24 March 2022
EMA/211805/2022
Committee for Advanced Therapies (CAT)
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kymriah

International non-proprietary name: tisagenlecleucel

Procedure No. EMEA/H/C/004090/II/0044

Note

Variation assessment report as adopted by the CAT/CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

AE	adverse event
AESI	adverse events of special interest
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ASCT	autologous stem-cell transplant
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BOR	best overall response
CAR	chimeric antigen receptor
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CKAS	cellular kinetics analysis set
Cmax	maximum concentration
CR	complete response
CRF	case report form
CRR	complete response rate
CRS	cytokine release syndrome
CSF	cerebro spinal fluid
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EAS	efficacy analysis set
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EOS	end of study
EQ-5D-3L	EuroQol-5 dimensional-3 response level
EQ-VAS	EuroQol-visual analogue scales
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FACT-Lym	functional assessment of cancer therapy – lymphoma
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FIHC	fluorescence immunohistochemistry
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	good clinical practice
GELF	Groupe d'Etude des Lymphomes Folliculaires
HSCT	hematopoietic stem-cell transplant
ICF	informed consent form
ICU	intensive care unit
ICANS	immune effector cell-associated neurotoxicity syndrome
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IL-6	interleukin 6
IRB	Institutional Review Board
IRC	independent review committee
ISRT	involved site radiation therapy
INRT	involved node radiation therapy
KM	Kaplan-Meier
LD	lymphodepleting
LDH	lactate dehydrogenase
mAb	monoclonal antibody
mCAR19	anti-mouse CAR19
mEAS	modified efficacy analysis set
MedDRA	Medical Dictionary for Regulatory Activities
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MUGA	multiple uptake gated acquisition
NCA	noncompartmental analysis

NHL	Non-Hodgkin’s lymphoma
NK-cells	natural killer cells
OOS	out-of specification
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
POD	progression of disease
PPS	per-protocol set
PR	partial response
PRO	patient-reported outcome
PT	preferred term
QoL	quality of life
qPCR	quantitative polymerase chain reaction
QTL	quality tolerance limit
r/r	relapsed or refractory
RCL	replication competent lentivirus
SAE	serious adverse event
SCT	stem-cell transplant
SD	stable disease
SF-36	short form health survey
SOC	system organ class
TBL	total bilirubin level
TLS	tumor lysis syndrome
TMTV	total metabolic tumor volume
TPAS	tocilizumab pharmacokinetic analyses set
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 31 August 2021 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult patients with follicular lymphoma (FL) after two or more lines of therapy who are refractory, or relapsed during or within 6 months after completion of anti-CD20 antibody maintenance, or relapsed after autologous haematopoietic stem cell transplantation (HSCT) for Kymriah. As a consequence, Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and corresponding sections in the Package Leaflet are updated accordingly. The RMP has been updated to version 4.0 to align with the indication extension. Lastly, the minor editorial corrections are made throughout the SmpC and package leaflet to align with the current QRD template version 10.2. The updates to Module 3 include mainly the incoming FL material characterization, final product characterization and FL batch analyses data.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Kymriah was designated as an orphan medicinal product under number EU/3/21/2464 on 19.07.2021. Kymriah was designated as an orphan medicinal product in the following indication:

Treatment of follicular lymphoma.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions EMEA 001654-PIP01-14-M03 and EMEA 001654-PIP02-17- M01 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0323/2019 and PIP P/0008/2019 were not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The MAH received Protocol assistance from the CHMP on 25 February 2021 (EMA/SA/0000047236). The Protocol assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CAT were:

Rapporteur: Rune Kjeken Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	31 August 2021
Start of procedure:	18 September 2021
CAT Rapporteur's preliminary assessment report circulated on	12 November 2021
PRAC Rapporteur's preliminary assessment report circulated on	19 November 2021
PRAC RMP advice and assessment overview adopted by PRAC on	2 December 2021
Updated CAT Rapporteur's assessment report circulated on	6 December 2021
Request for supplementary information and extension of timetable adopted by the CAT on:	10 December 2021
MAH's responses submitted to the CHMP on	17 January 2022
CAT Rapporteur's preliminary assessment report on the MAH's responses circulated on	18 February 2022
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	24 February 2022
Updated PRAC Rapporteur's assessment report on the MAH's responses circulated on	3 March 2022
PRAC RMP advice and assessment overview adopted by PRAC on	10 March 2022
Updated CAT Rapporteur's assessment report on the MAH's responses circulated on	14 March 2022
CAT Opinion adopted on	18 March 2022

Timetable	Actual dates
CHMP Opinion adopted on	24 March 2022
The CAT adopted a report on similarity of Kymriah with Gazyvaro on	18 March 2022
The CAT adopted a report on the significant clinical benefit in comparison with existing therapies in accordance with Article 14(11) of Regulation (EC) No 726/2004 on	18 March 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Follicular lymphoma (FL) is a systemic neoplasm of the lymphoid tissue displaying germinal centre (GC) B cell differentiation (Carbone, 2019). Tumorigenesis begins in precursor B cells and progresses until cells reach the GC maturation step. FL is preceded by an asymptomatic preclinical phase in which premalignant B cells carrying a t(14;18) chromosomal translocation accumulate additional genetic alterations, although not all of these cells progress to the tumour phase (Carbone, 2019). As it arises from B cells, FL is characterised by the expression of B-cell markers such as CD10, CD19, CD20, and CD22 (Swerdlow et al., 2016). FL is typically a slow-growing or indolent non-Hodgkin's lymphoma (iNHL), and accounts for approximately 20% of all NHLs, and 70% of indolent lymphomas (Swerdlow et al, 2017). Nonetheless, it is considered an incurable, chronic disease in most cases, as it is characterised by a relapsing nature. PFS is progressively shorter for each subsequent treatment, decreasing from 6.6 years after first-line therapy to 1.5 and 0.83 years after second and third-line therapies, respectively (Link et al., 2019). Death generally occurs due to histological transformation to DLBCL or because FL becomes refractory to chemotherapy. Most patients are diagnosed with advanced disease during the sixth decade of their life, but approximately 25% of patients are ≤ 40 years of age (Jaglowski et al 2009).

State the claimed therapeutic indication

The initially claimed indication was: "Kymriah is indicated for the treatment of adult patients with follicular lymphoma (FL) after two or more lines of therapy who are refractory, relapsed during or within 6 months after completion of anti-CD20 antibody maintenance, or relapsed after autologous haematopoietic stem cell transplantation (HSCT)"

Epidemiology

The estimated number of new cases of FL in the EU was 12,117 in 2013 (RARECAREnet). In the US, there were 74200 cases of NHL (12688 cases of FL) in 2019, with approximately 19970 disease-specific related deaths overall (SEER 2019). Immune suppression or auto-immune diseases, exposure

to herbicides and pesticides, and use of hair spray have been linked to the development of FL. The incidence is higher in industrialized countries than in developing countries, and higher in men than in women (Carbone et al 2019, Dada 2019). The aetiology of FL is unknown, but family history is thought to be important (Goldin et al., 2009).

Clinical presentation, diagnosis and stage/prognosis

Most FL patients have widespread disease at diagnosis, with peripheral and central lymph node, spleen, and bone marrow involvement. Staging is carried out according to the Ann Arbor classification system, with mention of bulky disease (>6 cm) when applicable (Dreyling et al., 2021). Ann Arbor staging further classifies patients with lymphoma into A or B categories, where A is without B-symptoms and B is with B-symptoms including unexplained fever of >38C, drenching night sweats or loss of >10% body weight within 6 months.

Histological grading of FL is carried out on lymph node biopsies and reflects the average number of centroblasts/high-power field (HPF). Grade 1-2 cases have a marked predominance of centrocytes (small to medium-sized cleaved follicular center cells), with few centroblasts (large non-cleaved follicular center cells). FL Grades 3a and 3b both have >15 centroblasts/HPF. The two can be distinguished in that grade 3b displays sheets of blasts, while grade 3a has centroblasts with intermingled centrocytes (Ott et al., 2002; Dreyling et al., 2021). The clinical aggressiveness of FL increases with increasing numbers of centroblasts, and subsequently grades. While grade 1, 2 and 3a are considered indolent (low-grade) disease, FL grade 3b is at an intermediate stage of large cell transformation and usually considered an aggressive (high-grade) lymphoma (Dreyling, 2021). Hence, grade 3b FL differs from other forms of FL, with a clinical course similar to that of DLBCL. Biologically, grade 3b FL is more closely related to DLBCL than to the other forms of FL (Swerdlow, 2017). As such, FL grade 3b is treated as DLBCL in clinical practice. Histological transformation from indolent to more aggressive lymphoma, typically DLBCL, occurs at a rate of 2-3% per year (Freedman 2018).

In terms of prognosis, a recent study found that for 80% of patients, overall survival was >10 years (Carbone, 2019), with another study finding a median survival of approximately 20 years (Tan et al 2013). A retrospective multicenter study of FL patients found median survival to be 7.6 years after second-line therapy, and 4.8 years after third-line therapy, with a 10-year survival rate of only 20% after third-line treatment (Rivas-Delgado et al, 2019). Prognosis is strongly influenced by duration of response (DoR) to first-line chemoimmunotherapy, with the 20% of patients experiencing POD within 2 years of initial chemoimmunotherapy exhibiting a 5 year OS of only 50% in one study (Casulo et al., 2015). These patients are referred to as POD24.

Another commonly used prognostic measure is the Follicular Lymphoma International Prognostic Index (FLIPI) score, which incorporates five clinical factors (age, stage, serum hemoglobin level, number of nodes involved, and lactate dehydrogenase level) (Brice et al 1997, Solal-Céligny et al 2004). Inclusion of the mutational status of seven genes (EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP and CARD11) along with the FLIPI score and ECOG Status led to the prognostic measure termed the m7 FLIPI, which improved prognostication of five-year failure-free survival (Pastore et al., 2015).

Further, prognosis is negatively impacted by histological transformation. Median survival after histological transformation to an aggressive lymphoma is 50 months. Prognosis is worse in patients with early (< 18 months) versus late (≥ 18 months) transformation after FL diagnosis (5-year OS: 22% vs. 76%) (Link et al 2013). A pooled study found histological transformation to be the leading cause of death in patients with newly-diagnosed FL (Sarkozy et al 2018).

Management

The aim of the treatment of FL is primarily the alleviation of symptoms, reversal of cytopenias, and improvement of QoL. Treatment largely depends on the tumour burden, stage of the disease, as well as patient age (Figure 1, Figure 2). In addition, Grades 1, 2 and 3a are considered indolent disease, while FL grade 3b is considered an aggressive lymphoma and is therefore typically recommended to be treated as such (Dreyling, 2021). At diagnosis, the majority of patients diagnosed with FL have advanced (stage III or IV) disease, with a minority of patients diagnosed with localised stages of FL (Stages I-II).

In the patient group with low tumor burden (Figure 1), patients with stage I/II FL are generally to be treated with involved-site radiation therapy (ISRT), which can be combined with single-agent rituximab. Watch-and-wait or rituximab monotherapy may also be considered. For patients with low tumor burden and stage III/IV FL, watch-and-wait is the standard approach, while rituximab monotherapy may also be considered. In case of relapse or progression, watch-and-wait is generally recommended, and rituximab monotherapy may also be considered. Depending on stage, involved node radiation therapy (INRT) or immuno chemotherapy or radiotherapy may also be considered.

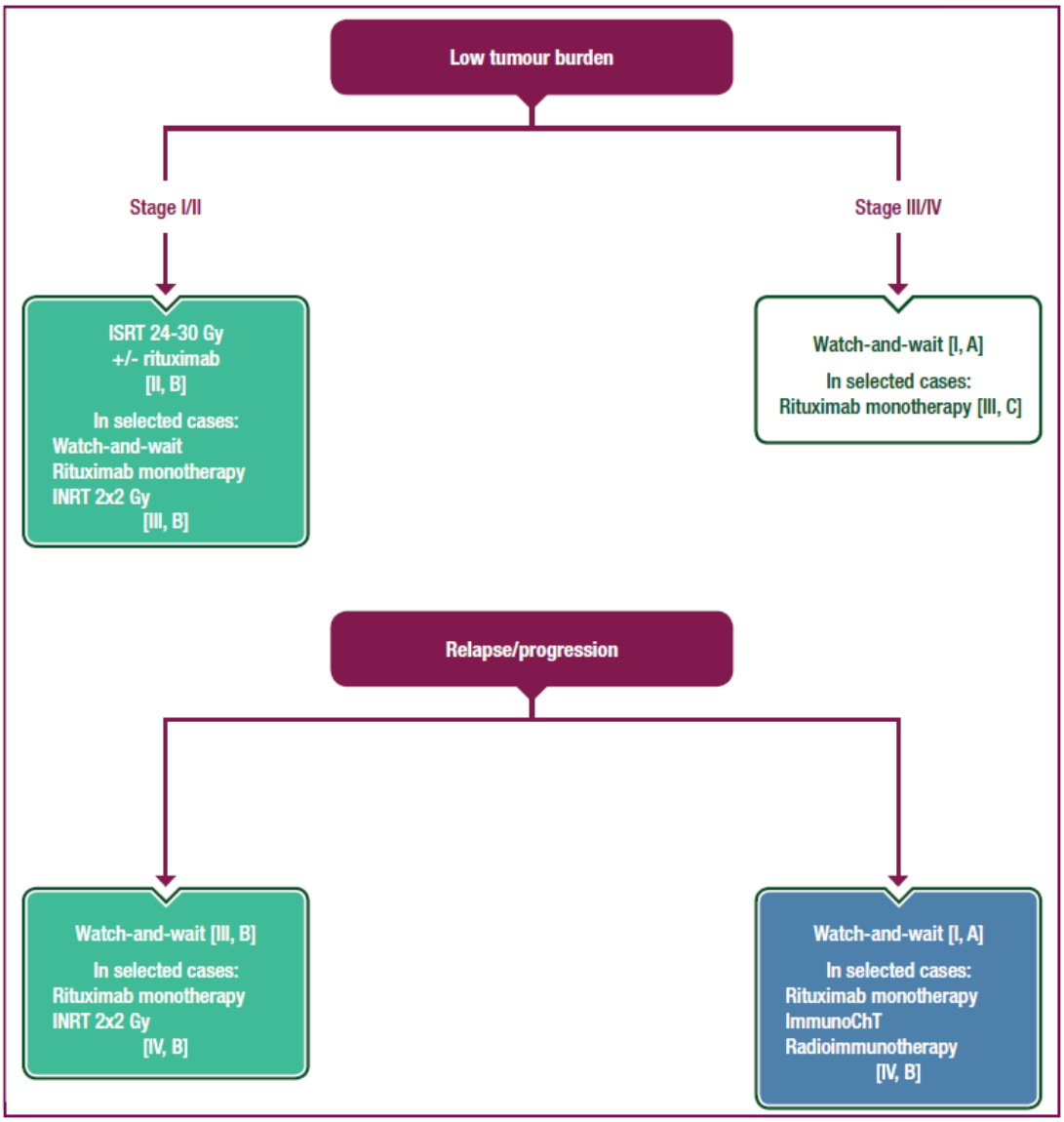


Figure 1 – ESMO Recommendations for low tumor burden FL (Dreyling, 2021)

In the patient group with high tumor burden and stage III/IV disease (Figure 2), treatment recommendations depend on the age of the patient, with separate recommendations for patients above or below 65 years old. For the majority of patients in both age groups with advanced FL (stage III or IV) at diagnosis, watch-and-wait is the standard approach in asymptomatic cases, with treatment initiated upon the development of symptoms, including B symptoms, hematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion, or rapid lymphoma progression. First-line therapy in both age groups in these patients generally consists of both induction and maintenance phases. In the induction phase, obinutuzumab or rituximab in combination with CHOP, CVP or bendamustine is used if complete remission and long PFS are the therapeutic goals, or if there is evidence of a more aggressive clinical course. Antibody monotherapy (rituximab, radioimmunotherapy) or chlorambucil plus rituximab can be alternatives for patients with a low-risk profile or when conventional chemotherapy is contraindicated. After immunochemotherapy, rituximab maintenance is recommended every 2 months for 2 years. Alternatively, radioimmunotherapy consolidation may be considered after chemotherapy (Dreyling et al., 2021). In stage I-II patients with a high tumour burden, adverse clinical prognostic features or in cases where ISRT is not feasible, systemic therapy, as indicated for advanced stages, should be applied (Dreyling et al., 2021).

The treatment of symptomatic relapsed or refractory FL in the patient group with high tumor burden and stage III/IV disease (Figure 2) in the EU includes non-cross resistant chemo-immunotherapy agents, radio-immunotherapy or rituximab monotherapy, the phosphatidylinositol-3-kinase (PI3K) inhibitor idelalisib and duvelisib, the combination of anti-CD20 monoclonal antibody rituximab and the immunomodulatory drug lenalidomide, and in selected cases autologous/allogeneic hematopoietic stem cell transplantation (HSCT) (Dreyling et al., 2021). The PI3K inhibitor idelalisib was approved by EMA in 2014, for the treatment of relapsed FL after at least two lines of systemic therapy based on study 101-09, which showed a complete response rate (CRR) of 14%, ORR of 56% and DOR of 11.8 months (Salles et al., 2017). Duvelisib is another PI3K inhibitor (approved by EMA in March 2021) for the treatment of adult patients with refractory FL who have received 2 or more prior systemic therapies. The pivotal study showed no 0% CR and 40% PR (Copiktra SmPC). The lenalidomide and rituximab combination (so called R2) was approved by EMA in 2019 for the treatment of FL patients after ≥ 1 line of therapy based on the phase 3 AUGMENT and supportive MAGNIFY trials. In AUGMENT, CRR was 34% and ORR was 81% (Rummel et al., 2020). High-dose therapy (HDT) followed by autologous HSCT can also be a therapeutic option for patients with relapsed FL. Median PFS for patients treated with autologous HSCT is around 1 year (Sesques et al., 2020). Allogeneic HSCT is a potentially curative therapy, and can be considered at relapse after autologous HSCT, but only a small fraction of patients with an available donor are candidates for it. Transplant-related mortality remains high at 8-17% at 1 year (Epperla et al., 2017). A more recent study found a 3-year OS of 66%, with treatment-related mortality of 25% at 3 years (Sureda et al., 2018).

The ESMO guidelines specify which treatments are appropriate for which groups in the relapsed/refractory FL population (Dreyling et al., 2021). In the case of relapsed disease, localised symptomatic disease may be managed with low-dose ISRT, while in early systemic relapses (<12-24 months), a non-cross resistant chemoimmunotherapy regimen is to be used. Rituximab should be added if the previous antibody-containing scheme achieved >6-12-month duration of remission. Rituximab maintenance therapy every 3 months for up to 2 years is recommended for most r/r FL patients, except for those who have relapsed during their first rituximab maintenance period. In rituximab-refractory cases or remissions lasting <6 months, obinutuzumab-bendamustine (or other chemotherapy regimen) plus obinutuzumab maintenance is recommended. High-dose chemotherapy with autologous stem cell transplant (ASCT) should be considered in patients who experience brief first remissions after rituximab-containing regimens. In relapsed FL, lenalidomide plus rituximab may be

considered for patients with short remissions after chemotherapy. Radioimmunotherapy may be considered in elderly patients with comorbidities.

In later relapses (Figure 2), immunochemotherapy is recommended in case of a long prior remission, or lenalidomide plus rituximab or rituximab monotherapy may be used. In selected cases in both age groups, radiotherapy may be used, or idelalisib may be used in double-refractory cases. ASCT may be used in selected cases in patients under 65 years old. In selected younger patients with later relapses with a high-risk profile or relapse after ASCT, allogeneic HSCT may be considered.

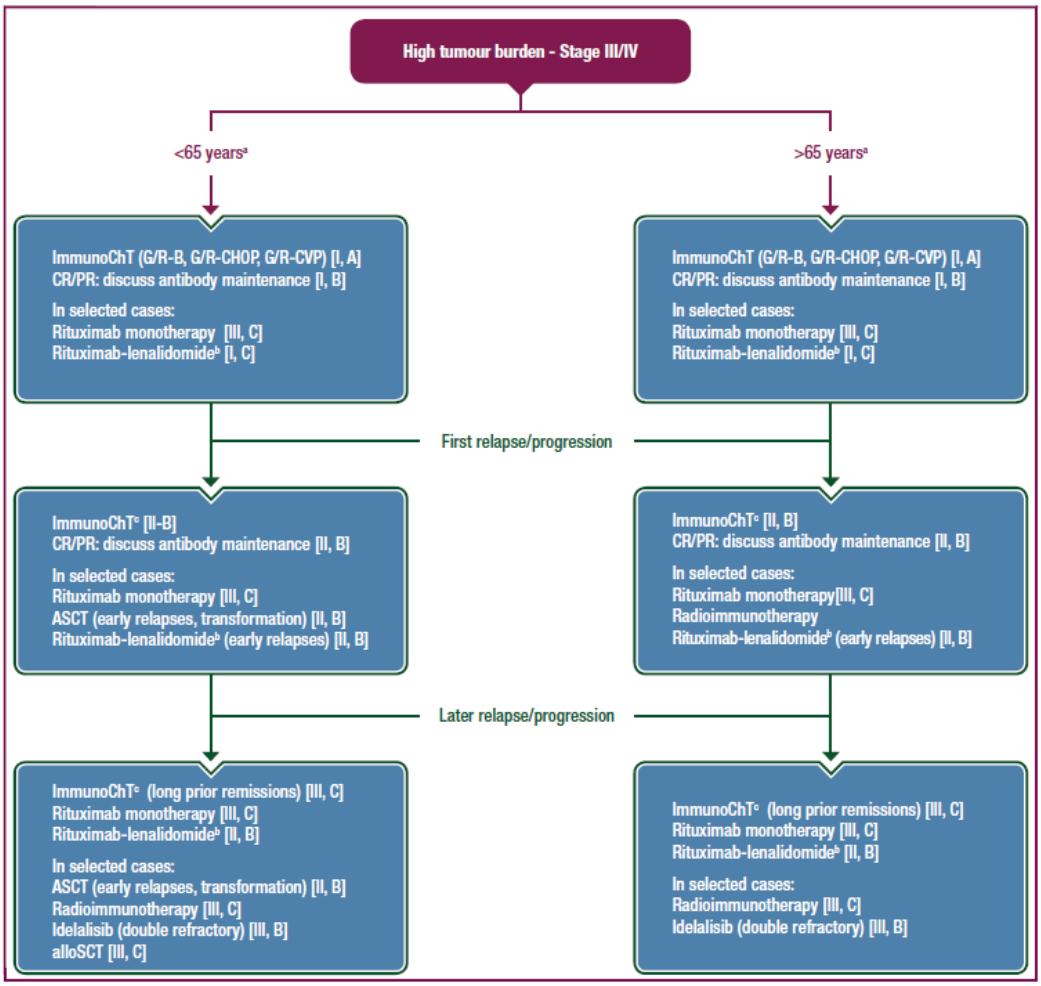


Figure 2 – ESMO Recommendations for high tumor burden FL (Dreyling, 2021)

The U.S. treatment guidelines (NCCN, 2021) for third-line and subsequent therapies differ somewhat from the European guidelines, and include PI3K inhibitors copanlisib, duvelisib and idelalisib in r/r patients after two prior therapies, and umbralisib after three prior therapies, also in elderly or infirm patients. In addition, the EZH2 inhibitor tazemotastat is recommended for EZH2 mutation positive r/r patients after two prior therapies and in EZH2 wild type or unknown r/r patients with no satisfactory treatment options. In addition, the CAR-T cell therapy axicabtagene clioleucel is also a treatment option after two or more lines of systemic therapy.

