4.3, 48.1)	6 (46.2) (19.2, 74.9)	9 (32.1) (15.9,52.4)

Source: Table 11-1, CSR.

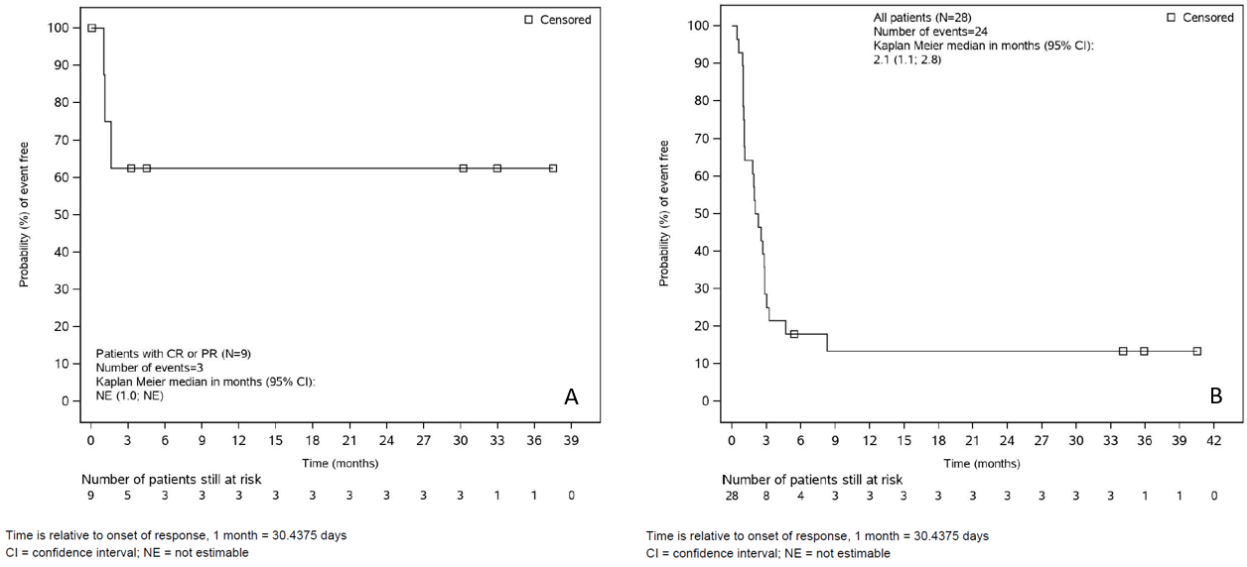


Figure 1 Kaplan-Meier plot of Duration of response (A) and Event-free survival (B) (EAS). Source: Figure 11-2 and 11-4, CSR.