There is an unmet medical need in relapsed and refractory (r/r) FL in that treatment efficacy and duration of remission decline with every successive line of therapy, with death occurring due to histological transformation to DLBCL or because FL becomes refractory to chemotherapy. Thus, there can be considered to be an unmet medical need in FL patients with frequent relapses, where therapies

generally result in modest CRR and responses are not durable, thus necessitating further treatments with associated toxicities and risk of histological transformation.

2.1.2. About the product

Tisagenlecleucel is a CD19-directed CAR-T cell therapy using reprogrammed autologous T cells. The T cells contain a transgene encoding a CD19-targeted CAR, containing a murine single chain antibody fragment recognizing CD19 fused to intracellular signaling domains from 4-1BB and CD3 zeta. The CD3 zeta component is critical for initiating T cell activation and antitumor activity, while 4-1BB enhances the expansion and importantly, persistence of CAR-positive viable T cells. The CAR-T cells are thus able to recognize CD19-expressing cells and mount a response where there is T cell activation, expansion, target cell elimination and persistence of the CAR-T cells. As CD19 is widely expressed on malignant B cells in B-cell lymphomas, including FL (Freedman 2014), but not on pluripotent stem cells or non-B cell tissues, this represents an attractive target.

Kymriah (INN: tisagenlecleucel; product code CTL019) was approved in the EU via a centralised procedure (Procedure No. EMEA/H/C/004090) on 23-Aug-2018 and is currently authorised for the treatment of two indications, as follows:

- 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 posttransplant 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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Kymriah is designated as an orphan medicinal product for the orphan condition "Treatment of follicular lymphoma" (EU/3/21/2464). A copy of this designation was provided in the application.

Novartis received the confirmation on 21 May 2021 that the PDCO is of the view that the proposed indication for adult patients with r/r FL after two lines of therapies fall under the scope of the Decision P/0323/2019, as the indication is considered to be covered by the condition "treatment of mature B-cell neoplasms" (EMEA-001654-PIP02-17-M01). The confirmation letter together with the above-mentioned Decision were included in the Application to fulfil the requirements of Article 8 of Regulation (EC) No 1901/2006.

The MAH sought CHMP Scientific advice on r/r FL in SA procedure EMA/SA/0000047236, dated 25-Feb-2021. The SA addressed questions related to the study design of CCTL019E2202 (hereafter referred to as study E2202), including patient population, indication wording, study endpoints, sample size and duration of follow-up. Further, the Scientific Advice included questions on the systematic literature review and the two real-world evidence (RWE) comparisons included in the application to contextualize study E2202.

2.1.4. General comments on compliance with GCP

The MAH has provided a statement to the effect that study E2202 conducted at sites outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC and the ICH E6 Guideline for GCP that have their origin in the Declaration of Helsinki.

Table 1: Health Authority Inspections

Country	Site No.	Investigator name	Health authority name	Start and end dates of inspection
Taiwan	3100	Ming Yao	Taiwan Food and Drug Administration	13-Nov-2019 to 13-Nov-2019

The MAH states that there were no audits conducted at investigator sites participating in this study. One health authority inspection was conducted, as listed in Table 1. The MAH committed to provide post-authorisation the inspection report, including a summary of the findings, of the inspection to one study site (1700), when available (LEG).

2.1. Quality aspects

Description of Quality changes

Kymriah (tisagenlecleucel) is an autologous T cell product formulated as single-dose cell dispersion for intravenous infusion. Tisagenlecleucel consists of autologous T cells genetically modified ex vivo to express an anti-CD19 chimeric antigen receptor (CAR) designed to specifically recognise CD19 expressing cells and to transduce the signal through the 4-1BB (CD137) and CD3ζ (TCRζ) signalling domain upon binding.

With this variation submission, the MAH is proposing the use of tisagenlecleucel in the adult FL indication under Scope C.I.6.a, and amendments are required in Module 3 with respect to the leukapheresis material and drug product when manufactured for the FL indication.

The variation includes information on leukapheresis material characterisation and final product characterisation. The results of the manufactured tisagenlecleucel final product batches are included in the batch analyses section. The current specifications, as registered for the DLBCL indication, are applicable to the FL indication and are justified based on additional final product testing results from FL batches.

The variation also includes editorial changes to include the FL indication.

2.1.1. Drug Substance

Characterisation of leukapheresis starting material for FL is presented. FL batches meet the proposed current specification and the commercial specification for the starting material is sufficient to assure successful manufacturing.

2.1.2. Drug Product

Specifications

The current specifications as registered for the DLBCL indication are applicable to the FL indication and are justified based on additional final product testing results from FL batches.

2.1.3. Conclusions on quality aspects

The current variation includes information on characterisation of leukapheresis material and final product characterisation for the proposed FL indication. There are no proposed changes to the

manufacturing process, which is therefore considered to be the same. Relevant batch data is presented No changes are proposed for PBMC of DP specifications for the FL indication, which is considered adequately justified.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

The "Environmental Risk Assessment – GMO" document has been updated from the initially submitted assessment. However, the changes consist of "Minor editorial updates to bring document to commercially manageable format". The conclusions on the environmental risk of the product have not been revised. This is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

An overview of clinical studies to support the current indication is shown in Table 2.

Table 2: Overview of all clinical studies pertinent to the claimed indication

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status & Reports of Study Results
Protocol: CCTL019E2202 **Countries**: Australia, Austria, Belgium, France, Germany, Italy, Japan, Netherlands, Norway, Spain, United Kingdom, United States **Start**: 12-Nov-2018 **End**: ongoing	**Design, purpose & population**: A phase II, single arm, multicenter open label trial to determine the efficacy and safety of tisagenlecleucel (CTL019) in adult patients with refractory or relapsed follicular lymphoma	**Total**: 98 **Age**: 29-73 (56.3) years **Groups**: 1 group	**Form(s)**: CTL019, an autologous cellular immunotherapy product, CD3+T cells that have undergone ex vivo T cell activation, gene modification, expansion and formulation in infusible cryomedia **Duration**: 2 years **Doses**: single IV infusion 0.6 – 6.0 x 10^8 CARpositive viable T cells	**Study Status**: ongoing **Report no**. [CCTL019E2202 extended follow-up analysis] **Report date**: 09-Jul-2021 **Other reports**: [DMPK RCCTL019E2202-iga-int1] [DMPK RCCTL019E2202-pd] [DMPK-RCCTL019E2202-pk] [DMPK RCCTL019E2202-igb-int1] [DMPK RCCTL019E2202-pkc] [DMPK RCCTL019E2202-pkb-int1] [DMPK RCCTL019E2202-pka-int1]

2.3.2. Pharmacokinetics

Introduction

Tisagenlecleucel is a cell-based product and thus no dedicated clinical pharmacology studies were conducted. The cellular kinetics of tisagenlecleucel in adult patients with r/r FL were characterised in the pivotal Study E2202**.** No dedicated clinical pharmacology/pharmacokinetic studies were conducted

The term cellular kinetics is used to describe the in vivo kinetics of tisagenlecleucel post infusion. Cellular kinetics of tisagenlecleucel were determined from peripheral blood and bone marrow samples analysed by qPCR that detected the CAR transgene levels (i.e. number of copies of CAR per µg of DNA), and flow cytometry methods that detected percentage of CTL019 expressing CD3+ cells. Key cellular kinetic parameters indicative of expansion (i.e. "absorption", maximal level of gene modified cells in vivo) and persistence (i.e. "elimination", duration that CTL019 cells are present in peripheral blood and tissues) were C_{max} and $AUC_{0\text{-}28d}$, $AUC_{0\text{-}84d}$, half-life ($t_{1/2}$), C_{last} and T_{last}, respectively.

Methods

- **Analytical methods**

For the r/r FL indication the MAH has provided three revised method validations.

Method DMPK R1580100-ig

Detection and titration of anti-CTL019 antibodies in human serum samples by flow cytometry. The purpose of this study is to cross-validate a method for the detection and titration of anti-mCAR19 antibodies in human serum to support clinical studies. Anti-mCAR19 antibodies are captured by Jurkat T cells transduced to express mouse CAR19 (CTL019 Jurkat cells). To differentiate the anti-drug antibodies from those specific to the Jurkat T cells, specimens are also tested separately on WT Jurkat T cells. During assay development it was found by the MAH that the majority of human sera from untreated individuals show antibody binding either to Jurkat WT cells or CAR19 Jurkat cells or both, to highly variable extents. For this reason it was decided to use immunoglobulin depleted sera for the validation and System Suitability Control sample(s) SSCs. It is expected that most if not all encountered study samples will screen assay positive for one or both cell lines. The observed antibody binding is assumed specific, as the humanised anti-CAR19 PC antibody does not bind unspecifically to the Jurkat WT cells and also the secondary antibody is removed easily. During method transfer at PRA (NPH514EL-155143-A) it was noticed that responses in blank matrices used by Novartis and PRA differed. To be able to compare the assay performance at PRA to the assay performance at Novartis a cross-validation was performed.

Method DMPK R1701054-pk

The purpose of this study was to validate an assay for the quantitation of Rituxan in human serum. This electrochemiluminescence assay used an anti-Rituximab antibody to capture the Rituxan drug and an anti-Rituximab detection antibody conjugated to biotin in conjunction with ruthenium-labelled Streptavidin (SA-SulfoTag) to detect the drug.

Validation of the method included calibration curve response and range, LLOQ and ULOQ, intra- and inter-assay precision and accuracy, selectivity, matrix interference, dilutional linearity, MRD, prozone effect, and target interference. Working calibration standards were prepared at nominal concentrations of 25600, 12800, 10000, 6400, 3200, 1600, 800, 400, 200, 100, and 50 ng/mL in neat pooled human

serum. Also, validation samples (VS) were prepared prior to validation by spiking Rituxan into pooled human serum at 12800 (ULOQ), 10000 (High), 1600 (Mid), 200 (Low), and 100 (LLOQ) ng/mL. The assay range was defined by the LLOQ and ULOQ, the lowest and highest VS, respectively, and the standard calibrators that meet acceptance criteria for intra- and interassay precision and accuracy.

Method GDX-RPT1324

Quantitative detection of Murine CART19 transgene DNA in human blood, human transfected T cells and human bone marrow by qPCR. The original validation was performed using human blood and bone marrow samples collected from healthy donors and spiked with varying amounts of Jurkat cells expressing the murine CART19 construct. These specimens were created in bulk and 200 µL volumes were aliquoted into micro-centrifuge tubes and frozen at -80°C. Samples were thawed and DNA extracted using the Promega Maxwell CSC in the original validation. The Promega Maxwell CSC DNA isolation method was replaced with the QIAamp DNA Blood Midi Kit in the addendum validation to accommodate processing of larger sample volumes. DNA was also extracted from 200 µL of transfected T cell specimens using the QIAamp DNA Blood Mini Kit. The concentrations of the stock DNA extracted from these samples were determined spectrophotometrically by taking optical density readings using the NanoDrop kit. OD readings were recorded at 260nm and 280nm to determine both concentration and purity. DNA was either used immediately post extraction or frozen at -20°C until required for use. The addendum validation was performed using remnant patient blood samples and human blood and bone marrow samples collected from healthy donors and spiked with varying amounts of murine CART19 plasmid DNA. The spiked specimens were created in bulk volume and aliquoted into micro-centrifuge tubes in volumes of 0.3, 1.0, and 2.0 mL and frozen at -80°C. Samples were thawed and DNA extracted using the QIAamp DNA Blood Midi Kit. The concentrations of the stock DNA extracted from these samples were determined by fluorometric quantitation using the Qubit kit. If the DNA concentration for a specimen was determined to be lower than the minimum required for the assay, the specimen DNA was concentrated using the Qiagen MinElute PCR Purification Kit and the concentration measured again. The DNA was either used immediately post extraction or frozen at -20°C until required for use. Parameters validated was linearity and dynamic range, limit of detection, lower limit of quantification, accuracy, robustness and precision.

- **Pharmacokinetic data analysis**

The cellular kinetics of tisagenlecleucel in adult patients with r/r FL were characterised in the pivotal Study **E2202** (see Table 3 for details). As both qPCR and flow cytometry were used to measure levels of transgene and percentage CD3+CAR+ cells, respectively, for the derivation of cellular kinetic parameters in Study **E2202**, a correlation analysis between these two assays was performed to evaluate the relationship between the presence of CAR transgene and the functional CAR. The r^2 for time-matched peripheral blood concentrations from qPCR and flow cytometry was 0.290 indicating a moderate degree of correlation between the data from these two different analytical methods (flow cytometry and qPCR). Unless stated otherwise, all cellular kinetic parameters presented henceforth in this section are based on qPCR methodology as it is a robust and sensitive method.

Table 3. Overview of study E2202 including sampling and analytical methods used

Study	Study title	Recommended dose	Manufacturing site of drug product	Frequency of collection in Blood/ bone marrow	Analysis method for transgene levels / transduced cells for cellular kinetic parameter estimation
Study E2202	A Phase II, single arm, multicenter open label trial to determine the efficacy and safety of tisagenlecleucel in adult patients with r/r FL	0.6 to 6.0×10^8 total CAR-positive viable T cells, administered by single iv infusion	Morris Plains, USA Stein, Switzerland Les Ulis, France Kobe, Japan	Intense/ sparse	q-PCR/ flow cytometry

According to the MAH, blood and bone marrow samples were collected from all patients for the assessment of tisagenlecleucel cellular kinetics. Additionally, serum samples were collected and assessed for rituximab and tocilizumab.

The entities measured are summarised below:

- CAR19 transgene levels as generated by qPCR
- CAR-positive viable T-cells measured by flow cytometry of
    - CD3+ cells
    - CD3+/CD4+ cells
    - CD3+/CD8+ cells

Cellular kinetic parameters assessed in this study are listed in Table 4. C_{max} reflects the level of maximal expansion of transgene in peripheral blood following the infusion while $AUC_{0\text{-}28d}$ and $AUC_{0\text{-}84d}$ indicate the exposure within the first 28 and 84 days, respectively. The pharmacokinetics of tocilizumab have been reported as it is used for the management of CRS.

Tisagenlecleucel concentrations in peripheral blood and bone marrow were listed, graphed and descriptively summarised by time points as assessed by the following:

- Tisagenlecleucel transgene levels as measured by qPCR
- CAR-positive T-cells measured by flow cytometry of CD3+ /CD4+ and CD3+/CD8+ CAR-positive viable T-cells.

Frequency of sampling was intense in blood and sparce in bone marrow. Planned study sampling is listed in section 7.2.3.1. in the study Protocol (Clinical Study Report Appendix 16.1.1, v1.0). The cellular kinetic parameters listed in Table 4 were estimated from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix® (Pharsight, Mountain View, CA).

Descriptive statistics of cellular kinetic parameters were summarised and reported by BOR and Month 3 disease response.

AUC and C_{max} were found to be strongly correlated, indicating that each could serve as a surrogate for the other (r^2 values of 0.950 and 0.868, respectively, for $AUC_{0\text{-}28d}$ and $AUC_{0\text{-}84d}$). $AUC_{0\text{-}28d}$ being a more robust indicator of cellular expansion and exposure for up to 28 days, this parameter has been used extensively in this document to discuss the relationships.

For patients whose tocilizumab PK data was collected during CRS, the tocilizumab concentrations were summarised by time points, relative to time of tocilizumab dose. Tocilizumab concentrations and PK parameters were summarised by CRS grade for the TPAS. Rituximab concentrations were also summarised by Month 3 and BOR for the EAS.

Table 4. Non-compartmental cellular kinetic parameters.

Parameter	Definition
AUC0-28d and/or AUC0-84d	The AUC from time zero to Day 28 and/or Day 84 and or other disease assessment days, in peripheral blood (%*days or days*copies/ µg)
Cmax	The maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration (% or copies/ µg)
Tmax	The time to reach maximum (peak) peripheral blood or other body fluid drug concentration after single dose administration (days)
T1/2	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood
Tlast	The time of the last observed measureable concentration after dose administration.
Clast	The last observed concentration after dose administration

Data from Study **E2202** were used to assess relationships between product attributes and in-process parameters, and cellular kinetic, infused dose, and best overall responses. The impact of intrinsic and extrinsic factors on cellular kinetics were assessed using cellular kinetic parameters determined from non-compartment analyses.

No population pharmacokinetic (popPK) models have been submitted in support of the current application.

- **Evaluation and Qualification of Models**

Dose-exposure, dose-response, and exposure-response modelling has been performed for both efficacy and safety endpoints. No modelling report describing model development have been submitted, consequently the methods has not been assessed in detail. Since the models are submitted for descriptive purposes and not for dose justification or evaluation of dosing strategies, this issue will not be further pursued in the current application.

Results

Dose proportionality and time dependencies

- **Dose proportionality**

The relationship between log-transformed cellular kinetic parameters C_{max}, $AUC_{0\text{-}84d}$ and $AUC_{0\text{-}28d}$, and total tisagenlecleucel cell dose are explored using scatter plot and linear regression. Results of the analysis indicated no strong relationship between the dose and the cellular kinetic parameters with r^2 values below or close to 0.1 for all cellular kinetic parameters analysed across the entire studied dose range of 0.1 to 6.0×10^8 CAR-positive viable T cells (Figure 3). Boxplots and summary of cellular kinetic parameters by dose quartiles demonstrated that estimated parameters were comparable and within overlapping ranges across all dose quartiles.

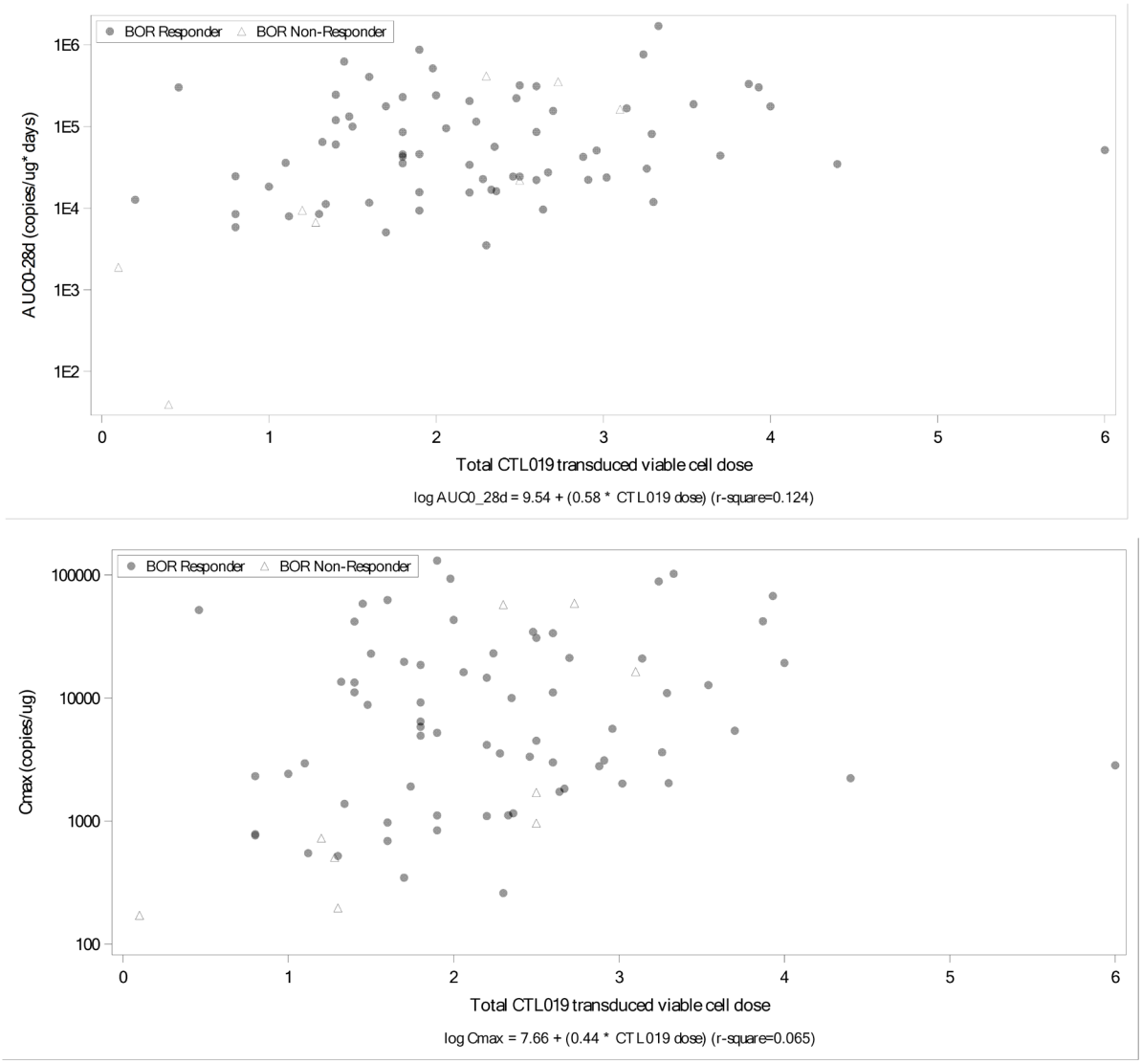


Figure 3. Relationships between qPCR cellular kinetic parameters and CTL019 transduced viable cell dose (Tisagenlecleucel Infused set).

- **Time dependency**

The product is intended for single administration only

Pharmacokinetics in target population

FL indication (study CCTL019E2202)

Demographics

The cellular kinetic analysis set (CKAS) (n=94) in study **E2202** consisted of patients in the efficacy analysis set (EAS) who provided an evaluable cellular kinetic profile (at least 1 cellular kinetic parameter). The CKAS includes all patients that received tisagenlecleucel manufactured at the US manufacturing facility (n=58), Stein, Switzerland (n=11), Les Ulis (formerly Cell for Cure), France (n=20), and Kobe, Japan manufacturing facility (FBRI) (n=8). The CKAS was used for summaries (tables and figures) of cellular kinetic data. The tisagenlecleucel infused set (all the patients who received tisagenlecleucel) was used for listings of cellular kinetic data. The tocilizumab

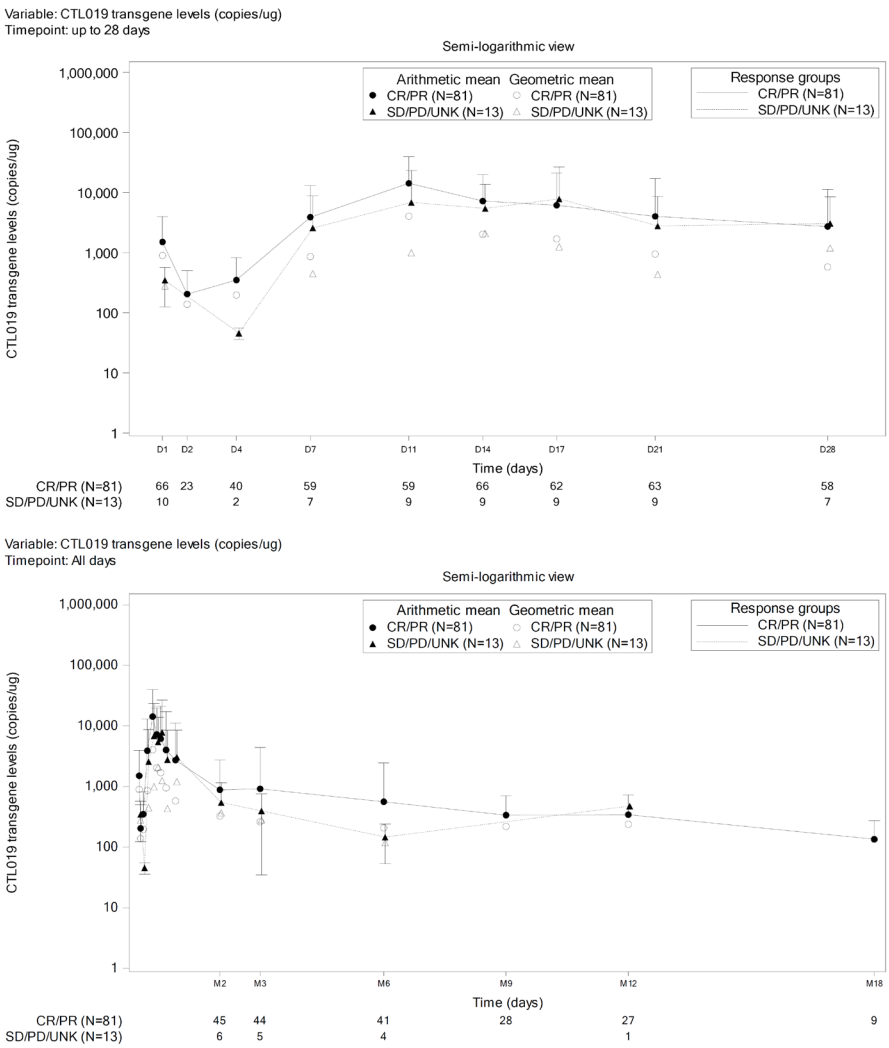
pharmacokinetic analyses set (TPAS) (n=11) consisted of patients in the tisagenlecleucel infused set who took at least one dose of tocilizumab and provided at least one tocilizumab PK concentration

Cellular kinetics in blood

The recommended tisagenlecleucel dose range in this study was 0.6 to 6.0×10^8 CAR-positive viable T-cells. All patients, except for 4, who received a lower dose than specified as per protocol (OOS range: 0.1 to 0.46×10^8 CAR-positive viable T-cells), received tisagenlecleucel within the targeted dose range. Additionally, one patient received tisagenlecleucel product that was OOS due to lower viability at 51.7% (specified: $\geq$ 70%) but with an overall dose of CAR-positive viable T-cells in the targeted dose range (dose received: 0.8×10^8 cells), and one patient received tisagenlecleucel product that was OOS due to a higher dose. However, the site was instructed by Novartis to infuse 91% of the volume and the patient was administered a dose of 6.0×10^8 CAR-positive viable T-cells that was within specification. The median dose administered was 2.06×10^8 CAR-positive viable T-cells (range: 0.1 to 6.0×10^8 cells). The median total viable cell count was 12×10^8 cells (range: 0.4 to 34.0 $\times10^8$ cells).

The median time from enrolment to infusion was 46 days (range: 23 to 127 days). The median duration of follow-up from infusion to the data cut-off date was 16.59 months (range: 10.3 to 25.7 months) for the Enrolled set and 16.85 months (range: 10.3 to 25.7 months) for the EAS.

Results: The time course of CAR transgene levels following infusion is presented by BOR in Figure 4. Following infusion, tisagenlecleucel typically exhibits an initial rapid expansion phase achieving maximal expansion (C_{max}) followed by a bi-exponential decline. The area under the curve ($AUC_{0\text{-}28d}$ or $AUC_{0\text{-}84d}$) of the cellular kinetic profile indicates the transgene exposure (up to 28 or 84 days from infusion), whereas the C_{max} indicates the level of maximal expansion of the tisagenlecleucel transgene. A representative cellular kinetic profile of an individual FL patient, with a complete response based on BOR, from Study **E2202** is presented in Figure 5.



Zero concentrations at individual timepoints are excluded from geometric mean computation

Figure 4. Geometric mean and arithmetic mean concentration-time profiles for tisagenlecleucel transgene levels by qPCR in peripheral blood by BOR and IRC assessment (EAS).

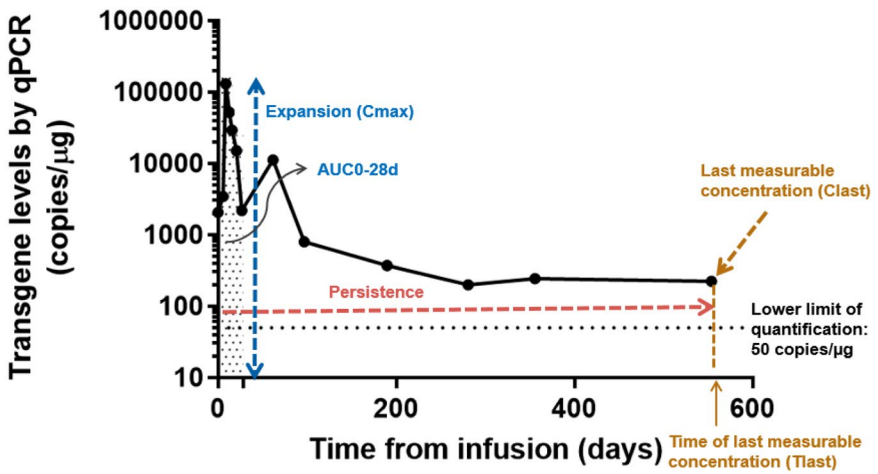


Figure 5. Typical cellular kinetic profile assessed by qPCR in a FL patient (Study E2202).

Summary of peripheral blood cellular kinetic parameters for tisagenlecleucel transgene levels by qPCR are shown in Table 5. Shortly for patients in the CKAS, the geometric mean $AUC_{0\text{-}84d}$ in responders (CR and PR) was similar to that in non-responders (SD and PD) based on clinical best overall response (BOR). However, the geometric mean $AUC_{0\text{-}28d}$ value of responders was 186% higher compared to non-responders, while the geometric mean C_{max} value was 109% higher in responders compared to non-responders. Figure 4 shows similar pattern of mean cellular kinetic profiles between responder and non-responder patients. The time to maximal expansion (T_{max}) was comparable between the two groups (median T_{max}: 10 days and 13 days in responder and non-responder patients, respectively). For 10 of the responder patients, the C_{max} values were not available or could not be reliably estimated due to inappropriate sample processing at the clinical site or because the patients missed 3 or more time points of PK assessment, which were documented as protocol deviations.

CAR-positive viable T cells demonstrated persistence of the tisagenlecleucel transgene for up to a maximum of 558 days in responders and a maximum of 366 days in non-responders, as demonstrated by maximum T_{last} value (time of last quantifiable concentrations) (Table 5, Figure 5).

Table 5. Summary of peripheral blood cellular kinetic parameters (excl. $t_{1/2}$) for tisagenlecleucel transgene levels by qPCR, based on BOR by IRC assessment (CKAS)

Parameter	Statistics	CR/PR N=81	SD/PD N=12	Unknown N=1	All subjects N=94
AUC0-28d (copies/ug*days)	n	66	7	1	74
	Mean (SD)	153000 (263000)	138000 (178000)	1890	150000 (254000)
	CV%	172	129	N/A	170
	Geo-mean	57500	20100	1890	49700
	Geo-CV%	261	18100	N/A	421
	Median	45700	21900	1890	44800
	[Min; Max]	[3510, 1700000]	[39.5, 415000]	[1890, 1890]	[39.5, 1700000]
AUC0-84d (copies/ug*days)	n	52	5	1	58
	Mean (SD)	293000 (631000)	302000 (296000)	4410	289000 (604000)
	CV%	216	98.0	N/A	209
	Geo-mean	112000	148000	4410	108000
	Geo-CV%	221	348	N/A	246
	Median	83700	306000	4410	83700
	[Min; Max]	[11300, 4350000]	[15200, 748000]	[4410, 4410]	[4410, 4350000]
Cmax (copies/ug)	n	67	8	1	76
	Mean (SD)	18300 (27400)	17100 (25900)	171	17900 (27000)
	CV%	150	151	N/A	151
	Geo-mean	6280	3000	171	5540
	Geo-CV%	331	1190	N/A	406
	Median	5420	1330	171	5070
	[Min; Max]	[260, 131000]	[196, 58800]	[171, 171]	[171, 131000]
Tmax (day)	n	67	8	1	76
	Median	9.92	13.0	20.1	10.0
	[Min; Max]	[2.62, 28.0]	[7.73, 16.0]	[20.1, 20.1]	[2.62, 28.0]
Tlast (day)	n	73	10	1	84
	Median	191	107	20.1	186
	[Min; Max]	[19.9, 558]	[18.7, 366]	[20.1, 20.1]	[18.7, 558]

SD in statistics means standard deviation
CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100

Table 6. Summary of peripheral blood cellular $t_{1/2}$ for tisagenlecleucel transgene levels by qPCR, by disease response and IRC assessment CKAS.

Variable: CTL019 transgene levels (copies/ug), Disease response: Best overall response

Parameter	Statistics	CR/PR N=81	SD/PD N=12	Unknown N=1	All subjects N=94
T1/2 (days)	n	43	6	0	49
	Mean (SD)	109 (145)	38.3 (35.0)	N/A	100 (138)
	CV%	133	91.3	N/A	138
	Geo-mean	43.8	24.4	N/A	40.8
	Geo-CV%	287	180	N/A	273
	[Q1; Q3]	[16.6, 144]	[19.7, 45.9]	N/A	[16.8, 127]
	Median	40.9	29.3	N/A	40.0
	[Min; Max]	[2.94, 601]	[2.91, 103]	N/A	[2.91, 601]

Cellular kinetics in bone marrow

Limited data on transgene levels (measured by qPCR) in bone marrow were available as the aspirate were collected only in patients with bone marrow involvement. By BOR, the geometric mean transgene level in responders (n=12) at Month 3 was 214 copies/µg DNA and range was 59.9 to 2620 copies/µg DNA. Further the geometric mean transgene levels in peripheral blood and bone marrow were similar at Month 3, demonstrating trafficking of CAR T cells from blood to bone marrow. Similar results were observed by Month 3 disease response.

Summary of partitioning of blood, bone marrow and lymph node concentrations at month 3, including the blood to bone marrow partitioning in bone marrow is shown in Table 7.

Table 7. Summary of partitioning of blood, bone marrow and lymph node concentrations by qPCR, by best overall response (Cellular kinetic analysis set).

Visit	Statistics	CR/PR N=81	SD/PD N=12	Unknown N=1	All patients N=94
Blood Month 3	n	45	6	0	51
	m	45	6		51
	Mean (SD)	902 (3440)	352 (341)		837 (3230)
	CV%	381.1	97.0		386.0
	Geo-mean	261	248		260
	Geo-CV%	174.8	114.0		165.1
	Median	228	237		228
	Min-Max	53.9-23100	74.0-1000		53.9-23100
Bone Marrow Month 3	n	12	0	1	13
	m	12		0	12
	Mean (SD)	423 (712)		0	390 (692)
	CV%	168.6			177.4
	Geo-mean	214			214
	Geo-CV%	146.5			146.5
	Median	183		0	151
	Min-Max	59.9-2620		0-0	0-2620
Blood:bone marrow ratio Month 3	n	9	0	0	9
	m	9			9
	Mean (SD)	0.605 (0.295)			0.605 (0.295)
	CV%	48.8			48.8
	Geo-mean	0.539			0.539
	Geo-CV%	56.7			56.7
	Median	0.580			0.580
	Min-Max	0.224-1.15			0.224-1.15

n = number of subjects with evaluable values, m = number of non-zero concentrations.

Cellular kinetics of tisagenlecleucel by CRS

The cellular kinetics of tisagenlecleucel were evaluated by CRS grade to determine whether there are differences in expansion by CRS category. To note, no cases of CRS ≥ grade 3 were observed within 8 weeks of tisagenlecleucel infusion.

C_{max} was greater in patients with grade 1 or 2 CRS relative to patients with no CRS. The geometric mean C_{max} (geometric-CV%) was 10100 (381%) copies/µg in patients with grade 1 or 2 CRS (n=40) and 2990 (282%) copies/µg in patients with no CRS (n=35). Similar results were observed with AUC_{0-28d} estimates. The T_{max} was approximately 9 days in patients with grade 1 or 2 CRS (n=40), and 13 days in patients with no CRS (n=35). Consistent with these results, higher expansion was observed in patients that received tocilizumab (n=17, tisagenlecleucel infused set), as the administration of tocilizumab is associated with the management of CRS, as per the CRS management algorithm.

The in vivo persistence of tisagenlecleucel (i.e., median T_{last}) was similar across all CRS categories, suggesting no apparent impact of CRS on *in vivo* persistence. The median apparent half-life ($T_{1/2}$) was approximately 37 days in patients with grade 1 or 2 CRS (n=31), and 86 days in patients with no CRS (n=18).

Relationship between product attributes and cellular kinetics, dose or response

The MAH presents data from a number of analyses that were designed to evaluate the relations between in-process parameters, final product attributes and cellular kinetics, dose and in vivo performance parameters (Table 8).

Table 8. Evaluation of product attributes vs cellular kinetics, infused dose, and BOR

	In vivo performance characteristic		
Product attribute	**Cellular kinetic parameters (AUC0-28d, Cmax)** (Section 2.1.6.1)	**Infused dose** (Section 2.1.6.2)	**BOR** (Section 2.1.6.3)
-Percentage T cells -Total cell count -Transduction efficiency by qPCR -Cellular viability -Transduction efficiency by flow cytometry -IFN-gamma	Regression and scatter plots were generated for each of the product attributes	Regression and scatter plots were generated for each of the product attributes	Box plots were generated for each of the product attributes

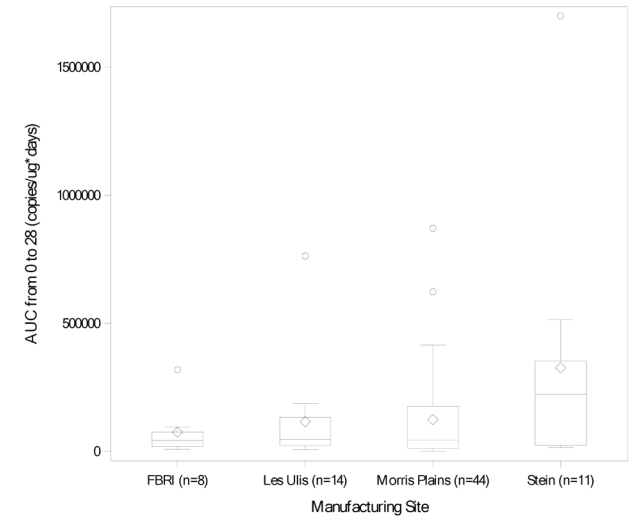
The results for FL were similar to that in r/r DLBCL.

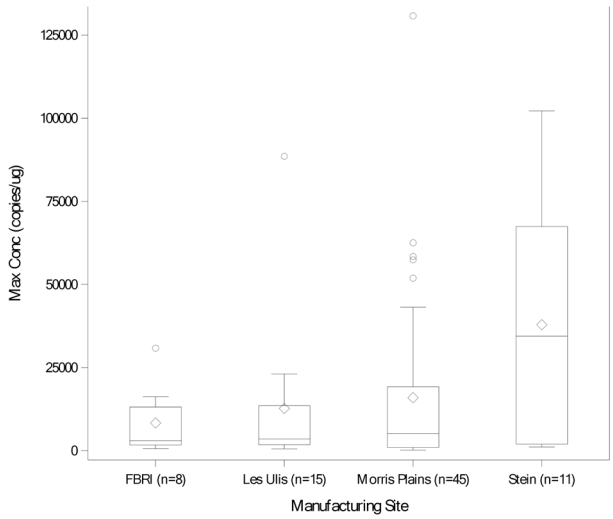
Infused doses were either not correlated or only weakly correlated with both product attributes and in-process parameters. Thus, dose selection for individual patients would not be affected by the rate of in vitro expansion of the product or the final release specifications. From an efficacy perspective, clinical responders were observed across the entire range of specifications for release of the final product. There was no apparent relationship between product attributes, namely, percentage T cells, total cell count, transduction efficiency by flow cytometry, cell viability (%), transduction efficiency by qPCR, and IFN-gamma release level and BOR to treatment with tisagenlecleucel when administered within the attribute ranges required for use (Table 9).

Table 9. Summary of the relationship between product attributes, in process parameters, and cellular kinetic parameters.

Product attributes	Cellular kinetics	Inference
Percentage T cells	AUC0-28d, Cmax	The percentage of T cells in the final product does not impact the in vivo exposure (Section 2.1.6.1).
Total cell count	AUC0-28d, Cmax	Total cell count does not impact the in vivo exposure (Section 2.1.6.1).
Transduction efficiency by qPCR	AUC0-28d, Cmax	Transduction efficiency, as measured by CAR qPCR, is another measure of purity of the product. There was no correlation with cellular kinetic parameters (Section 2.1.6.1).
Cellular viability	AUC0-28d, Cmax	Viable cells in the manufactured product demonstrates the purity and activity of the cell product. The results demonstrate that viability does not have an impact on the in vivo exposure (Section 2.1.6.1).
Transduction efficiency by flow cytometry	AUC0-28d, Cmax	Transduction efficiency by flow cytometry demonstrates the discrete surface expression of CAR protein in the cell product. The lack of a correlation indicates that surface expression of CAR protein does not influence the in vivo exposure (Section 2.1.6.1).
cPDL	AUC0-28d, Cmax	No apparent relationship between cellular kinetic parameters (AUC0-28d and Cmax) and cPDL in the manufactured product showing that in vitro expansion does not influence in vivo expansion and cellular kinetic parameters (AUC0-28d and Cmax) (Section 2.1.7.1).
IFN-gamma	AUC0-28d, Cmax	Potency by IFN-gamma release did not demonstrate any apparent relationship with cellular expansion (Section 2.1.6.1).

A comparison of cellular kinetic parameters by manufacturing site was also performed. The geometric mean (geometric-CV%) of C_{max} were 4850 (449.4), 3950 (233.9), 5170 (226.8), and 14400 (496.5) for patients with batches manufactured at Morris Plains (n=45), FBRI (n=8), Les Ulis (n=15), and Stein (n=11), respectively. Boxplots of expansion by manufacturing site showed similar mean expansion for the product manufactured at the Morris plains, Les Ulis, and FBRI sites, with seemingly higher expansion at for product manufactured at Stein facility (Figure 6).





Diamond represents the mean and circle represents values outside of 1.5*IQR.
Lower and the upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3 respectively.

Figure 6 Boxplot of cellular kinetic parameters by qPCR by manufacturing site (Tisagenlecleucel infused set).

Comparison of cellular kinetics across indications

The MAH has provided a comparison of the results observed in patients with r/r FL (Study **E2202**), r/r DLBCL (Study **CTL019C2201**), and paediatric ALL (Study **CTL019B2202**) indications is presented in Table 10.

Table 10. Comparison between adult patients with r/r FL, r/r paediatric ALL, and r/r DLBCL.