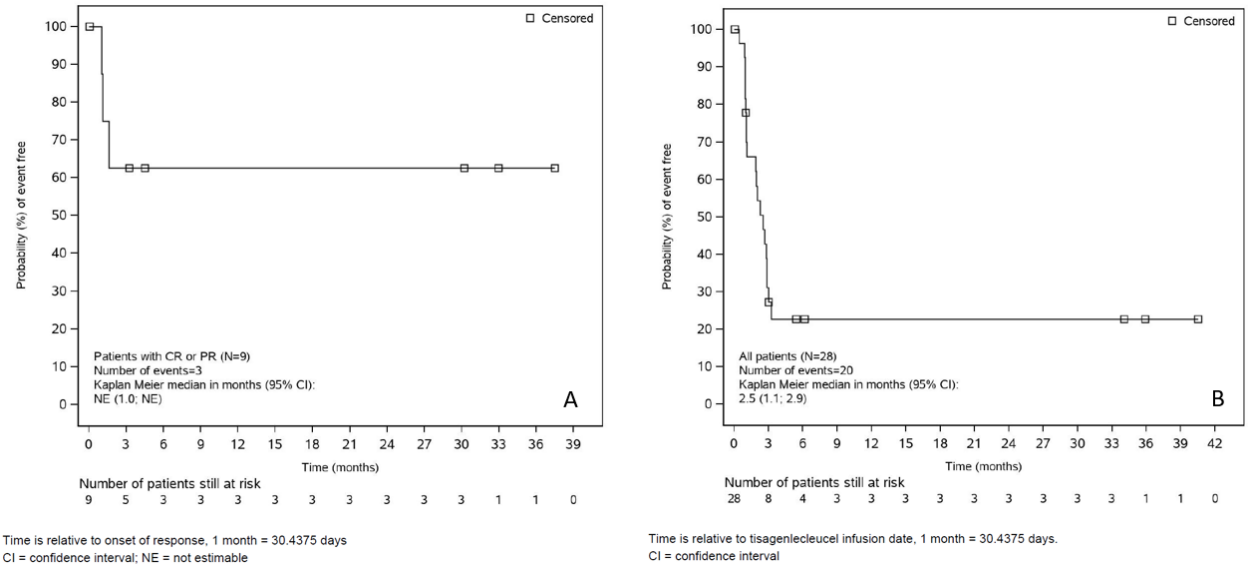
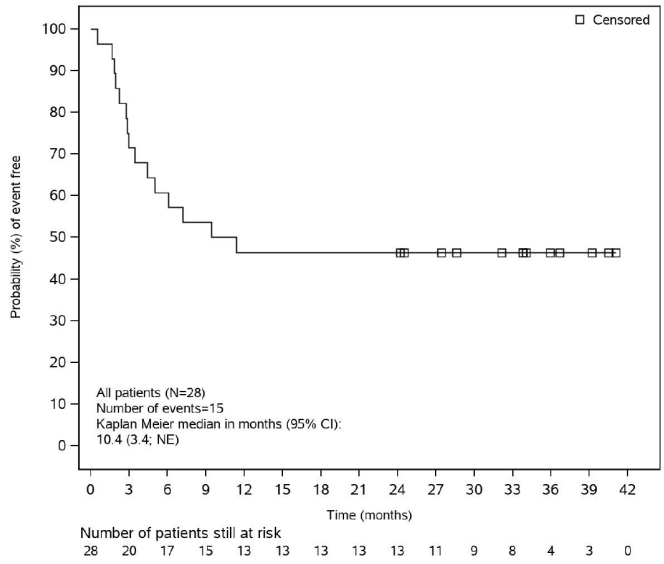


Figure 2 Kaplan-Meier plot of relapse-free survival (A) and Progression-free survival (B) (EAS). Source: Figure 11-6 and 11-8, CSR.

Overall survival

At the time of primary analysis, median OS was 11.4 months (95% CI: 3.4, NE). There were 14 events (subject deaths), and 14 subjects were censored with a maximum follow-up of 28.1 months. The sensitivity analysis censoring for HSCT resulted in a median OS of 11.4 months (95% CI: 3.4, NE). At the time of the final analysis, there was 1 additional death since the primary analysis. Overall median OS was 10.4 months (95% CI: 3.4, NE) and the probability of survival at 24 months was 46% (95% CI: 27.6, 63.3). The updated sensitivity analysis censoring for HSCT resulted in a median OS of 6.1 months (95% CI: 1.9, NE).



Time is relative to tisagenlecleucel infusion date, 1 month = 30.4375 days.
CI = confidence interval; NE = not estimable

Figure 3 Kaplan-Meier plot of overall survival (EAS). Source: Figure 11-10, CSR.

Assessor's comment:

In sum, the increase in median observation time from the primary analysis (16.1 months) to final analysis (34.6 months), did not change the overall picture from the primary analysis: The ORR is unchanged 32.1%. One more subject reached CR as BOR, so the proportion of CR increased from 7.1% to 10.7%. One additional death since the primary analysis resulted in a reduction of median OS from 11.4 to 10.4 months.

Safety results

According to the MAH, the overall safety profile in paediatric and young adult subjects with CD19+ r/r mature B-cell NHL infused with tisagenlecleucel was consistent with the known safety of tisagenlecleucel. No new safety signals were observed.

Adverse events prior to tisagenlecleucel infusion

Among subjects who received lymphodepleting chemotherapy prior to tisagenlecleucel infusion, 72% experienced at least 1 AE and 47% had grade ≥ 3 AEs. AEs suspected to be related to lymphodepleting chemotherapy were reported in 47% of subjects, with 31% of subjects having ≥ grade 3 AEs.

Adverse events post-tisagenlecleucel infusion

All subjects who were infused with tisagenlecleucel experienced at least 1 AE and at least 1 grade ≥3 AE post-tisagenlecleucel infusion. The most commonly reported grade ≥ 3 AEs were neutrophil count decreased (30%), anemia and white blood cell count decreased (24% each), and neutropenia and platelet count decreased (21% each).