	FL	Pediatric ALL	DLBCL
Cellular kinetic	Similar geometric mean AUC0-84d and higher AUC0-28d and Cmax values in responders were observed compared to non-responders, which could be attributed to the high inter-individual variability, small number of non-responders, overlapping expansion ranges observed between responders and non-responders. Therefore, the exposure differences should be interpreted with caution (Section 2.2)	~ 2 fold difference in expansion between responder (CR/CRi) and non-responder (NR) in PB [SCP ALL-Section 3.2.1.1]	No difference in expansion between responders (CR/PR) and non-responders (SD/PD/Unknown) in PB [SCP DLBCL-Section 3.2] -Note: Differences in the location and burden of disease between indications may impact expansion.
Intrinsic factors			
Age / race / body weight/ gender	No apparent impact of intrinsic factors on expansion and persistence (Section 2.3.1)	No impact of intrinsic factors on expansion and persistence [SCP ALL-Section 3.2.1.3.1]	No apparent impact of intrinsic factors on expansion and persistence [SCP DLBCL-Section 3.3.1]
Prior disease	No clinically relevant impact by disease stage at study entry, number of lines of therapy on expansion/persistence (Section 2.1)	No impact by baseline cytogenetics, disease status on expansion/persistence [SCP ALL-Section 3.2.1.3.1]	No clinically relevant impact by prior disease status, disease stage at study entry, bulky disease and WBC counts prior to infusion on expansion/persistence [SCP DLBCL-Section 3.3.1]
Pre-infusion tumor burden	Higher expansion in patients with high FLIPI relative to low or intermediate FLIPI (Section 2.3.1.5)	Increased expansion in patients with higher pre-infusion tumor burden [SCP ALL-Section 3.2.1.3.1]	Not evaluated. Burden of disease in peripheral blood and bone marrow are not directly applicable in lymphomatous diseases
Extrinsic factors			
Prior therapy	No clinically relevant impact of prior HSCT status, prior bendamustine use, types of LD chemotherapy, number of lines of prior therapy on expansion. Only 5 patients received bendamustine as LD chemotherapy, and therefore a definitive conclusion cannot be made regarding the impact of type of LD chemotherapy (fludarabine + cyclophosphamide vs. bendamustine) (Section 2.3.2)	No impact of number of lines of prior therapy, prior SCT, and treatment with LD regimens on expansion [SCP ALL-Section 3.2.1.3.2]	No impact of prior HSCT status, types of LD chemotherapy, number of lines of prior therapy on expansion [SCP DLBCL-Section 3.3.2]
Concomitant therapy			
CRS management with tocilizumab	Higher AUC0-28d and Cmax observed in patients who received tocilizumab, however, it could be confounded due to the reason that patients with CRS generally have greater expansion and these patients with CRS may require tocilizumab. Transgene continues to expand and persist following tocilizumab infusion (Section 2.3.2.5.1)	Higher AUC0-28d and Cmax observed in CR/CRi patients treated with tocilizumab compared with CR/CRi patients that did not receive tocilizumab [SCP ALL-Section 1.2.1.1.2] CAR-positive viable T cells continue to expand and persist following tocilizumab infusion. High tumor burden at baseline resulted in higher expansion, as a result these patients experienced CRS requiring the administration of tocilizumab or corticosteroids, depending on the severity. Therefore, the higher expansion observed following tocilizumab administration cannot be directly attributed to the use of tocilizumab [SCP ALL - Section 3.2.1.3.2].	Higher AUC0-28d and Cmax observed in patients who received tocilizumab. Patients with higher grade CRS generally have greater expansion and these patients with high grade CRS require tocilizumab [SCP DLBCL-Section 3.3.2.4]. Therefore, the higher expansion following tocilizumab cannot be directly attributed to the use of tocilizumab. Transgene continues to expand and persist following tocilizumab infusion.
Treatment with corticosteroid	Three patients received corticosteroid for management of CRS, while all other patients received corticosteroid for reasons other than CRS, therefore, the impact of corticosteroid use on expansion cannot be studied (Section 2.3.2.5.3)	Higher AUC0-28d observed in CR/CRi patients who received corticosteroid compared with patients that did not receive steroids. High variability in exposure observed in patients treated with corticosteroid [SCP ALL-Section 3.2.1.3.2].	Higher AUC0-28d observed in CR/PR patients who received corticosteroid than patients that did not receive. However, the effect might be confounded by the administration of tocilizumab, CRS event, or tumor burden [SCP DLBCL-Section 3.3.2.4]
Dose-efficacy			
Dose-response	No overall impact with slightly lower probability of response at the lower end of the dose	For patients >50 kg, an increasing trend in probability of response for doses <1.0×10^8 total	No impact of dose on Month 3 response [SCP DLBCL-Section 3.7.1.1]

	FL	Pediatric ALL	DLBCL
	range (<1.0×10^8 cells). Favorable clinical responses (CR/PR) were observed across the entire recommended dose range (Section 2.6.1.1)	transduced viable T cells while the probability of response plateaus for doses higher than 1.0×10^8 total transduced viable T cells. Similarly, for patients ≤ 50 kg, the dose-response curve shows an moderate increasing trend in probability of response for doses <2.0×10^6 transduced viable T cells per kg, while the probability plateaus for higher doses. The increasing trend should be interpreted with caution as there is limited data at lower doses. [SCP ALL-Section 3.6.1.1]	
Dose-DOR/Dose-time to response	No apparent impact of dose on DOR or PFS (Section 2.6.1.2 and Section 2.6.1.3)	No apparent impact of dose on DOR in patients with body weight ≤ 50 kg. Limited number of events and follow-up for patients >50kg to draw a definitive conclusion. [SCP ALL-Section 3.6.1.3]	No apparent impact of dose on DOR and time to response [SCP DLBCL-Section 3.7.1.2]
Dose-Safety			
Dose-CRS	No apparent relationship. No cases of CRS ≥ grade 3 observed within 8 weeks of infusion (Section 2.6.2.1)	No impact of dose on probability of CRS (any grade and grade 3/4) [SCP ALL-Section 3.6.2]. Increased risk of grade 4 CRS with higher dose, but CRS is generally manageable.	Increasing probability of CRS (any grade and grade 3/4) with increasing dose [SCP DLBCL-Section 3.7.2.1]. CRS is manageable [SCE DLBCL]
Dose-serious neurological events	No impact (Section 2.6.2.2)	NA	No impact of dose on neurological events [SCP DLBCL- Section 3.7.2.2]
Dose-time to resolution of hematopoietic cytopenias	No apparent impact (Section 2.6.2.3)	NA	No apparent impact of dose on thrombocytopenia and neutropenia [SCP DLBCL-Section 3.7.2.3]
Exposure-efficacy			
Exposure-response	AUC0-28d and Cmax were higher in responding patients compared to non-responding patients (similar mean AUC0-84d estimates), however this should be interpreted with caution due to the large variability and the limited number of non-responding patients with evaluable Cmax (Section 2.7)	CR/CRi patients tend to have higher exposure compared with NR patients [SCP ALL-Section 3.6.3.2]	No impact of exposure on Month 3 response [SCP DLBCL-Section 3.8.1.1]
Exposure-DOR	A longer DOR was associated with increasing exposure (Section 2.7.1.2)	The DOR did not appear to be impacted by exposure [SCP ALL-Section 3.6.3.3]	No impact of exposure on DOR [SCP DLBCL -Section 3.8.1.2]
Exposure-Safety			
Exposure-CRS	Higher tisagenlecleucel exposure was associated with higher probability of any grade CRS. No cases of CRS ≥grade 3 were observed within 8 weeks of infusion (Section 2.7.2.1)	Higher exposures were associated with increasing CRS grades [SCP ALL-Section 3.6.4.1]	Higher probability of any grade or grade 3/4 CRS was associated with higher tisagenlecleucel exposures [SCP DLBCL-Section 3.8.2.1]
Exposure-serious neurological events	No impact of exposure on neurological events (Section 2.7.2.2)	NA	No impact of exposure on neurological events [SCP DLBCL-Section 3.8.2.3]
Exposure-cytopenias	No apparent impact of exposure on time to resolution of cytopenias and serious neurologic events, despite the limited number of patients who experienced long term cytopenias (Section 2.7.2.3)	NA	No definitive conclusion can be drawn regarding the impact of exposure on time to resolution of cytopenias due to limited number of patients with prolonged cytopenia [SCP DLBCL-Section 3.8.2.4]
Immunogenicity			
Immunogenicity (humoral and cellular)	No impact of anti-mCAR19 antibodies (humoral) and cellular immunogenicity on cellular kinetics and BOR (Section 2.8)	No impact of anti-mCAR19 antibodies on cellular kinetics and Day 28 response [SCP ALL-Section 4.1]	No impact of anti-mCAR19 antibodies (humoral) and cellular immunogenicity on cellular kinetics and Month 3 response [SCP DLBCL-Section 4.1]

DLBCL: adult patients with relapsed or refractory diffuse large B-cell lymphoma
pediatric ALL: pediatric and young adult with r/r B-cell acute lymphoblastic leukemia
CR: complete response
PR: partial response
SD: stable disease
PB: peripheral blood
CRS: cytokine release syndrome
DOR: duration of response
PFS: progression-free survival
CRi: Complete remission with incomplete hematologic recovery
PD: progressive disease
NA: not available

Special populations

The impact of intrinsic and extrinsic factors on cellular kinetics of tisagenlecleucel are summarised by descriptive statistics, box plots, and scatter plots.

The intrinsic parameters evaluated were age, gender, body weight, race, Follicular Lymphoma International Prognostic Index (FLIPI) at enrolment, histological grade, baseline lactate dehydrogenase (LDH), disease stage, POD 24 (patients primary refractory or experiencing progression of disease within 24 months from initiation of a first-line anti-CD20 mAb containing treatment), and refractoriness to last therapy, using summary statistics as well as graphically.

Extrinsic factors such as the effect of concomitant medication and prior therapy were evaluated similarly (assessed in the section *Pharmacodynamic interactions with other medicinal products or substances)*.

- **Impaired renal and hepatic function**

No dedicated renal or hepatic impairment studies have been conducted.

- **Gender**

Comparison of cellular kinetic parameters by gender showed 106% and 111% higher geometric mean $AUC_{0\text{-}28d}$ and C_{max} values, respectively, for female patients compared with male patients. The geometric mean $AUC_{0\text{-}28d}$ in copies/µg×days (geometric-CV%) was 78400 (247.4%) and 38000 (487.4%) for female and male, respectively and the geometric mean C_{max} in copies/µg (geometric-CV%) was 9070 (269.5%) and 4290 (436.8%) for female and male, respectively. However, considering the high variability and overlapping ranges, gender does not appear to influence tisagenlecleucel expansion.

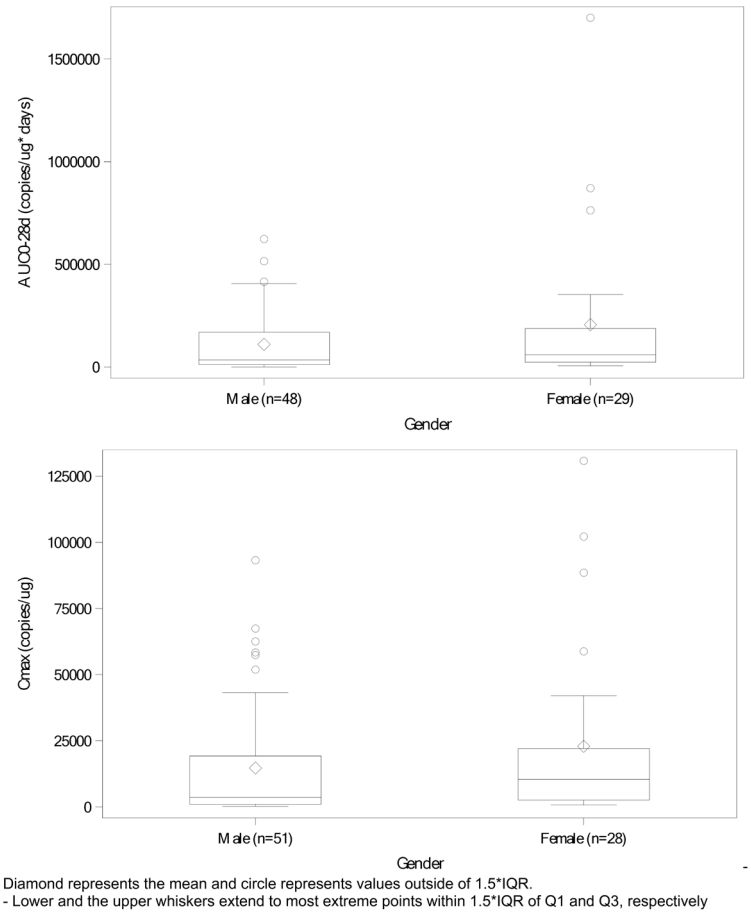


Figure 7. Boxplot of qPCR cellular kinetic parameters for tisagenlecleucel by gender (Tisagenlecleucel infused set).

- **Race**

Boxplots and summary statistics showed overlapping ranges of cellular kinetic parameters, suggesting that race does not appear to impact tisagenlecleucel exposure metrics (C_{max}, $AUC_{0\text{-}28d}$, $AUC_{0\text{-}84d}$, and T_{max}). Race which is self-reported included White (N=73, 75.3%), Asian (N=13, 13.4%) or missing (N=10, 10.3%) (N=1 African American patient did not have valid PK parameters and thus was not included in the analysis). After adjusting for covariates of age, baseline weight and gender, the

geometric mean ratios (Asian vs. white) are 0.86 (95% CI: 0.32 to 2.31) and 0.53 (95% CI: 0.206 to 1.36) for $AUC_{0\text{-}28d}$ and C_{max}, respectively; however, considering the limited number of evaluable patients in Asian group and the large variability, these results should be interpreted with caution.

- **Age**

The impact of age on cellular kinetics was evaluated across the age range of 29 to 73 years. The scatter plots of cellular kinetic parameters versus age revealed no apparent relationship between age and expansion parameters; AUCs ($AUC_{0\text{-}28d}$ and $AUC_{0\text{-}84d}$), C_{max}, and T_{max} (r^2 value ranged from 0.012 to 0.064) (Figure 8).

Boxplots (Figure 9) and summary statistics of cellular kinetic parameters by age categories (<65 years (N=73) or ≥65 years (N=24)) shows that estimated parameters ($AUC_{0\text{-}28d}$ and C_{max}) are within comparable ranges with lower geometric means in patients ≥65 years, and the differences are not considered relevant due to high inter-individual variabilities associated with the parameters.

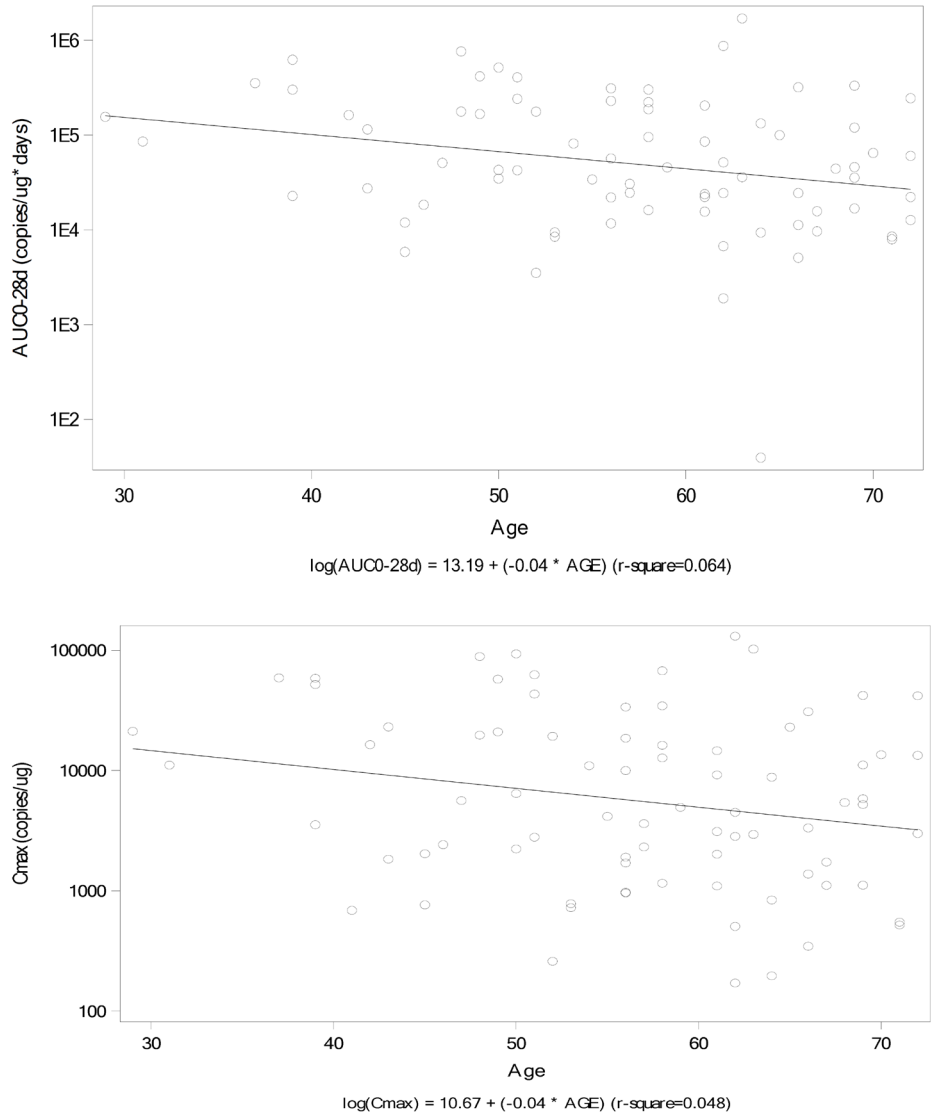
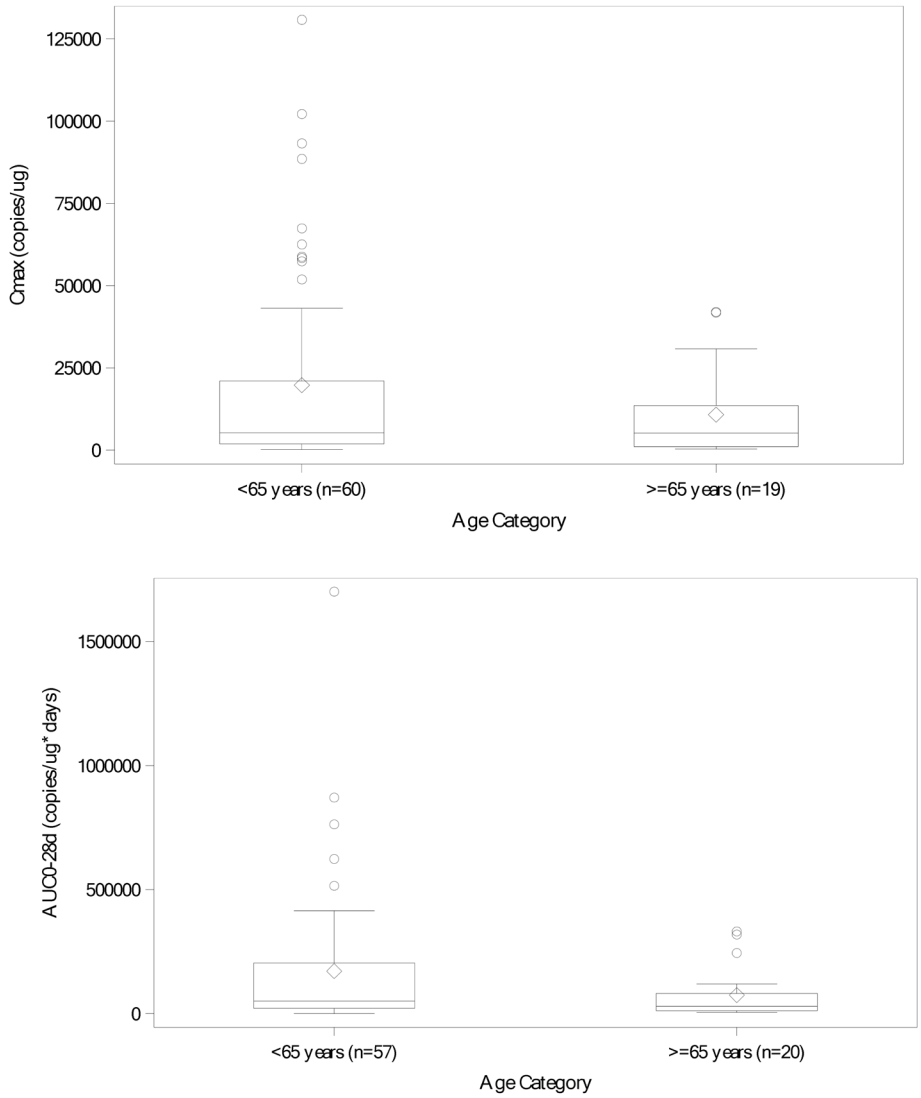


Figure 8 Scatter plot of qPCR cellular kinetic parameters of tisagenlecleucel vs. age (Tisagenlecleucel infused set).



Diamond represents the mean and circle represents values outside of 1.5*IQR.
Lower and upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3, respectively.

Figure 9. Boxplot of qPCR cellular kinetic parameters by age group (Tisagenlecleucel Infused set).

- **Weight**

Baseline body weight does not have an effect on the cellular kinetics of tisagenlecleucel. Across the weight ranges (44.3-127.7 kg), the scatter plots of cellular kinetic parameters versus weight revealed no relevant relationship between the kinetic parameters and baseline weight. The r^2 values were close to zero, ranging from 0.009 to 0.047. The analysis of baseline weight by quartiles of $AUC_{0\text{-}28d}$ and C_{max} suggested a consistent result. Weight did not influence the expansion of tisagenlecleucel.

- **Other factors influencing cellular kinetics**

Disease stage

Categories of disease stage at study entry did not impact tisagenlecleucel cellular kinetics (Table 11). However, due to the small number of patients with evaluable cellular kinetic parameters in Stage I/II category (n=13) relative to the number of patients in Stage III/IV category (n=64), and the large variability associated with cellular kinetic parameters, results should be interpreted with caution.

Table 11. Summary of peripheral blood cellular kinetic parameters for tisagenlecleucel by disease stage at study entry (Tisagenlecleucel infused set).

Parameter	Statistics	I/II N=14	III/IV N=83	All patients N=97
AUC0-28d (copies/µg×days)	n	13	64	77
	Geo-mean	51900	49600	50000
	Geo-CV%	113.1	500.3	399.8
	Median	51400	43400	45500
	[Min; Max]	[8490, 177000]	[39.5, 1700000]	[39.5, 1700000]
AUC0-84d (copies/µg×days)	n	10	50	60
	Geo-mean	94300	109000	106000
	Geo-CV%	97.9	279.8	240.5
	Median	85900	82600	83700
	[Min; Max]	[21500, 361000]	[4410, 4350000]	[4410, 4350000]
Cmax (copies/µg)	n	13	66	79
	Geo-mean	5130	5690	5600
	Geo-CV%	171.5	456.9	389.6
	Median	4940	5320	5210
	[Min; Max]	[520, 22900]	[171, 131000]	[171, 131000]
Tmax (days)	n	13	66	79
	Median	9.02	10.7	9.96
	[Min; Max]	[5.75, 15.8]	[2.62, 28.0]	[2.62, 28.0]
Tlast (days)	n	14	73	87
	Median	231	185	187
	[Min; Max]	[28.0, 374]	[18.7, 558]	[18.7, 558]
T1/2 (days)	n	8	42	50
	Median	38.9	38.8	38.8
	[Min; Max]	[9.61, 144]	[2.91, 601]	[2.91, 601]

N: number of patients; n: patients with non-missing values
CV% = coefficient of variation (%) = sd/mean*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Follicular Lymphoma International Prognostic Index (FLIPI) at enrolment

Comparison of cellular kinetic parameters by FLIPI at enrolment (low/intermediate (n=39) vs. high (n=58)) demonstrated 47% and 62% higher $AUC_{0\text{-}28d}$ and C_{max} geometric mean values, respectively, in patients with high FLIPI ($AUC_{0\text{-}28d}$: n=46, C_{max}: n=47) relative to low or intermediate FLIPI ($AUC_{0\text{-}28d}$: n=31, C_{max}: n=32).

Histological grade

Comparison of cellular kinetic parameters by histological grade at study entry (grade 1-2, low grade (n=87) vs. grade 3A (n=10)) demonstrated 105% and 113% higher $AUC_{0\text{-}28d}$ and C_{max} geometric mean values, respectively, in patients with grade 1-2 FL ($AUC_{0\text{-}28d}$: n=68, C_{max}: n=70) relative to grade 3A FL ($AUC_{0\text{-}28d}$/C_{max} n=9). However, these data should be interpreted with caution due the small number of patients in the grade 3A group and the large associated variability. The geometric mean $AUC_{0\text{-}28d}$ in copies/µg×days (geometric-CV%): 54300 (426.5%) and 26500 (204.8%) for grade 1-2 and grade 3A, respectively, and geometric mean C_{max} in copies/µg: 6100 (400.5%) and 2860 (269.7%) for grade 1-2 and grade 3A, respectively.

Baseline lactate dehydrogenase (LDH)

Comparison of cellular kinetic parameters by baseline LDH (≤upper limit of normal (ULN) (n=65) vs. >ULN (n=31)) demonstrated comparable $AUC_{0\text{-}28d}$ and C_{max} geometric-mean values between the two categories, considering the high variability associated with these parameters. The geometric mean $AUC_{0\text{-}28d}$ in copies/µg×days (geometric-CV%) 49800 (469.0%) and 53700 (294.8%) for ≤ULN (n=53) and >ULN (n=23), respectively, and geometric mean Cmax in copies/µg (geometric-CV%) were 5540 (405.7%) and 6190 (372.2%) for ≤ULN (n=55) and >ULN (n=23), respectively.

POD 24 (patients primary refractory or experiencing progression of disease within 24 months from initiation of a first-line anti-CD20 mAb containing treatment)

Comparison of cellular kinetic parameters for patients who did not report progression of disease (POD) within 24 months from anti-CD20 containing first-line therapy (POD24) (n=36) vs. patients who reported POD24 (n=61) demonstrated 98% and 199% higher $AUC_{0\text{-}28d}$ and C_{max} geometric mean values, respectively, in patients who did not report POD24 relative to patients reporting POD24. The geometric mean $AUC_{0\text{-}28d}$ in copies/µg×days (geometric-CV%) were 37000 (211.1%) and 73100 (769.0%) for patients with POD24 (n=43) and patients without POD24 (n=34), respectively and C_{max} in copies/µg (geometric-CV%) were 3550 (317.4%) and 10600 (370.5%) for patients with POD24 (n=46) and patients without POD24 (n=33), respectively. These results indicate that patients who did not progress within 24 months following the first line anti-CD20 therapy demonstrated higher expansion compared to patients who experienced POD24.

Refractoriness to last therapy

Comparison of cellular kinetic parameters for patients by refractoriness to last therapy (patients relapsed (n=18) vs. those who had refractory disease (n=75)) demonstrated 115% higher $AUC_{0\text{-}28d}$ and C_{max} geometric mean values in patients who relapsed relative to patients who had refractory disease. The geometric mean $AUC_{0\text{-}28d}$ in copies/µg x day (geometric-CV%) for patients who relapsed (n=17) was 94400 (428.5%) and 43900 (389.4%) for patients who had refractory disease (n=57). The geometric mean C_{max} in copies/µg (geometric-CV%) for patients who relapsed (n=17) was 10700 (494.5%) and 4980 (356.4%) for patients who had refractory disease (n=59).

Pharmacokinetic interaction studies

No pharmacokinetic drug interaction studies have been performed with tisagenlecleucel as there is no mechanistic basis for a pharmacokinetic drug interaction. T-cells are known to be susceptible to immuno-suppressive agents. Immuno-suppressive agents should be used with caution when administered following infusion of tisagenlecleucel since such agents may be lymphotoxic.

2.3.3. Pharmacodynamics

No additional clinical pharmacodynamics data have been submitted for this application.

Pharmacodynamic interactions with other medicinal products or substances

There are potential pharmacodynamic interactions that may occur between tisagenlecleucel, and agents administered as part of bridging and/or lymphodepletion conditioning regimens prior to tisagenlecleucel treatment.

Rituximab

Rituximab is an anti-CD20 monoclonal antibody that is known to cause long term B cell aplasia (Dotan et al 2010). Tisagenlecleucel has previously been shown to cause long term B cell aplasia in other indications and is an expected effect. In this study, all the patients had received rituximab as a prior antineoplastic therapy. With a long terminal half-life (median $T_{1/2}$=22 days) of rituximab (anti-CD20 monoclonal antibody) reported in NHL patients (Rituxan® USPI), it was not unexpected that high levels of rituximab were still measurable at Day 28 and Month 3 following tisagenlecleucel infusion. B cell counts in peripheral blood were summarised at baseline and by time point.

At baseline, in all the patients, the mean cell counts for B-cells cells were low, which could be attributed to the heavy pre-treatment. Post-tisagenlecleucel infusion, the mean cell counts of B-cells increased over time in some of the patients with corresponding decline in the transgene levels. The majority of these patients, however, remained in remission despite the recovery B cell and the decline in the transgene level, consistent with the observation noted in DLBCL patients.

In Study **E2202**, by BOR, the geometric mean concentrations of rituximab (geometric-CV%) (ng/mL) at pre-dose, for responders (n=36) and non-responders (n=6) were 3360 (787.0%) ng/mL and 9810 (165.9%) ng/mL, respectively. At Day 28 post-infusion the geometric mean concentration (geometric-CV%) for responders (n=29) was 2230 (679.4%) ng/mL and for non-responders (n=6) it was 5230 (224.4%) ng/mL. The rituximab levels were overlapping in responders and non-responders with high inter-individual variability, at pre-infusion and at post-infusion visits, and therefore does not seem to have a relationship with response.

Similar results were observed by Month 3 disease response.

Prior bendamustine use

Comparison of cellular kinetic parameters for patients by prior bendamustine use (patients who received prior bendamustine (n=66) vs. those who did not (n=31)) demonstrated 83% and 15% higher $AUC_{0\text{-}28d}$ and C_{max} geometric mean values, respectively, in patients who did not receive prior bendamustine relative to patients who did receive prior bendamustine. The geometric mean $AUC_{0\text{-}28d}$ in copies/µg×days (geometric-CV%) for patients with prior bendamustine use was 41700 (365.7%) (n=54) vs. 76400 (458.9%) for patients who had no prior use (n=23). The geometric mean Cmax in copies/µg (geometric-CV%) was comparable between the patients with prior use, 5360 (327.7%) (n=54) relative to patients with no use, 6150 (594.6%) (n=25). These results indicate that bendamustine has no effect on tisagenlecleucel expansion in the studied population.

Number of prior lines of anti-neoplastic therapy

Overall, the number of lines of prior therapy did not impact tisagenlecleucel exposure described by $AUC_{0\text{-}28d}$, and C_{max}. The exposure parameters were comparable across patients with different number of prior therapy lines, considering the overlapping ranges and variability associated with the parameters. The geometric mean C_{max} (geometric-CV%, n) was similar between patients with ≤2 lines of prior therapy (4040 copies/µg, 398.0%; n=22) and in patients with >4 lines of prior therapy (4730 copies/µg, 415.4%; n=22); however, the mean C_{max} was observed to be higher in patients with 3-4 lines of prior therapy (7640 copies/µg, 364.8%; n=35).

Prior hematopoietic stem cell treatment (HSCT) status

Comparison of cellular kinetic parameters for patients by prior HSCT (patients who received HSCT (n=35) vs. those who did not (n=62)) demonstrated 69% and 61% higher $AUC_{0\text{-}28d}$ and C_{max} geometric mean values, respectively, in patients who received prior HSCT ($AUC_{0\text{-}28d}$: n=28, C_{max}: n=27) relative to patients who did not receive prior HSCT ($AUC_{0\text{-}28d}$: n=49, C_{max}: n=52). This difference is considered not to have a clinically relevant impact.

Bridging therapy

Of the 97 patients infused, 44 patients (45.4%) received optional antineoplastic bridging therapy prior to tisagenlecleucel infusion. All infused patients received LD chemotherapy prior to tisagenlecleucel infusion. In 5 patients, only corticosteroids were administered as bridging therapy. Furthermore, 2 patients received bridging radiotherapy – 1 patient received only radiotherapy and the other patient received radiotherapy and corticosteroids.

Comparison of cellular kinetic parameters by bridging therapy demonstrated 96% and 27% higher $AUC_{0\text{-}28d}$ and C_{max} geometric mean values, respectively, in patients who received bridging therapy relative to patients who did not received bridging therapy. The geometric mean $AUC_{0\text{-}28d}$ in copies/µg×days (geometric-CV%) for patients who received bridging therapy (n=31) was 74600 (245.8%), compared to 38100 (510.2%) for patients who did not receive bridging therapy (n=46). The geometric mean C_{max} in copies/µg (geometric-CV%) for patients who received bridging therapy (n=35) was 6380 (390.8%), compared to 5040 (396.8%) for patients who did not receive bridging therapy (n=44) (Appendix 1-Figure 2.2.8.1 and Appendix 1-Table 2.2.8.1).

Lymphodepletion

All infused patients received LD chemotherapy prior to tisagenlecleucel infusion. The majority of patients (n=92) received fludarabine + cyclophosphamide, and the remaining 5 patients received bendamustine.

Patients who received prior bendamustine had approximately 19% and 42% higher $AUC_{0\text{-}28d}$ and C_{max} geometric mean values compared to patients who received fludarabine + cyclophosphamide. However, due to small number of patients that received bendamustine as the LD chemotherapy and high variability associated with the parameters, no strong conclusion can be drawn. The geometric mean $AUC_{0\text{-}28d}$ in copies/µg×days (geometric-CV%): 59000 (118.2%) and 49400 (432.3%) for patients who received prior bendamustine and patients who received fludarabine + cyclophosphamide, respectively and C_{max} in copies/µg: 7780 (143.2%) and 5470 (415.5%) for patients who received prior bendamustine and patients who received fludarabine + cyclophosphamide, respectively.).

CRS management with tocilizumab and corticosteroids

In study **E2202**, 48 patients (49.5%) experienced CRS event. A total of 17 patients (17.5%) in the Tisagenlecleucel infused set received anti-cytokine medication for CRS. All 17 patients received tocilizumab and 4 of them received corticosteroids in addition (Table 12).

Table 12 Anti-cytokine medications administered during CRS by maximum CRS grade Tisagenlecleucel infused set.

ATC Class Preferred term	No CRS N=49 n (%)	Grade 1/2 N=47 n (%)	Grade >=3 N=1 n (%)	All subjects N=97 n (%)
Number of subjects with at least one anti-cytokine medication	0	16 (34.0)	1 (100)	17 (17.5)
Antineoplastic and immunomodulating agents	0	16 (34.0)	1 (100)	17 (17.5)
Tocilizumab	0	16 (34.0)	1 (100)	17 (17.5)
Systemic hormonal preparations, excl. sex hormones and insulins	0	3 (6.4)	1 (100)	4 (4.1)
Methylprednisolone	0	2 (4.3)	1 (100)	3 (3.1)
Dexamethasone	0	1 (2.1)	0	1 (1.0)
Vasopressin	0	0	1 (100)	1 (1.0)

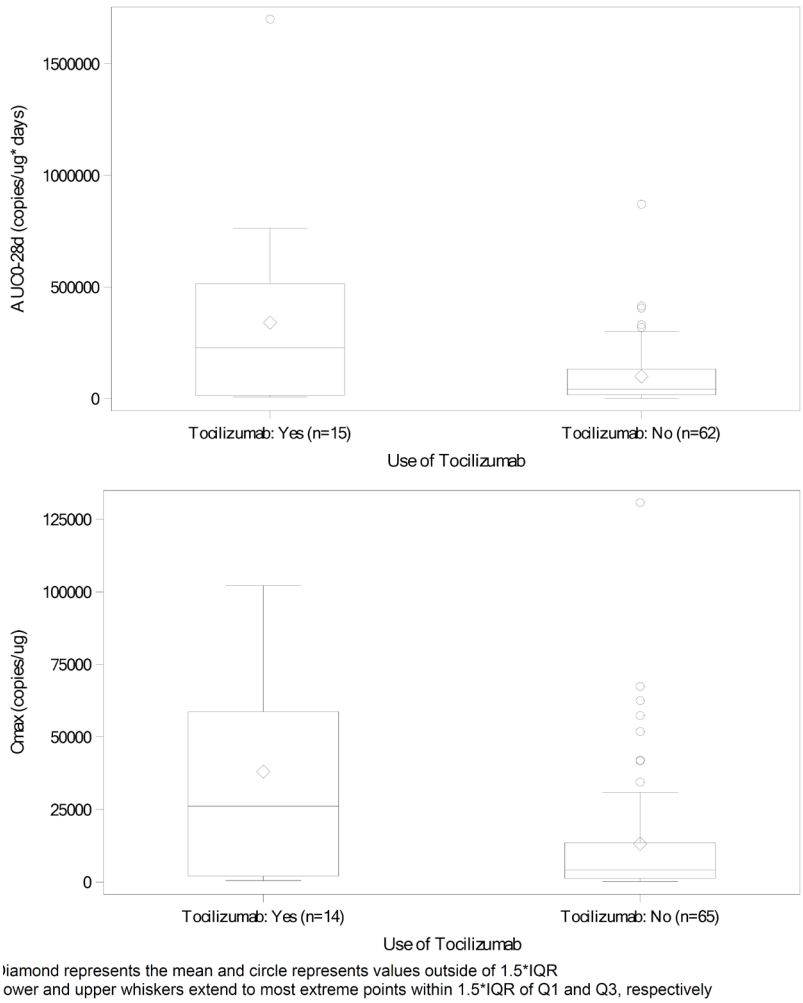
Impact of tocilizumab on cellular kinetics of tisagenlecleucel

In Study **E2202**, tocilizumab was administrated to patients for the management of CRS, and the impact of the anti-cytokine medication on the cellular kinetics of tisagenlecleucel was investigated. In the study, 48 patients (49.5%) had experienced CRS event. Sixteen patients in the safety population, required tocilizumab: 8 patients received one dose, 5 patients received two doses and 3 patients received 3 doses. In all the patients, the dose of tocilizumab administered was 8 mg/kg, with the

exception of one patient who received a slightly higher dose of 8.84 mg/kg. Tocilizumab concentrations were collected at different time points post-infusion in patients who received tocilizumab for the management of CRS.

The extent of maximal expansion (C_{max}) estimates was nearly 312% higher in patients who received tocilizumab for CRS management (n=11, geometric mean Cmax (geometric-CV%): 18300 (628.5%) copies/µg) relative to patients who did not receive tocilizumab (n=62, geometric mean C_{max} (geometric-CV%): 4440 (344.2%) copies/µg). Similarly, the geometric mean $AUC_{0\text{-}28d}$ was nearly 245% higher for patients that received tocilizumab (n=12, geometric mean AUC0-28d estimate: 137000 (604.9%) copies/µg×days), compared to patients that did not receive tocilizumab (n=59, geometric mean $AUC_{0\text{-}28d}$ estimate: 39700 (371.3%) copies/µg×days). However, the time of maximal expansion (T_{max}) for tisagenlecleucel transgene was approximately 10 days, irrespective of use of tocilizumab. Boxplot of $AUC_{0\text{-}28d}$ and C_{max} by use of tocilizumab (Tisagenlecleucel infused set) are shown in Figure 10.

The MAH states that the true influence of tocilizumab on expansion cannot be ascertained directly since this observation may have been confounded as tocilizumab is given for management of CRS and positive correlation was observed for exposure-CRS relationship. Model based analysis had demonstrated that transgene continued to expand and persist following tocilizumab administration (Stein et al 2019).



iamond represents the mean and circle represents values outside of 1.5*IQR
ower and upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3, respectively

Figure 10. Boxplot of qPCR cellular kinetic parameters by use of tocilizumab (Tisagenlecleucel infused set).

Summary of cellular kinetic parameters by use of corticosteroids

All patients received corticosteroids post tisagenlecleucel infusion, however only 3 patients received corticosteroids for the management of CRS. Systemic anti-cytokine treatment with tocilizumab or corticosteroids was required for the management of CRS in 16 patients (34.0%), 13 of whom required only 1 (n=8) or 2 (n=5) doses of tocilizumab, and 3 patients required both tocilizumab and corticosteroids (i.e. dexamethasone (n=1) and methylprednisolone sodium succinate (n=2)). As per the protocol CRS management algorithm, tocilizumab 8 mg/kg could be administered every 8 hours starting from grade 2 CRS (for a maximum of 3 doses within 24 h).

Three patients received corticosteroids for the management of CRS. Higher $AUC_{0\text{-}28d}$ observed in patients who received corticosteroid for the management of CRS relative to patients that received it for other reasons. However, the effect might be confounded by the administration of tocilizumab, CRS event, or tumor burden and should be interpreted with caution due to the small number of patients receiving corticosteroids for CRS management.

Relationship between dose, cellular kinetics and effect

The dose-response, dose-safety, and dose-cellular kinetics analyses were performed using the data obtained from r/r FL patients (data cut-off date: 29-March-2021) in Phase 2 study (Study **E2202**) to assess the impact of dose on exposure, response, and selected safety endpoints in order to select safe and efficacious doses for use in the prescribing setting (commercial).

Dose–response relationships

The relationship between tisagenlecleucel dose and response (efficacy and safety) was explored. Dose-efficacy and dose-safety analyses were based on efficacy and safety analysis sets, respectively. The relationship between log-transformed cellular kinetic parameters C_{max}, $AUC_{0\text{-}84d}$ and $AUC_{0\text{-}28d}$, and total tisagenlecleucel cell dose are discussed above in the section *Dose proportionality and time dependency*.

Doses administered to r/r FL patients in Study **E2202** ranged from 0.1 to 6.0×10^8 CAR-positive viable T cells, where four patients received a dose lower than the specified clinical trial dose. The lowest dose at which CR was observed was 0.46×10^8 CAR-positive viable cells, similar to the currently approved lower end of dose range in DLBCL patients (i.e., 0.6×10^8 CAR-positive viable cells), although patient progressed on Day 560 with a duration of remission of 476 days. Four patients received a dose of 0.8×10^8 CAR-positive viable cells, all with a best overall response of complete response and of which three patients are ongoing responders without an event (with longest duration of remission of 451 days.

Dose-efficacy relationship

Efficacy endpoints evaluated for dose-response analysis included BOR, DOR, PFS and time to new anti-lymphoma therapy. The specific analyses are detailed in Table 13, and were performed using the EAS (N=94).

Table 13. Dose-efficacy analysis

Efficacy endpoints	Analyses performed	Methods
BOR	BOR vs. CAR-positive viable cell dose	Logistic regression
	BOR vs. CAR-positive viable cell dose quartiles	Summary statistics by dose quartiles
DOR, PFS, and time to start of new anti-lymphoma therapy	DOR, PFS and time to start of new anti-lymphoma therapy vs. CAR-positive viable cell dose	Kaplan-Meier plot and Cox Regression
	DOR and PFS vs. CAR-positive viable cell dose quartiles	Summary statistics by dose quartiles

BOR: Best overall response
DOR: Duration of response
PFS: Progression free survival

Dose-BOR analysis

The relation between CAR-positive viable cell dose and the probability of achieving BOR of CR only or CR/PR was analysed by logistic regression across the entire studied dose range (0.1 to 6.0×10^8) (Figure 10). Additionally, BOR was summarized by CAR-positive viable cell dose quartiles.

Favourable clinical responses (CR/PR) were observed across the entire recommended dose range. Based on a logistic regression analysis, the odds of achieving a BOR of CR/PR upon doubling the dose were estimated to be increased by 67% (OR: 1.67, 95% CI: 0.95 to 2.95).

Dose-response curve for the probability of CR/PR is showing an increasing trend of probability with increase in dose towards the lower end of the dose range ($<1.0\times10^8$ cells). The dose-response curve reached a plateau at doses greater than 1.0×10^8 CAR-positive viable cells. It should be noted that 4 patients were infused with doses $<0.6\times10^8$ and the lowest dose at which CR was observed was 0.46×108 CAR-positive viable cells. Moreover, similar response rates were observed across CAR-positive viable cell dose-quartiles.

Table 14. Best overall response by independent review committee (IRC) assessment by quartile of CTL019 transduced viable cell dose (Efficacy Analysis Set).

	Dose <=1.4 N=25		1.4< Dose <=2 N=23		2< Dose <=2.6 N=23		Dose >2.6 N=23		All patients N=94	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Best overall response										
CR	17 (68.0)		17 (73.9)		13 (56.5)		18 (78.3)		65 (69.1)	
PR	2 (8.0)		6 (26.1)		6 (26.1)		2 (8.7)		16 (17.0)	
SD	2 (8.0)				1 (4.3)				3 (3.2)	
PD	3 (12.0)				3 (13.0)		3 (13.0)		9 (9.6)	
Unknown (UNK)	1 (4.0)								1 (1.1)	
Overall Response Rate (ORR: CR+PR)	19 (76.0)	(54.9 ,90.6)	23 (100.0)	(85.2 ,100.0)	19 (82.6)	(61.2 ,95.0)	20 (87.0)	(66.4 ,97.2)	81 (86.2)	(77.5 ,92.4)

CR=Complete response; PR=Partial response; SD=Stable disease; PD=Progressive disease.
The 95% CIs are exact Clopper-Pearson CIs.
Dose are expressed *10^8 cells.

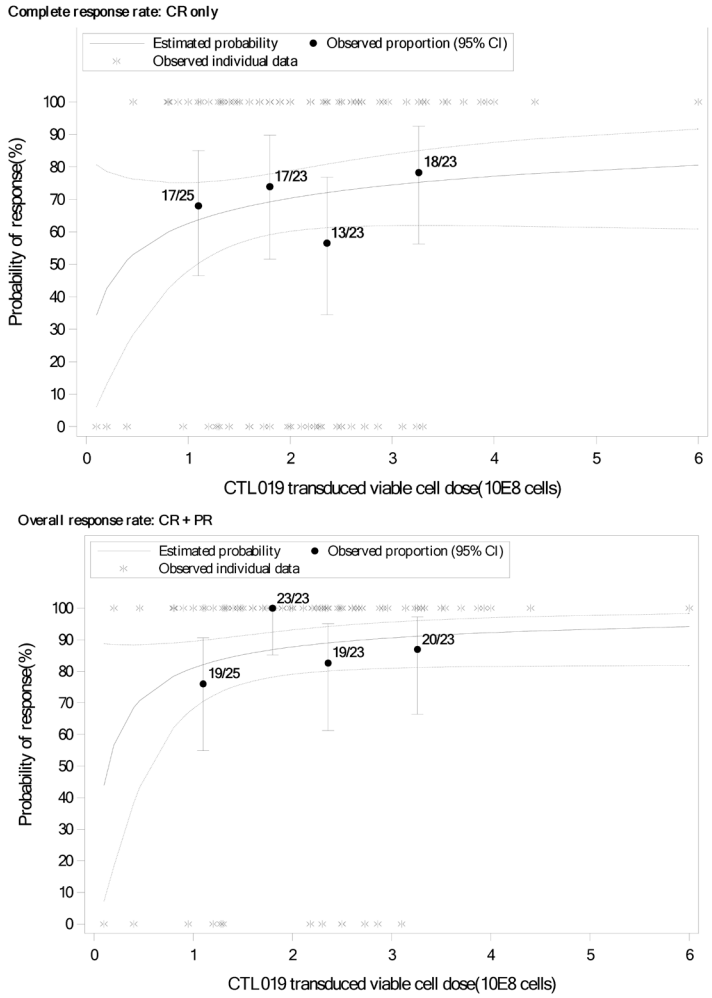


Figure 11. Logistic regression of BOR vs. CTL019 transduced viable cell dose, overlaid with observed proportions (Efficacy analysis set).

Dose-Duration of response analysis

In Study **E2202**, the median dose for Efficacy analysis set was 2.06×10^8 CAR-positive viable T cells. The Kaplan-Meier analysis of duration of response (DOR, time from achievement of CR or PR to an event of PD or death due to FL) for patients indicated a similar DOR in patients treated with doses greater (N=39) than and equal/less (N=42) than the median cell dose. Based on the Cox regression model of DOR by log of dose, doubling the dose is associated with hazard ratio of 0.66 (95% CI: 0.390, 1.108) indicating no statistically significant difference in DOR depending on dose. Similarly, analysis by quartile of dose infused shows no difference in DOR among the quartiles of dose.

Dose-Progression free survival analysis

The relationship between dose and PFS was evaluated using Kaplan-Meier analyses. Similar PFS was observed in patients treated with doses greater than and equal or less than median viable cell dose with median PFS not yet estimable in either dose category. Based on the Cox regression model of PFS by log of dose, doubling the dose is associated with hazard ratio of 0.75 (95% CI: 0.494, 1.138) indicating no clinically relevant difference in PFS depending on dose.