Adverse events at any time post-tisagenlecleucel infusion

AEs suspected to be related to tisagenlecleucel were reported in 85% of subjects, with 73% of subjects having grade ≥ 3 events, at any time after the first tisagenlecleucel infusion. The most commonly reported AE suspected to be related to tisagenlecleucel was cytokine release syndrome, CRS (70%) and the grade ≥3 was neutrophil count decreased (21%)

Serious adverse events

Regardless of relationship to tisagenlecleucel, 73% of subjects infused with tisagenlecleucel experienced at least 1 SAE during the study. The most commonly reported SAEs (> 10% in all subjects) were CRS (24%) and pyrexia (21%). Of these, 1 subject had a grade ≥3 SAE of CRS and 2 subjects had a grade ≥3 SAE of pyrexia. The most frequently reported PTs in the final analysis were similar to those reported in the primary analysis.

Table 3 Adverse events (AEs) at any time post-tisagenlecleucel administration, suspected to be study drug related, by preferred term, maximum CTC grade, and histology (≥10% in all subjects) (Safety set). Source: Table 12-3, CSR.

	Burkitt lymphoma N=18 n (%)		Large B-cell lymphoma N=15 n (%)		All subjects N=33 n (%)	
Preferred term	All grades n (%)	≥ Grade 3 n (%)	All grades n (%)	≥ Grade 3 n (%)	All grades n (%)	≥ Grade 3 n (%)
Number of subjects with at least 1 AE	17 (94.4)	14 (77.8)	11 (73.3)	10 (66.7)	28 (84.8)	24 (72.7)
Cytokine release syndrome	16 (88.9)	1 (5.6)	7 (46.7)	2 (13.3)	23 (69.7)	3 (9.1)
Pyrexia	7 (38.9)	1 (5.6)	2 (13.3)	0	9 (27.3)	1 (3.0)
Neutrophil count decreased	3 (16.7)	3 (16.7)	4 (26.7)	4 (26.7)	7 (21.2)	7 (21.2)
Headache	2 (11.1)	0	4 (26.7)	1 (6.7)	6 (18.2)	1 (3.0)
Nausea	5 (27.8)	1 (5.6)	0	0	5 (15.2)	1 (3.0)
Platelet count decreased	3 (16.7)	2 (11.1)	2 (13.3)	1 (6.7)	5 (15.2)	3 (9.1)
Anaemia	2 (11.1)	1 (5.6)	2 (13.3)	2 (13.3)	4 (12.1)	3 (9.1)
White blood cell count decreased	2 (11.1)	2 (11.1)	2 (13.3)	2 (13.3)	4 (12.1)	4 (12.1)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for the same preferred term was only counted with the maximum grade, a subject with multiple AEs was only counted with the maximum grade in the 'Number of subjects with at least 1 event' row.
Preferred terms are presented in descending frequency of all grades column, as reported in the All subjects column.
MedDRA version 26.0, CTCAE version 5.0

Deaths

At the time of primary analysis, 16 subjects (49%) died after tisagenlecleucel infusion, with the majority of subjects dying due to study indication (14 subjects; 42%) and occurred > 30 days post tisagenlecleucel infusion (15 subjects; 46%). At the time of final analysis, a total of 17 subjects (51.5%) died after tisagenlecleucel infusion. The majority of subjects died due to study indication (15 subjects; 46%) and 1 death occurring within 30 days of the tisagenlecleucel infusion. Two subjects (6%) died due to other causes (1 due to pseudomonas infection and 1 due to respiratory failure). Both events were considered not related to the study treatment by the Investigator.

Adverse events of special interest based on important identified risks

Regardless of relationship to tisagenlecleucel, AESIs based on important identified risks of tisagenlecleucel were experienced by 97% of subjects, with 82% having a grade ≥ 3 event. The overall (grade ≥ 3) incidence of specific important identified risks any time post tisagenlecleucel infusion were:

- CRS, 70% (15%)
- Hematological disorders including cytopenias, 79% (76%)
- Infections, 36% (18%)
- Serious neurological adverse reactions, 30% (15%)

- Prolonged depletion of normal B-cells or agammaglobulinemia, 18% (3%)
- Tumor lysis syndrome, 0% (0%)

Cytokine release syndrome

Cytokine release syndrome events, which were expected with tisagenlecleucel treatment, were reported in 70% of subjects, with 15% of subjects experiencing grade ≥ 3 events. When analysed by disease response, CRS was less prominent when subjects had a complete or partial response. According to the MAH, this is likely due to the fact that subjects with a histology of BL had a higher incidence of CRS (16 of 18 subjects, 89%) than those with a histology of LBCL (7 of 15 subjects, 47%) and the proportion of subjects with CR or PR was lower in subjects with a histology of BL (3 of 15 subjects, 20%) than those with a histology of LBCL (6 of 13 subjects, 46%).