Dose-Time to start of new anti-lymphoma therapy analysis

The relationship between dose and time to start of new anti-lymphoma therapy was evaluated using Kaplan-Meier analyses. Similar results were observed in patients treated with doses greater than and

equal or less than median viable cell dose with median time to new therapy not yet reached in both dose categories. Based on the Cox regression model, doubling the dose is associated with hazard ratio of 0.45 (95% CI: 0.287, 0.695). Despite the observed relationship between the dose and start of new anti-lymphoma therapy, the effect may not be clinically relevant due to limited sample size (only 20 patients required new anti-lymphoma therapy). In addition, the Kaplan-Meier analysis showed similar time to start of new anti-lymphoma therapy by median dose.

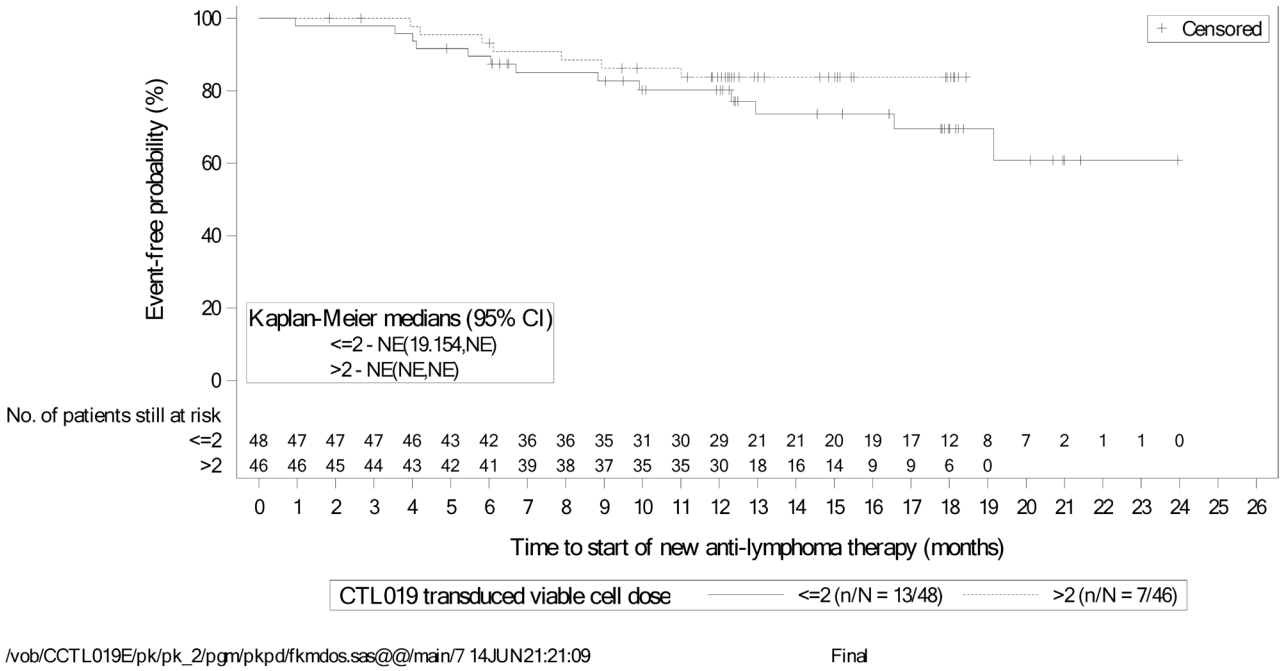


Figure 12. Kaplan-Meier plot of time to start new anti-lymphoma therapy by median CTL019 transduced viable cell dose (Efficacy analysis set).

Dose-safety analyses

To evaluate the impact of dose on safety endpoint, occurrence of cytokine release symptom, impact on serious neurological events and time to resolution of hematopoietic cytopenias were explored using the safety analysis set (N=97). Only events within 8 weeks of infusion were included in all analyses of CRS and serious neurological events. Details of the dose-safety analysis are shown in Table 15.

Table 15. Dose-safety analysis

Safety endpoints	Analysis by endpoints	Methods
CRS, serious neurological events	CRS and serious neurological events vs. CAR-positive viable cell dose	Logistic regression Statistics by dose quartiles
hematopoietic cytopenias	Time to resolution of hematopoietic cytopenias vs. CAR-positive viable cell dose	Kaplan-Meier plot and Cox Regression

Dose-CRS analysis

Across the entire studied dose range, no high-grade CRS (grade 3 or higher) was observed within 8 weeks of infusion, as 47/97 (48.5%) patients experienced CRS of maximum grade 1 or 2. Moreover, CRS was manageable with the steps outlined in the CRS management algorithm. Logistic regression results shows relatively flat relationship between probability of any grade CRS and dose at higher doses ($>1\times10^8$) indicating that there is no apparent increased risk of CRS with higher CAR-positive viable T cell doses. Based on the model estimates, the odds ratio for any grade CRS with doubling of

the infused cell dose was estimated to be 1.41 (95% CI: 0.855 to 2.326). Lower incidence of grade 1 or grade 2 CRS was observed (32%) at the lowest dose quartile ($\leq 1.4 \times 10^8$) compared to ~54% at all other dose quartiles.

Figure 13. Logistic regression of CRS vs. CTL019 transduced viable cell dose, overlaid with observed proportions (Safety analysis set).

Dose-serious neurological events analysis

Across the entire studied dose range, only 9 patients (9.3%) out of 97 experienced serious neurologic events post tisagenlecleucel infusion within the initial 8 weeks post-tisagenlecleucel infusion, including 6 events in the lower dose category ($\leq 2.1 \times 10^8$) and 3 events in the higher dose category ($>2.1 \times 10^8$). Logistic regression shows a flat relationship between the probability of serious neurologic events and CAR-positive viable T cell dose which indicates that there is no apparent impact of CAR-positive viable cell dose on the probability of serious neurological events. Based on model estimates, with two-fold increase in dose, the odds ratio for any grade serious neurological event is 0.74 (95% CI: 0.383 to 1.419).

Dose-hematopoietic cytopenias analysis

A Cox regression model and Kaplan-Meier plot were used to explore the relationship between dose and time to resolution of hematopoietic cytopenias (based on laboratory data), including neutropenia and thrombocytopenia. The results showed no apparent impact of dose on the time to the resolution of neutropenia and thrombocytopenia; however, the data are limited and insufficient to support a definitive conclusion.

Exposure-response relationships

The relationship between tisagenlecleucel exposure and response (efficacy and safety) was explored. Exposure-efficacy and exposure-safety analyses were based on efficacy and safety analysis sets, respectively.

Exposure-efficacy relationship

Exposure-BOR relationship

Desirable clinical outcomes (CR and PR) were achieved across the entire range of the observed in vivo exposure following tisagenlecleucel infusion. BOR by independent review committee (IRC) assessment is summarized by quartile of qPCR exposure parameters (C_{max} and $AUC_{0\text{-}28d}$) in Appendix 1-Table 4.1-5. The overall response rates (CR/PR) are comparable across all quartiles of $AUC_{0\text{-}28d}$.

Logistic regressions analysis was performed to evaluate the relationship between disease response and exposure parameters of tisagenlecleucel determined by qPCR (C_{max} and $AUC_{0\text{-}28d}$) (Figure 13). The probability of response appears to be lower for lower exposure levels, however, no strong conclusion can be made due to limited number of non-responder patients. As evident from the figure data, several of the non-responders are clustered towards the lower end of the exposure curve which may further influence the shape of the curves. The model estimated odds ratios for achieving CR or CR/PR with two-fold increase in the $AUC_{0\text{-}28d}$ were 1.23 (95% CI: 0.976, 1.538) and 1.33 (95% CI: 0.992, 1.788), respectively, suggesting no overall statistically significant impact of exposure on BOR.

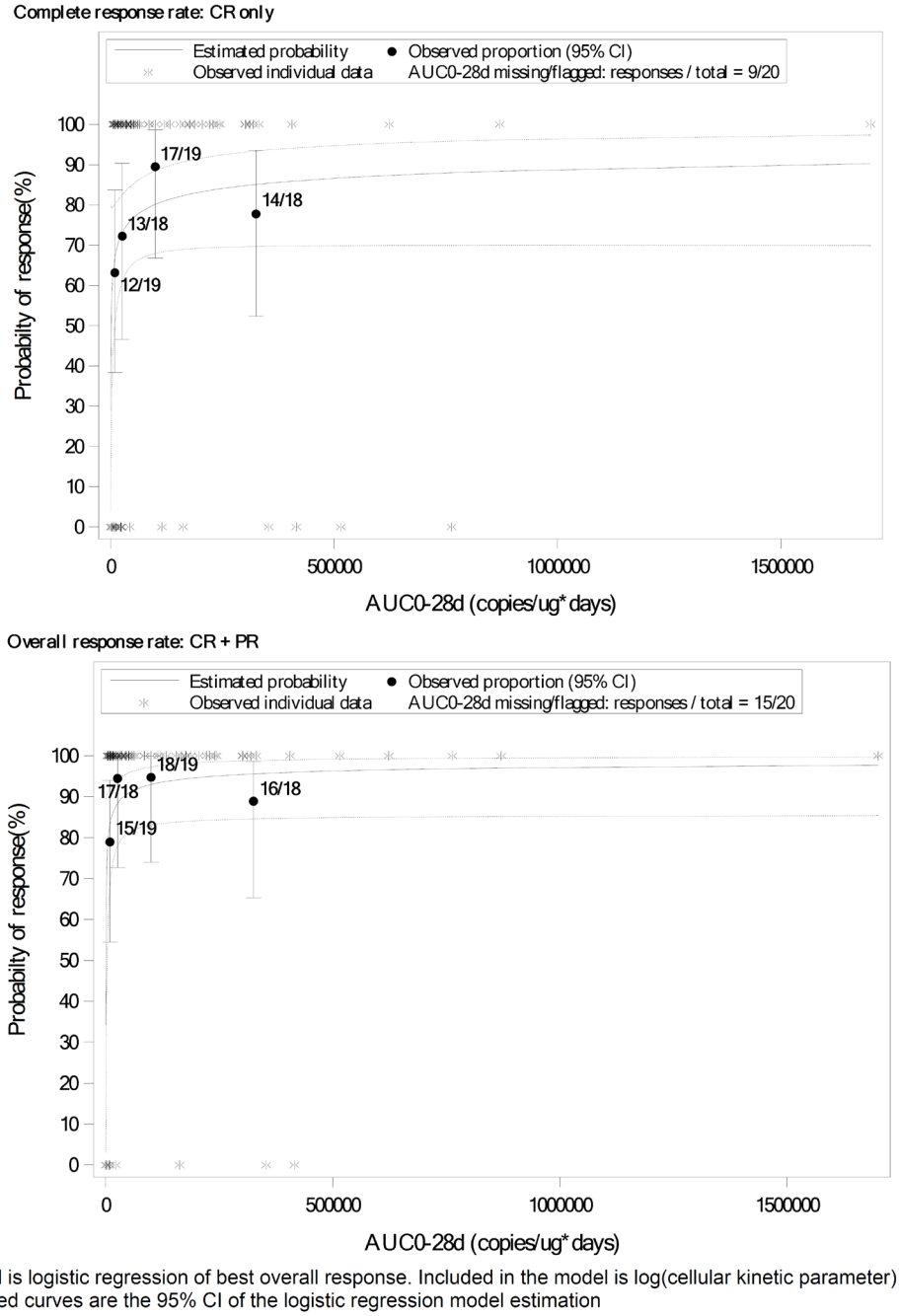


Figure 14. Logistic regression of BOR vs. peripheral blood CTL019 cellular kinetic parameters by qPCR, with observed proportions (Efficacy analysis set).

Exposure-Duration of response relationship

Kaplan-Meier plots show a favourable trend in DOR in patients with higher than the median exposure (median DOR not yet estimable in either exposure category). The Cox regression model showed a trend towards a DOR benefit with increasing exposure. Specifically, the associated HR (95% CI) for a 2-fold increase in Cmax was 0.73 (95% CI: 0.558, 0.951) and for $AUC_{0\text{-}28d}$ was 0.70 (95% CI: 0.509, 0.969).

Summary of DOR by quartiles of exposure parameters shows that the probability estimates were higher for event-free survival with increasing exposure at Month 6, Month 9, and Month 12.

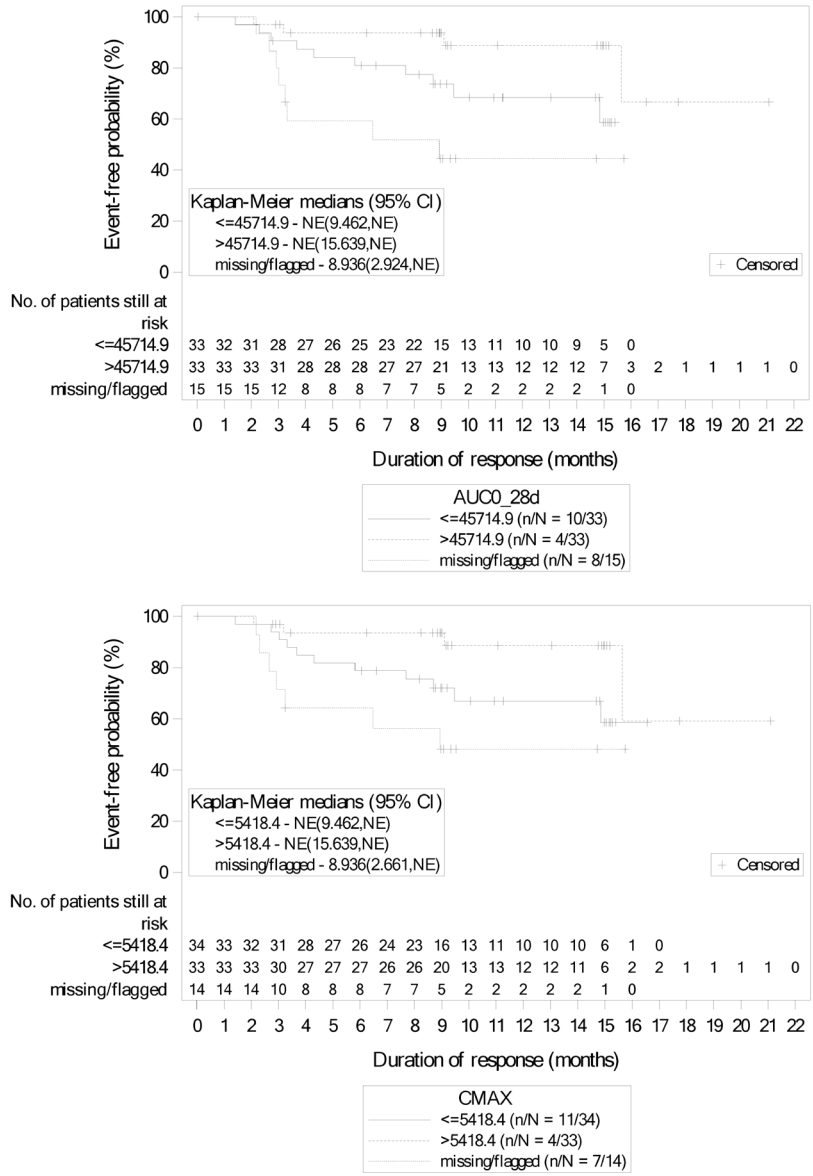


Figure 15. Kaplan-Meier plot of DOR by median of qPCR cellular kinetic parameters (Efficacy analysis set).

Exposure-Progression free survival relationship

Similar PFS was observed in patients with low and high $AUC_{0\text{-}28d}$ (greater than vs. equal or less than median) values, with median PFS not yet estimable in high exposure category ($AUC_{0\text{-}28d}$ greater than median). The Cox regression model showed a trend towards a better PFS benefit with increasing exposure. Specifically, the associated HR (95% CI) for a 2-fold increase in C_{max} was 0.78 (0.641, 0.951) and for $AUC_{0\text{-}28d}$ was 0.80 (0.680, 0.951).

Summary of PFS by C_{max} and $AUC_{0\text{-}28d}$ quartiles showed no obvious difference in the event free probability across all quartiles.

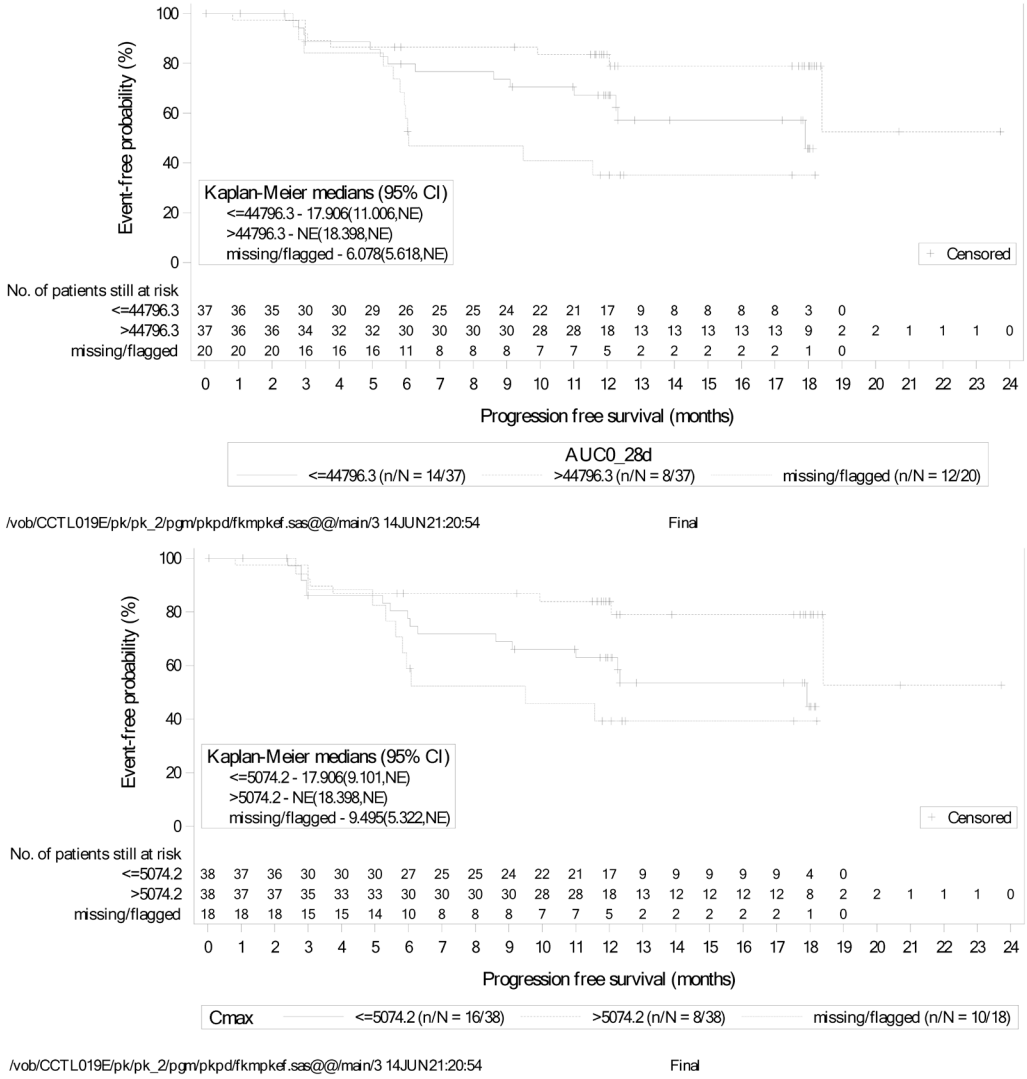


Figure 16. Meier plot of PFS by median of qPCR cellular kinetic parameters (Efficacy analysis set).

Exposure-Time to start of new anti-lymphoma therapy analysis

Patients with lower $AUC_{0\text{-}28d}$ and C_{max} tend to have shorter time to start of new anti-lymphoma therapy.

Exposure-safety relationship

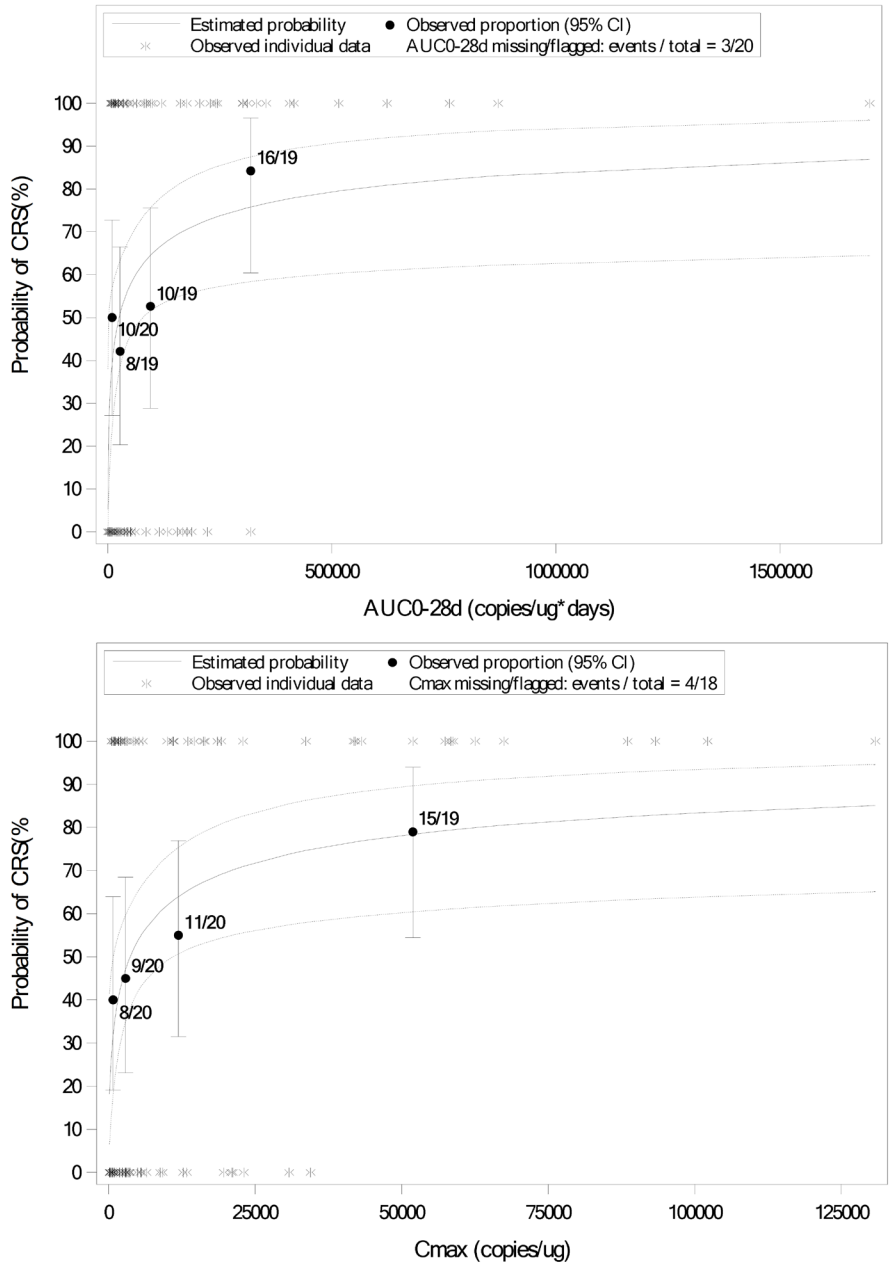
Safety endpoints	Analysis by exposure endpoints	Methods
CRS	CRS vs. tisagnelecleucel exposure parameters (Cmax and AUC0-28d) determined by qPCR	Logistic regression Boxplots of Exposure parameters by CRS Statistics by quartiles of exposure parameters
Serious neurological events	Serious neurological events vs. tisagenlecleucel exposure parameters (Cmax and AUC0-28d) determined by qPCR	Logistic Regression Statistics by quartiles of exposure parameters
Hematopoietic cytopenias	Time to resolution of hematopoietic cytopenias vs. tisagenlecleucel exposure (Cmax and AUC0-28d) determined by qPCR Hematopoietic cytopenias vs. qPCR Cmax, qPCR AUC0-28d and total CTL019 dose	Cox regression and Kaplan-Meier plots

Exposure-CRS relationship

Logistic regression analysis evaluating the impact of tisagenlecleucel exposures on CRS indicated that higher tisagenlecleucel exposure is associated with higher probability of any grade CRS. However, in Study **E2202**, none of r/r FL patients did experience high grade CRS (grade 3 or higher) within the 8-week infusion. Two cellular kinetic parameters, $AUC_{0\text{-}28d}$ and C_{max}, which represent the expansion phase were selected for the analysis because CRS is generally resolved within 7 days of the tisagenlecleucel infusion, and these parameters are useful for characterizing expansion. Based on the logistic regression model, the odds ratios for a two-fold increase in C_{max} and $AUC_{0\text{-}28d}$ were 1.4 (95% CI 1.131, 1.740) and 1.37 (95% CI 1.083, 1.7124) respectively.