Neurological events (Immune effector cell-associated neurotoxicity syndrome)

In total, 30% of subjects experienced serious neurological adverse reactions with 15% experiencing a grade ≥ 3 event. Of these, 64% of the neurological events resolved with an estimated probability of resolution of 46% (95% CI: 22.0, 77.1) on Day 7.

Hematopoietic cytopenias and infections

Hematopoietic cytopenias are a common occurrence after tisagenlecleucel infusion and tisagenlecleucel activity targeting normal B-cells. Prolonged hematocytopenias not resolved by day 28 are considered a consequence. The etiology of the cytopenias may be either the CAR-T-cell therapy per se or prior anti-cancer treatment, such as chemotherapy (i.e., multiple lines and cycles), radiation, lymphodepleting chemotherapy or a combination, exerting cytotoxic effects. Prolonged neutropenia has been associated with increased risk of infection. Hematological disorders including cytopenias were reported in 79% of subjects, with majority experiencing grade ≥ 3 events. Majority of these hematological disorders were resolved by Month 6 with no subjects at risk at Month 9. Infections of any grade were reported in 36% of subjects, with 18% of subjects experiencing grade ≥3 events.

Immunogenicity

According to the MAH, pre-existing/humoral immunogenicity does not seem to have any impact on exposure. The preexisting antibodies, i.e., at enrolment, or maximum fold change from baseline to post infusion were not associated with any impact on clinical response. The scatter plot for net response (%) versus the exposure metrics suggested no apparent relationship between the cellular immunogenicity responses and in vivo expansion and persistence of tisagenlecleucel transgene or clinical response.

2.3.3. Discussion on clinical aspects

As noted in the previous report of the primary analysis from 2021, the study's single arm nature, the limited number of subjects included, the relatively short follow-up duration, and the subsequent anti-

neoplastic treatment after tisagenlecleucel infusion, entails that the results should be interpreted with caution.

The final results following a longer observation time are overall in line with the results from the primary analysis. The conclusion from the primary analysis is still valid: The primary endpoint result in study C2202 may seem to be somewhat in line with, although numerically lower, than the ORR obtained in the adult DLBCL patients enrolled in the pivotal study C2201 with ORR 53% (95%CI: 43.5, 62.4) and CRR 39%. In absence of an estimate for median DOR, the clinical relevance of the observed ORR can still not be assessed.

Furthermore, these results are equally constrained by the study limitations as the primary analysis; A single arm study design, the limited number of subjects included, and the subsequent anti-neoplastic treatment.

No SmPC updates have been raised by the MAH, based on the final analysis results. According to EMA SmPC guideline, the information in SmPC section 5.1 should be updated when 'new relevant information becomes available'. Information regarding observation time, response rates and time-to-event endpoints could be considered new and relevant. Especially an estimate for median DOR to support the observed ORR could be relevant. Unfortunately, a median DOR is still not estimable.

In the study protocol, no pre-defined time point for the final analysis has been made. From a statistical point of view, the primary analysis is considered to be the inferential analysis and the results from the present and final analysis can be interpreted as supportive to the earlier results.

Considering the interpretation limitations to the C2202 study as outlined and the supportive nature of the final analysis, no changes, or further additions to the SmPC are considered necessary.

The benefit-risk evaluation remains unchanged and positive.

3. Overall conclusion and recommendation

The final analysis results from the CCTL019C2202 study have been reported by the MAH, since the primary analysis in 2021. No SmPC updates have been raised by the MAH in this procedure.

The final ORR of 32% is unchanged from the ORR from the primary analysis. The ORR is in line with, although numerically lower, than the ORR obtained in the adult DLBCL patients, 53%. Despite longer observation time, a median DOR is still not estimable, and it is therefore challenging to assess the clinical relevance of the observed ORR. Only small changes in BOR and OS are seen in the closing analysis.

Considering the interpretation limitations to the C2202 study as outlined above and the non-inferential nature of the final analysis, no changes, or further additions to the SmPC are considered necessary.

☒ **Fulfilled:**

No regulatory action required.