An overall trend of an increasing risk in any grade CRS within 8 weeks of infusion was observed with increasing $AUC_{0\text{-}28d}$ and C_{max} based on quartile analyses for any grade CRS. Patients within the highest quartile of $AUC_{0\text{-}28d}$ and C_{max} showed higher probability of having CRS than patients within the lower quartiles of exposure.

Boxplots of exposure parameters (C_{max} and $AUC_{0\text{-}28d}$) by CRS show that patients with CRS grade ½, have higher ranges of exposure than patients with no CRS.



- The model is logistic regression of CRS. Included in the model is log(cellular kinetic parameter).
- Dashed curves are the 95% CI of the logistic regression model estimation.
- Observed proportions are calculated for each range of cellular kinetic parameters (≤25%, >25%-50%, >50%-75%, >75%).
- n/N is the number of subjects with events/total number of subjects in the quartile range

Figure 17. Logistic regression of CRS vs. qPCR cellular kinetic parameter, with observed proportions (Safety set).

Exposure-serious neurological events relationship

The results of logistic regression analysis indicated that there was no impact of tisagenlecleucel exposure ($AUC_{0\text{-}28d}$ and C_{max}) on probability of serious neurological events (any grade). With increasing exposure ($AUC_{0\text{-}28d}$ and C_{max}), no increase in the probability of any grade serious neurological events was observed. These non-serious and serious events were reported in 11 patients, of which 9 patients had these events within 8 weeks post-tisagenlecleucel infusion; grade ¾ AEs were reported in 3 patients.

Analysis of exposure and time to resolution of hematopoietic cytopenias

Post-tisagenlecleucel infusion, 76 patients (78.4%) had hematological disorders including cytopenias, mostly of grade ≥ 3 (74.2%) severity, regardless of causality. Of these 76 patients, 42 patients (43.3%) had AEs suspected to be related to tisagenlecleucel. These AEs were reported more frequently within the initial 8 weeks post-tisagenlecleucel infusion than in the periods from >8 weeks to 1 year after infusion and >1 year after infusion (75.3% vs. 42.7% and 11.3%). Based on Kaplan-Meier analysis of hematological laboratory parameters, by Month 6 the probability of resolution of all the cytopenias (leukopenia, anemia, thrombocytopenia, neutropenia and lymphopenia) ranged from 70% to 100%.

The time to resolution of hematopoietic cytopenias post-tisagenlecleucel infusion exposure was presented. No definitive conclusion can be drawn due to limited number of patients with prolonged cytopenias.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics

No dedicated clinical pharmacology/pharmacokinetic studies were conducted which is acceptable considering the type of medicinal product presented in the current MAA (Guideline on human cell-based medicinal products EMEA/CHMP/410869/2006).

Bioanalytical methods

Validation procedures and acceptance criteria were based on the US Food and Drug Administration (FDA) Guidance for Industry Bioanalytical Method Validation (2001), EMA Guidelines; ICH Guideline S6 (R1) and USP; White papers: Neyer et al. (2006) and Shankar et al. (2008). The method validation from all three methods covers the regulatory expectations for validation of methods used in clinical trials. Relevant parameters have been included as well as cross-validation/bridging/stability and interference studies where applicable. All three methods are considered to be in line with regulatory requirements for this medicinal product.

Pharmacokinetic methods

The MAH has used standard NCA to describe cellular kinetics of tisagenlecleucel in patients with FL, which is acceptable. qPCR was considered as the most sensitive assay for the determination of cellular kinetics, although flow cytometry provides a more functional measure of the transgene (measures CAR receptor expression). Cellular kinetic data derived from qPCR has been reported if not otherwise stated.

Dose-exposure, dose-response, and exposure-response modelling has been performed for both efficacy and safety end points.

Dose proportionality

No apparent relationships between the investigated doses and the observed exposure were identified, which is not unexpected considering the nature of tisagenlecleucel, i.e., proliferation of the CAR T-cells after administration.

Pharmacokinetic in target population

The tisagenlecleucel cellular kinetic profile showed an initial rapid expansion phase achieving maximal expansion around Day 10, followed by a bi-exponential decline with median persistence (T_{last}) of 186 days (range 18.7 to 558). C_{max} and $AUC_{0\text{-}28d}$ were 109% and 186% higher respectively in CR/PR

patients relative to SD/PD patients. Median T_{max} was comparable between CR/PR and SD/PD patients. Longer persistence was observed in responders vs. non-responders with median T_{last} of 191 vs. 107 days, respectively, and the geometric mean $t_{1/2}$ was approximately 80% longer in CR/PR patients relative to SD/PD patients. However, these values should not be directly compared because both T_{last} and $t_{1/2}$ are dependent on the time of data cut of/follow up period.

The MAH provided a typical cellular kinetic profile from a single FL patient where a second peak appears in the cellular kinetic profile, possibly reflecting a secondary expansion phase in the respective patient. Based upon investigation of listings of plasma concentrations, similar second peaks were identified in several patients, although the peak was not present in summary plots. No discussion or possible explanation of the second peak was provided by the MAH.

The geometric mean transgene levels in peripheral blood (n=45) and bone marrow (n=12) were comparable at Month 3. The geometric mean blood to bone marrow ratio was 0.539 and is included in the SmPC.

Higher expansion (C_{max} and $AUC_{0\text{-}28d}$) of CAR-positive viable T cells was seen in patients experiencing CRS grad 1 or 2 compared to patients not experiencing CRS. There is apparently no impact of CRS on in vivo persistence.

Special populations

The presented data indicate that there is no relevant impact of the intrinsic factors age (range 29 to 73 years), body weight (range 44.3 to 127.7 kg), disease stage at study entry or baseline lactate dehydrogenase levels on cellular kinetics. Small subgroups and large variability in cellular kinetic parameters prevent firm conclusions concerning race. Female patients with FL had slightly higher exposure compared to males, 111% and 106% for C_{max} and $AUC_{0\text{-}28d}$ respectively, and the exposure observed in patients $\geq$ 65 years was lower than in patients <65 years, approximately 40% and 30% lower for $AUC_{0\text{-}28d}$ and C_{max} respectively. High FLIPI at enrolment was associated with 47% and 61% higher $AUC_{0\text{-}28d}$ and C_{max} respectively, compared to low or intermediate FLIPI. Similarly histological grade at study entry demonstrated 105% and 113% higher $AUC_{0\text{-}28d}$ and C_{max} geometric mean values, respectively, in patients with grade 1-2 FL relative to grade 3A FL. Further, patients who did not progress within 24 months following the first line anti-CD20 therapy demonstrated higher expansion ($AUC_{0\text{-}28d}$ and C_{max}) compared to patients who experienced POD24. When evaluating the impact of refractoriness to prior therapy on cellular kinetics of tisagenlecleucel, a 115% higher $AUC_{0\text{-}28d}$ and C_{max} geometric mean values was seen in patients who relapsed relative to patients who had refractory disease. Even though several of the intrinsic factors evaluated showed rather large impact on the cellular kinetics of tisagenlecleucel, the small subgroups and large variability in cellular kinetic parameters in study **E2202** prevent firm conclusions to be made.

Relationship between product attributes and cellular kinetics, dose or response

No apparent relationship between product attributes and in vivo cellular kinetics has been observed.

The cellular kinetics in patients treated with product from the Stein facility in Switzerland (n=11) had higher exposures compared to patients treated with products from the other three facilities. Especially for C_{max}, the inter-individual variability was considerably higher for patients treated with product from the Stein facility compared to patients treated with product from the other manufacturing sites.

Pharmacodynamics and Pharmacokinetics-Pharmacodynamics (PK/PD)

Pharmacodynamic interactions with other medicinal products or substances

Overall, based on the provided data, the type of LD chemotherapy, prior bendamustine use, number of prior lines of therapy, prior HSCT status or type of bridging therapy does not seem to impact the

cellular kinetic (C_{max} and $AUC_{0\text{-}28d}$) to a large extent. However, the relatively small subgroups and large variability in cellular kinetic parameters, prevent firm conclusions to be made.

CRS management with Tocilizumab and corticosteroids

Higher expansion (C_{max} and $AUC_{0\text{-}28d}$) of CAR-positive viable T cells was seen in patients who required tocilizumab to treat CRS. CAR T-cell activation is accompanied by extensive release of toxic levels of pro-inflammatory cytokines which can cause CRS. Thus, patients with higher expansion could be prone to develop treatment-requiring CRS. Hence, the true influence of tocilizumab on expansion cannot be ascertained directly since, the observation may have been confounded as tocilizumab is given for CRS treatment and CRS is associated with higher expansion.

Relationship between dose, cellular kinetics, and effect

Dose-exposure, dose-response, and exposure-response modelling was performed for both efficacy and safety end points. However, no modelling report describing model development was submitted, consequently the methods has not been assessed in detail. Since the models are mainly for descriptive purposes and not for dose justification or evaluation of dosing strategies, this issue has not been further pursued in the current application.

Dose-response

Based on logistic regression and summary statistics by dose quartiles, there was a trend of slightly lower response at the lower end of the dose range ($<1.0\times10^8$ cells). Still, favourable clinical responses were observed across the entire recommended dose range ($0.6 – 6.0 \times 10^8$ CAR-positive viable T cells).

Results from Cox regression model and Kaplan-Meier analyses indicates minimal difference in DOR and PFS depending on dose. An apparent dose-time to start of new anti-lymphoma therapy analysis relationship was identified based on a Cox regression model. Contrary, the Kaplan-Meier analysis showed similar time to start of new anti-lymphoma therapy by median dose. Considering the small number of patients requiring new anti-lymphoma therapy (n=20) and large variability in cellular kinetic parameters**,** firm conclusions cannot be made.

At the higher doses, the logistic regression analysis shows a relatively flat relationship between probability of any grade CRS and dose. Overall, the results indicates that there is no apparent increased risk of CRS with higher CAR-positive viable T cell doses, although there appears from the logistic regression model, that the risk of CRS is slightly lower at the lower end of the dosing interval (32% risk at lowest dose quartile ($\leq1.4\times10^8$) compared to ~54% at all other dose quartiles). There seems to be no apparent impact of dose on neurological events and time to resolution of cytopenias.

Exposure-response

The presented exposure-response analyses should not be interpreted as exposure-response analyses in its traditional sense, because the "exposure" for CAR-T products is dependent on the drug response. High exposure could be considered an expression of the drug response rather than the causal driver of the drug response. Thus, these analyses are mainly descriptions of the correlation between two variables partly expressing the same information. The exposure-efficacy analyses revealed an apparent exposure-response relationship, with DOR being longer in patients with exposure above the median exposure (C_{max} and $AUC_{0\text{-}28d}$). The exposure-BOR analysis shows that the exposure (C_{max} and $AUC_{0\text{-}28d}$) was higher in responding patients compared to non-responding patients. Due to few non-responding patients with evaluable C_{max} (n=4), as well as high inter individual variability, the findings should be interpreted with caution.

The results of logistic regression analysis for exposure parameters (C_{max} and AUC_{0-28d}) and CRS, indicates higher probability of any grade CRS with increasing transgene expansion, i.e. higher tisagenlecleucel exposures. Anti-cytokine therapies were administered according to a treatment algorithm to solve adverse drug reactions regarding CRS (see Clinical Safety). Logistic regression analysis indicates no impact of exposure on neurological events. Concerning cytopenias, although there seems to be no apparent impact of exposure on time to resolution of cytopenias, it is difficult to draw any definitive conclusions due to limited number of patients experiencing long term cytopenias.

2.3.5. Conclusions on clinical pharmacology

The cellular kinetics in FL patients have been characterised and showed higher expansion in CR/PR patients relative to SD/PD patients. Longer persistence was observed in responders vs. non-responders, however, the measures of persistence (T_{last} and $t_{1/2}$) should not be directly compared between responders and non-responders because they are both dependent on the time of data cut of/follow up period.

The impact of intrinsic and extrinsic factors on cellular kinetics were assessed using cellular kinetic parameters determined from NCA. The small subgroups and large variability in cellular kinetic parameters in study **E2202** prevent firm conclusions to be made concerning impact of intrinsic and extrinsic factors on cellular kinetics.

Dose-exposure, dose-response, and exposure-response modelling was performed for both efficacy and safety end points. Considering the nature of tisagenlecleucel, i.e., proliferation of the CAR T-cells after administration, the lack of relationship between the investigated doses and the observed exposure is not unexpected. A trend of slightly lower response at the lower end of the dose range of tisagenlecleucel ($<1.0\times10^8$ cells) was observed, still, favourable clinical responses were observed across the entire recommended dose range. The exposure-response analyses should not be interpreted as exposure-response analyses in its traditional sense, because the "exposure" for CAR-T products is dependent on the drug response. High exposure could be considered an expression of the drug response rather than the causal driver of the drug response. Thus, these analyses are mainly descriptions of the correlation between two variables partly expressing the same information.

2.4. Clinical efficacy

2.4.1. Dose response studies

No formal dose-response studies have been carried out for the indication follicular lymphoma. The recommended dose for the main study CCTL019E2202 is a single infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells, which is based on data from studies in CLL, ALL and NHL. The dose-response, dose-safety, and dose-cellular kinetics analyses were performed using the data obtained from r/r DLBCL patients (data cut-off [DCO] date: 8-March-2017) in Phase 2 study (Study C2201) to assess the impact of dose on exposure, response, and selected safety endpoints in order to select safe and efficacious doses for use in the prescribing setting (commercial) and Study E2202.

2.4.2. Main study

The primary evidence of efficacy of tisagenlecleucel in FL is obtained from one pivotal phase 2, single arm, multicenter open label registration study called E2202. The study was designed to determine the efficacy and safety of tisagenlecleucel (product code: CTL019) in adult patients with r/r FL.

Study CCTL019E2202: A Phase II, single arm, multicenter open label trial to determine the efficacy and safety of tisagenlecleucel(CTL019) in adult patients with refractory or relapsed FL.

Methods

Study participants

The target population for study E2202 was adult patients ≥18 years with FL grades 1, 2 or 3A who were either refractory to a second line or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent) or relapsed within 6 months after completion of a second line or later line of systemic therapy or relapsed during anti-CD20 antibody maintenance (following at least two lines of therapies) or within 6 months after maintenance completion or relapsed after autologous HSCT.

Key Inclusion Criteria:

1. ≥18 years of age at the time of ICF signature
2. FL (grade 1, 2, 3a) confirmed histologically by central pathology review before tisagenlecleucel infusion.
3. FL meeting one of the following criteria:
    a. Refractory to a second line or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent) or relapsed within 6 months after completion of a second line or later line of systemic therapy
    b. Relapsed during anti-CD20 antibody maintenance (following at least two lines of therapies as above) or within 6 months after maintenance completion
    c. Relapsed after autologous HSCT

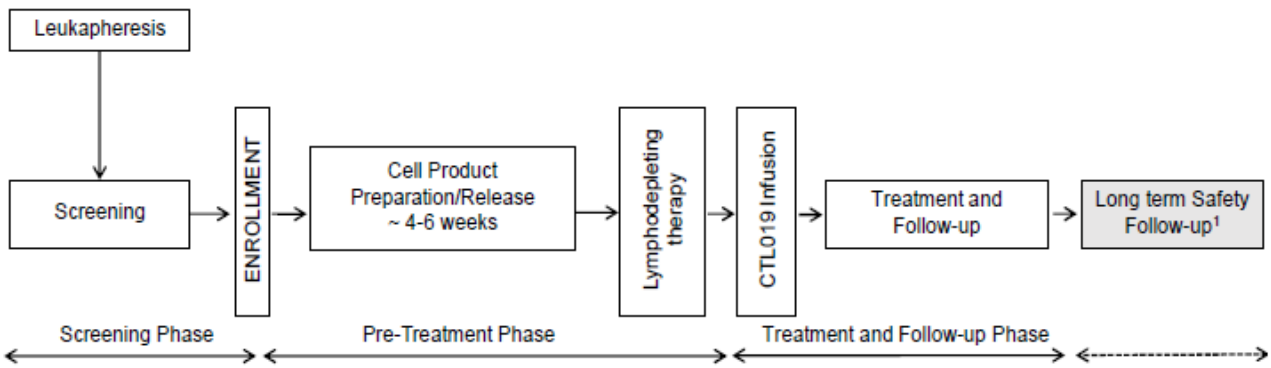
    Previous treatment with other FL-targeting medications (e.g. PI3K inhibitors) is allowed, provided patients recovered from all treatment-related adverse events.
4. Radiographically measurable disease at screening defined as:
    a. At least one nodal lesion greater than 20 mm in the long axis, regardless of the length of the short axis AND/OR
    b. Extranodal lesions (outside lymph node or nodal mass, including liver and spleen) greater than 10 mm in long AND short axis
5. Eastern Cooperative Oncology Group (ECOG) performance status that is either 0 or 1 at screening
6. Patients must meet the following laboratory values without transfusion at screening:
    a. Absolute neutrophil count (ANC) ≥ 1,000/mm^3 (≥ 1×10^9/L)
    b. Absolute lymphocyte count (ALC) > 300/mm^3 (> 0.3×10^9/L)
    c. Absolute number of CD3+ T cells > 150/mm^3 (> 0.15×10^9/L)
    d. Platelets ≥ 50 000/mm^3 (≥ 50×10^9/L)
    e. Hemoglobin ≥ 8.0 g/dl (≥ 4.9 mmol/L)
    f. A serum creatinine of ≤1.5 times ULN or eGFR ≥ 60 mL/min/1.73 m^2
    g. ALT/AST ≤ 5 times the ULN
    h. Total bilirubin ≤ 1.5 times ULN (with the exception of patients with Gilbert's syndrome. Patients with Gilbert's syndrome may be included if their total bilirubin is ≤ 3.0 times ULN and direct bilirubin ≤ 1.5 times ULN
7. Adequate pulmonary function defined as:
    a. No or mild dyspnea (≤ Grade 1)
    b. Oxygen saturation measured by pulse oximetry > 90% on room air

8. Must have a leukapheresis product of non-mobilized cells accepted for manufacturing

Key Exclusion Criteria:

1. Evidence of histologic transformation
2. FL grade 3b
3. Prior treatment with anti-CD19 therapy, gene therapy or any adoptive T cell therapy
4. Prior allogeneic HSCT
5. Active CNS involvement by malignancy
6. Active neurological autoimmune or inflammatory disorders (e.g. Guillain-Barre syndrome, Amyotrophic Lateral Sclerosis)
7. Investigational medicinal product within the last 30 days or five half-lives (whichever is longer) prior to screening NOTE**:** Investigational therapies must not be used at any time while on study until the first progression following tisagenlecleucel infusion
8. Presence of active or prior hepatitis B or C as indicated by serology.
9. Presence of HIV antibody.
10. Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to tisagenlecleucel infusion)
11. Cardiac or cardiac repolarization abnormality.
12. Previous or concurrent malignancy with the following exceptions:
    a. Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to enrollment)
    b. *In situ* carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to enrollment
    c. A primary malignancy which has been completely resected and in complete remission for ≥ 3 years at the time of enrollment
13. Pregnant or nursing (lactating) women.
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, and sexually active males, **unless** they are using highly effective methods of contraception while taking study treatment and for at least 12 months after the tisagenlecleucel infusion and until CAR T-cells are no longer present by qPCR on two consecutive tests. In addition, male participants must not donate sperm for the period specified above.

Treatments



1. Long term safety follow-up as per health authority guidance conducted under a separate LTFU protocol (CTL019A2205B).

Figure 18: Schematic of Study Design

The single arm study E2202 had the following sequential phases: Screening, Pre-treatment, Treatment and Follow-up. During the Screening phase and prior to enrolment into the study, a patient's white blood cells were collected via leukapheresis. In the Pre-treatment phase, the patient could undergo optional bridging therapy and LD chemotherapy. The Treatment and Follow-up Phase included tisagenlecleucel infusion, and safety and efficacy follow-up. After the end of this study, patients who have received tisagenlecleucel infusion will continue to be followed for long-term safety, efficacy and survival under the long-term follow-up protocol CCTL019A2205B for 15 years post infusion per health authority guidelines.

Bridging therapy was administered in some cases, and adhered to the recommendations concerning prohibited medications described under concomitant therapies, below.

A PET-CT scan was performed after bridging therapy and prior to tisagenlecleucel infusion, except when the bridging therapy consisted of steroids only. Patients with no measurable disease at baseline after bridging therapy still received tisagenlecleucel infusion.

Prior to tisagenlecleucel infusion, all patients were required to receive LD chemotherapy. This step was to be omitted in case of significant cytopenia (e.g. WBC <1000 cells/µL, ALC <200 cells/µL) or any condition that, in the Investigator's opinion, precluded LD chemotherapy. The purpose of this chemotherapy was to induce lymphopenia to facilitate engraftment and homeostatic expansion of the administered CAR-positive viable T-cells.

Lymphodepleting (LD) chemotherapy started 1 week before tisagenlecleucel infusion so that the CAR-positive viable T-cells were given 2 to 6 days after completion of the LD chemotherapy. The LD chemotherapy start date varied based on the selected chemotherapy. For LD chemotherapy, cyclophosphamide-based regimens were preferred agents due to the vast experience with the use of these agents in facilitating adoptive immunotherapy. The first option as LD regimen was fludarabine (25 mg/m^2 i.v. daily for 3 doses) and cyclophosphamide (250 mg/m^2 i.v. daily for 3 doses starting with the first dose of fludarabine). If there was previous grade 4 hemorrhagic cystitis with cyclophosphamide, or the patient demonstrated resistance to a previous cyclophosphamide-containing regimen, then a regimen with bendamustine 90 mg/m^2 i.v. daily for 2 days was allowed. No other regimen was allowed for LD chemotherapy.

Premedication was recommended prior to tisagenlecleucel infusion, as side effects from T cell infusion can include fever, chills and/or nausea. All patients should be pre-medicated with acetaminophen (paracetamol) and diphenhydramine or another H1 antihistamine. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved with acetaminophen (paracetamol). Steroids should NOT be used for premedication. It is recommended that patients not receive systemic corticosteroids other than physiologic replacement, except for serious emergency, since this may have an adverse effect on tisagenlecleucel cell expansion and function.

The tisagenlecleucel product was intended to be prepared and released by the manufacturing facility to the study site approximately 4-6 weeks after manufacturing had commenced, provided all required safety and quality release criteria had been met. Tisagenlecleucel is an autologous cellular immunotherapy product. The recommended dose for adult patients with r/r FL is 0.6 to 6.0 × 10^8 CAR-positive viable T-cells administered via a single infusion. Concurrent use of systemic steroids or immunosuppressant medications was prohibited except if required for physiologic replacement of hydrocortisone, or in the case of a life-threatening emergency, since this could have had an adverse effect of tisagenlecleucel cell expansion and function.

The safety and efficacy follow-up lasted for at least 24 months. For all patients who received tisagenlecleucel infusion, additional survival followup was to be performed to determine survival status every 3 months. Efficacy was evaluated using PET/CT/MRI at Months 3, 6, 9, 12, 18, 24 post-infusion and every 6 months thereafter, until EOS, (EOS is defined as when all patients have completed their Month 24 evaluation or discontinued prematurely). Also, onsite assessments were to be performed at any time disease progression or relapse was suspected, until disease progression or relapse, start of new anticancer therapies, death, lost to follow-up or withdrawal of consent. After the end of this study, patients who have received tisagenlecleucel infusion will continue to be followed for long-term safety, efficacy and survival under the long-term follow-up protocol CCTL019A2205B for 15 years post infusion.

Concomitant therapies:
The patient was to notify the investigational site about any medications he/she takes. All clinically significant prescription and nonprescription medication, excluding vitamins, and herbal and nutritional supplements, and procedure-related (inpatient or outpatient) medications taken by the patient during the 30 days prior to screening was to be recorded. At every visit following the screening visit up to the end of the study, concomitant medications were to be recorded in the medical record and on the appropriate CRF. During selected trial phases, concomitant medication collection was to be modified to capture tisagenlecleucel-related toxicity, severity, interventions and response/resolution following intervention. Any additions, deletions, or changes of these medications was to be documented.

The following guidelines must be adhered to during the study:
• Granulocyte macrophage-colony stimulating factor (GM-CSF) should be avoided due to the potential to worsen CRS symptoms. Short acting granulocyte colony stimulating factor (G-CSF) should not be given within 72 hours of tisagenlecleucel infusion and long acting G-CSF should not be given within 10 days of tisagenlecleucel infusion. The effects of granulocyte colony stimulating factor (G-CSF) on the other hand, are unknown.
• Steroids or other immunosuppressant drugs should NOT be used as pre-medication for tisagenlecleucel therapy or following tisagenlecleucel infusion, except as required for physiological glucocorticoid replacement therapy, or under life threatening circumstances. Use of steroids with blood product administration should be eliminated just prior to and following tisagenlecleucel if possible or at least minimized.
• Patients with moderate to severe signs and symptoms attributable to CRS should be managed with supportive care and administration of tocilizumab.

Prohibited medications prior to tisagenlecleucel infusion, including during bridging therapy:
a. Steroids or other immunosuppressant drugs
b. Antibody use
c. CNS disease prophylaxis or intrathecal therapy
d. Radiation therapy
e. Investigational therapies
f. Live vaccines
g. Granulocyte macrophage-colony stimulating factor
h. Antiproliferative therapies
i. Short acting drugs used to treat primary disease

The investigational Leukapheresis Cryopreservation and Scheduling Manual included guidance and recommendations for stopping therapies prior to leukapheresis. Patients should not receive long-acting growth factors (e.g. pegfilgrastim) within 14 days of the leukapheresis procedure. The use of short-

acting growth factors or drugs used for cell mobilization (eg, granulocyte colony-stimulating factor/filgrastim, plerixafor) is not necessary and should be stopped at least 5 days before the leukapheresis procedure. Short-acting drugs used to treat leukemia or lymphoma (eg, hydroxyurea, tyrosine kinase inhibitors) should not be given within 3 days before the leukapheresis procedure. Other cytotoxic drugs, including low-dose daily or weekly maintenance chemotherapy, should not be given within 2 weeks before leukapheresis. Pegylated asparaginase should be stopped at least 4 weeks before leukapheresis. Clofarabine should not be administered within 8 weeks before leukapheresis collection. Vincristine should not be administered within 2 weeks before leukapheresis. It is recommended holding intrathecal (IT) chemotherapy before leukapheresis collection. If clinically indicated, IT cytarabine may be given and leukapheresis collection started any time following IT cytarabine. Leukapheresis collection may be started 1 week or more after IT methotrexate. T-cell lytic agents (eg, alemtuzumab) should not be administered within 8 weeks before leukapheresis collection. Therapeutic doses of steroids should be stopped at least 3 days before leukapheresis. Physiological replacement doses of steroids are allowed, up to 12 mg/m2/d hydrocortisone or equivalent in pediatric patients, up to 40 mg/m2/d hydrocortisone or equivalent in adult patients, or as specified in Clinical Trial Protocol. Immunomodulatory drugs should be stopped at least 2 weeks before leukapheresis. These include checkpoint inhibitors (monoclonal antibodies and small molecule modulators). At least 12 weeks should have passed from allogeneic stem cell transplant at the time of leukapheresis. Donor lymphocyte infusions should be completed at least 4 weeks before leukapheresis. If an allogeneic stem cell transplant occurs after leukapheresis collection, the leukapheresis material cannot be used. Any systemic drug used to prevent or treat grade 2 to 4 acute graft-vs-host disease (GVHD) or extensive chronic GVHD should be stopped at least 2 weeks before leukapheresis (eg, calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-tumor necrosis factor α, anti-IL-6, or anti-IL-6R). Topical steroids for localized treatment of GVHD are allowed. If grade 2 to 4 acute GVHD or extensive chronic GVHD develops after leukapheresis collection, the leukapheresis material cannot be used.

Objectives

Primary objective:

To evaluate the efficacy of tisagenlecleucel as measured by complete response rate (CRR) determined by independent review committee (IRC). The study was considered successful if the lower bound of the 2-sided exact CI for ORR was >15%, so that the null hypothesis that the CRR was less than or equal to 15% could be rejected. The null hypothesis employed a 1-sided cumulative 2.5% level of significance. The reference CR rate of 15% used for hypothesis testing was defined based on the observed CRR (14%) for idelalisib in r/r FL after two lines of therapy (Salles et al 2017). Idelalisib was the therapy with best CRR among the approved and widely used treatment options for r/r FL after two or more lines of treatment at time of study set up.

Secondary objectives:

- To evaluate the efficacy of tisagenlecleucel as measured by additional efficacy measures, including overall response rate (ORR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS).
- To evaluate safety of tisagenlecleucel
- To characterize the in vivo cellular kinetics (levels, expansion, persistence) of tisagenlecleucel transduced cells into target tissues (blood, bone marrow, and other tissues if available) and CD3+ tisagenlecleucel cells in peripheral blood, summarized by clinical response
- To characterize the incidence and prevalence of tisagenlecleucel immunogenicity (humoral and cellular)

- To characterize the impact of pre-existing and treatment induced immunogenicity (cellular and humoral) on cellular kinetics, efficacy, and safety
- To describe the effect of tisagenlecleucel therapy on patient reported outcomes (PRO)

Exploratory objectives:

The current CSR contains only those exploratory assessments that were evaluated at the time of the current DCO, namely:

- Characterize B-cell levels and relationship with clinical response
- Summarize rituximab PK and explore the relationship between rituximab PK and clinical response
- Describe composition of T-cell subsets (immunophenotyping in peripheral blood), summarized by clinical response
- Describe the profile of blood soluble immune factors (e.g. IL-6, gamma interferon) and their correlation with cytokine release syndrome (CRS) grade

Outcomes/endpoints

Primary Endpoint:

The primary endpoint was Complete response rate (CRR) determined by an Independent Review Committee (IRC) in the efficacy analysis set (EAS) based on Lugano 2014 classification response criteria (Cheson et al 2014).

CRR was defined as the proportion of patients with a BOR of CR recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever came first. Patients in this study who were of unknown clinical response were treated as non-responders. The analysis of the primary endpoint was performed on the Enrolled set, Tisagenlecleucel infused set, and per-protocol set (PPS) using the same methodology, as well as on the mEAS and EAS excluding patients who achieved CR at the radiologic assessment at baseline per IRC.

Efficacy was evaluated using PET/CT/MRI at Months 3, 6, 9, 12, 18, 24 post-infusion and every 6 months thereafter, until EOS, (EOS is defined as when all patients have completed their Month 24 evaluation or discontinued prematurely). Also, onsite assessments were to be performed at any time disease progression or relapse was suspected, until disease progression or relapse, start of new anticancer therapies, death, lost to follow-up or withdrawal of consent. After the end of this study, patients who have received tisagenlecleucel infusion will continue to be followed for long-term safety, efficacy and survival under the long-term follow-up protocol CCTL019A2205B for 15 years post infusion.

Secondary Endpoints:

The secondary endpoints included ORR, DOR, PFS, OS, safety, PK (cellular kinetics), immunogenicity, and PRO. IRC assessment was used in the main analysis of secondary endpoints that involved disease response. All analyses of the secondary efficacy endpoints were performed on the EAS. In addition, selected analyses were performed for the mEAS, Tisagenlecleucel infused set, and/or for the Enrolled set.

- **ORR** is defined as the proportion of patients with a BOR of CR or PR. The ORR was summarized along with the 2-sided 95% exact Clopper-Pearson CI.
- **DOR** applies to patients whose BOR was CR or PR. It is defined as the time from the date of first documented disease response (CR or PR) to the date of first documented progression or

death due to FL. If a patient did not have an event prior to the earliest censoring event, DOR was censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be: ongoing without an event, lost to follow-up, withdrew consent, new anticancer therapy (incl. HSCT), adequate assessments no longer available. If there were any patients who responded to tisagenlecleucel but experienced death due to any reason other than FL, death due to a reason other than FL was considered as a competing risk event to other events of interest (progression or death due to FL). In this analysis, the median DOR (if appropriate) as well as proportion of patients without events following response (progression or death due to FL) at 3, 6, 9, 12 months, etc. were presented with 95% CI using the cumulative incidence function (CIF). Distribution of DOR was also estimated using KM methodology, in which, the competing risk event, i.e. death due to reason other than FL was censored at the date of the last assessment with response of CR or PR on or prior to the censoring event. As HSCT is an important treatment option in responding patients, the date of HSCT was considered as censoring date, instead of censoring at the last tumor assessment date. Distribution of DOR was estimated using the KM method. DOR was summarized for patients with CR only as well as with CR or PR.

- **PFS** is defined as the time from the date of tisagenlecleucel infusion to the date of first documented progression or death due to any cause. Progression free survival was also analyzed as time from enrollment to the date of event defined as the first documented progression or death due to any cause for Enrolled set. In case a patient did not have progression or death prior to the earliest censoring event, PFS was censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reasons and PFS estimates by KM methodology are the same as for DOR. Patients who proceeded to HSCT after tisagenlecleucel were censored at the time of HSCT. PFS will be estimated using the Kaplan-Meier method and the median PFS as well as proportion of patients without event at 3, 6, 9, and 12 months will be presented along with 95% confidence interval.
- **OS** was defined as the time from the date of tisagenlecleucel infusion to the date of death due to any reason. If a death was not observed by the DCO, OS was censored at the date of last contact. The distribution function of OS was estimated using the KM method. Overall survival was also analyzed as time from enrollment to the date of death due to any reason for Enrolled set.
- **Summary scores of PRO** measured by SF-36 version 2, EQ-5D-3L and FACT-Lym QoL questionnaires.

Sample size

The proposed sample size of 90 patients was based on the null hypothesis of CRR ≤ 15% and assuming an underlying CRR of 30%, with a power of 90%, using a 2-look Lan-DeMets group sequential design with O'Brien-Fleming type boundary and an exact confidence interval at one-sided cumulative 0.025 level of significance (see also section below on interim analyses). With these assumptions a CRR of 21/90=23.3% would be needed to claim success. The reference CR rate for hypothesis testing was defined based on the observed CRR (14%) for the two PI3K inhibitors idelalisib and copanlisib in refractory FL (Salles et al 2017, FDA 2017).

Assuming 20% enrolled patients would not be infused due to reasons such as manufacturing failure, worsening of patient's condition, etc., it was estimated that at least 113 patients would need to be enrolled to ensure 90 patients are treated and hence would be used for the primary analysis.

Randomisation

Not applicable. E2202 is a single arm, open-label, multi-center, phase 2 study.

Blinding (masking)

Not applicable. E2202 is a single arm, open-label, multi-center, phase 2 study.

Statistical methods

Analysis populations

The **screened set** comprised all subjects who have signed informed consent and have been screened in the study.

The **enrolled set** comprised all subjects who have been enrolled in this study, defined as the point at which the patient meets all inclusion/exclusion criteria, and the patients' leukapheresis product is received and accepted by the manufacturing facility.

The **tisagenlecleucel infused set** comprised all subjects who have received tisagenlecleucel.

The **efficacy analysis set (EAS)** includes all subjects who have received tisagenlecleucel and had measurable disease at baseline per IRC. Non-measurable disease at baseline is defined as absence of index lesion at baseline disease evaluation (i.e. no disease at baseline).

The **modified efficacy analysis set (mEAS)** includes the first 90 subjects who have received tisagenlecleucel and had measurable disease at baseline per IRC.

At the time of interim analysis, the **Interim Efficacy Analysis Set (IEAS)** comprised all subjects who have received tisagenlecleucel infusion at least 166 days (i.e. 6 months considering 14 days time-window) prior to the DCO date, had measurable disease at baseline per IRC and have either completed Month 6 assessment visit or discontinued efficacy follow-up earlier.

The **safety set** comprised all subjects who have received tisagenlecleucel, i.e. the same subjects as the tisagenlecleucel infused set.

The **per-protocol set (PPS)** consisted of a subset of subjects in the IEAS or EAS (at time of the interim and primary analysis respectively). Protocol deviations leading to exclusion from the PPS include: No diagnosis of FL at baseline, Missing or incomplete documentation of disease, and Receiving a dose less than the recommended dose of 0.6×10^8 tisagenlecleucel transduced viable T cells (i.e. total CAR-positive viable T cell count).

The **cellular kinetic analysis set (CKAS)** consisted of subjects in the IEAS or EAS (at time of the interim and primary analysis respectively) who provide an evaluable cellular kinetic profile (at least one cellular kinetic parameter). The CKAS will be used for summaries (tables and figures) of cellular kinetic data. The tisagenlecleucel infused set will be used for listings of cellular kinetic data. Note that subjects may be removed from the estimation of certain CK parameters on an individual basis depending on the number of available samples. These subjects will be identified at the time of the analyses.

The **tocilizumab pharmacokinetic analysis set (TPAS)** consisted of subjects in the tisagenlecleucel infused set who have taken at least one dose of tocilizumab and provided at least one tocilizumab PK concentration.

Hypothesis – Primary Endpoint CRR

The primary endpoint was the CRR defined as the proportion of patients with a best overall response of CR recorded from tisagenlecleucel infusion until progressive disease as determined by IRC or start of new anticancer therapy, whichever comes first. Patients who were of unknown clinical response were to be treated as non-responders.

CRR was to be analyzed at the interim look and final look of a group sequential design, based on the data observed in the IEAS and the EAS, respectively. The CRR was to be summarized along with the 2-sided exact Clopper-Pearson confidence intervals (CI) with coverage level determined by the O'Brien-Fleming type α-spending approach according to Lan-DeMets as implemented in East 6.3 (Lan and DeMets, 1983). The study was to be considered successful if the lower bound of the 2-sided exact CI was greater than 15%, equivalent to that the null hypothesis that the CRR is less than or equal to 15% could be rejected. A p-value from a binominal exact test was to be provided.

A sensitivity analysis was to be performed using the local investigator response assessments instead of the IRC assessment. The primary analysis will also be performed on the Enrolled Set, tisagenlecleucel infused set, and PPS using the same methodology as well as on the mEAS and EAS excluding subjects who achieved CR at the radiologic assessment at baseline per IRC.

Secondary Efficacy Analysis

IRC assessment will be used in the main analysis of secondary endpoints that involve disease response. Unless otherwise specified, all analyses of the secondary efficacy endpoints were to be performed on the IEAS and the EAS at interim and primary analysis, respectively. In addition, selected analyses were to be performed for the mEAS, tisagenlecleucel infused set, and/or for the Enrolled set.

ORR, defined as the proportion of patients with a best overall disease response of CR or PR. The Best overall response (BOR) was defined as the best response recorded until progressive disease or start of new anticancer therapy or the DCO date, whichever was earlier. The ORR was to be summarized along with the 2-sided 95% exact Clopper-Pearson confidence Intervals.

DOR, defined as the time from the date of first documented disease response (CR or PR) to the date of first documented progression or death due to FL. DOR was to be summarized for patients with CR only, as well as with CR or PR. If a patient had not had an event, duration of overall response was to be censored at the date of the last adequate assessment. In case a patient did not have progression or death due to FL prior to data cutoff, DOR was to be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be: Ongoing without event, Lost to follow-up, Withdrew consent, New anticancer therapy, and Adequate assessments no longer available. As HSCT is an important treatment option in responding patients, it was seen as appropriate to consider the date of HSCT as censoring date, instead of censoring at the last tumour assessment date. In the main analysis of DOR, death due to reason other than FL was to be considered as a competing risk event to other events of interest (progression or death due to FL). In this analysis, the median response duration (if appropriate) as well as proportion of patients without events following response (progression or death due to FL) at 3, 6, 9, 12 months, etc. was to be presented with 95% confidence intervals using the cumulative incidence function (CIF). The distribution function of DOR was also to be estimated using the Kaplan-Meier method where the competing risk event, i.e. death due to reason other than FL, was censored at the date of the last assessment with response of CR or PR on or prior to the censoring event.

PFS, defined as the time from the date of first tisagenlecleucel infusion to the first documented progression or death due to any cause. If a patient had not had an event, progression-free survival was to be censored at the date of the last adequate assessment. In case a patient did not have progression or death prior to data cutoff, PFS was to be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be: Ongoing

without event, Lost to follow-up, Withdrew consent, New anticancer therapy (incl. HSCT), Adequate assessments no longer available.

PFS was to be estimated using the Kaplan-Meier method and the median PFS, proportion of patients without event at 3, 6, 9, and 12 months presented along with 95% confidence intervals. The PFS was also to be analyzed as time from enrollment to the date of event defined as the first documented progression or death due to any cause for Enrolled set.

Overall survival (OS), defined as the time from date of first tisagenlecleucel infusion to date of death due to any reason. If a death had not been observed by the date of analysis cutoff, OS was to be censored at the date of last contact. The distribution function of OS was to be estimated using the Kaplan Meier (KM) method, and the median OS and the proportion of patients alive at 3, 6, 12, 18, and 24 months with 95% confidence intervals presented. OS was also to be analyzed as time from enrollment to the date of death due to any reason for the Enrolled set

Interim analyses / Multiplicity

One interim analysis for overwhelming efficacy was planned for the study when approximately 50 patients of the planned 90 (55.6%) have received tisagenlecleucel infusion and have either completed 6 months from study day 1 infusion or discontinued earlier. At the interim analysis it was expected that all patients would have been treated, and therefore the study would not be stopped for outstanding efficacy regardless of the interim analysis results. An α-spending function according to Lan-DeMets (O'Brien-Fleming), as implemented in EAST 6.3, was to be used to construct the efficacy stopping boundary based on the actual number of patients included when the interim analysis would take place. For example, a 2-sided 99.48% exact confidence interval for CRR would need to be greater than 15% to declare statistical significance, and therefore a CRR of 16/50=32% would be needed to claim success at the interim analysis. Correspondingly, at the final analysis when 90 patients are treated and followed for at least 6 months, a 2-sided 95.16% exact CI would be used, requiring an CRR of 21/90=23.3% to claim success.

Subgroup analyses

The following subgroup of interest was to be used for the supporting efficacy analysis of the Complete response rate (CRR):

- Age: <65 years, ≥ 65 years
- Gender: Male, Female
- Race: Asian (i.e. Chinese, Indian, Japanese Korean or Vietnamese), Black or African
- American, White, Native Hawaiian or Other Pacific Islander or American Indian, Alaska Native
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Follicular Lymphoma International Prognostic Index (FLIPI) at study entry: low/intermediate, high
- Histological grade: 1, 2, 3A
- Number of prior lines of anti-neoplastic therapy: ≤2 lines, 3 to 4 lines, >4 lines
- PI3K inhibitor use: naïve, pretreated
- Prior HSCT therapy: yes or no; In addition, subjects who relapsed ≤12 months from HSCT and >12 months from HSCT will be displayed.
- Disease status to last line of prior anti-neoplastic therapy: refractory, relapsed
- Progression of disease within 24 months (POD24) from initiation of first-line anti-CD20 mAb containing therapy: yes, no
- Bulky disease at baseline (defined per IRC as imaging showing any nodal or extra nodal tumor mass that is >7 cm in diameter or involvement of at least 3 nodal sites, each with a diameter >3 cm): yes or no
- Bridging therapy: yes or no
- Lactate dehydrogenase (LDH) at study entry: ≤ULN or >ULN
- R2 use (Lenalidomide + Rituximab, within same regimen): naïve, pretreated
- Us sites: yes, no

- Total Metabilic tumor volume (MTV) at baseline: Low tumor burden (tumor volume ≤510 cm3 or High tumor burden (tumor volume >510 cm3).
- Double refractory (defined as subjects who failed to respond or relapsed within 6 months following therapy with anti-CD20 and alkylating agents, any regimen): yes, no

Results

Participant flow

At the time of the DCO for the main extended follow-up analysis (29-Mar-2021), 119 patients were screened. Of these, 98 (84.5%) patients were enrolled in the study. Median time from screening to enrolment for all enrolled patients was 30 days (range 14-72 days). Only one patient was not enrolled due to a failure of apheresis.

The participant flow is shown in Figure 19 below.

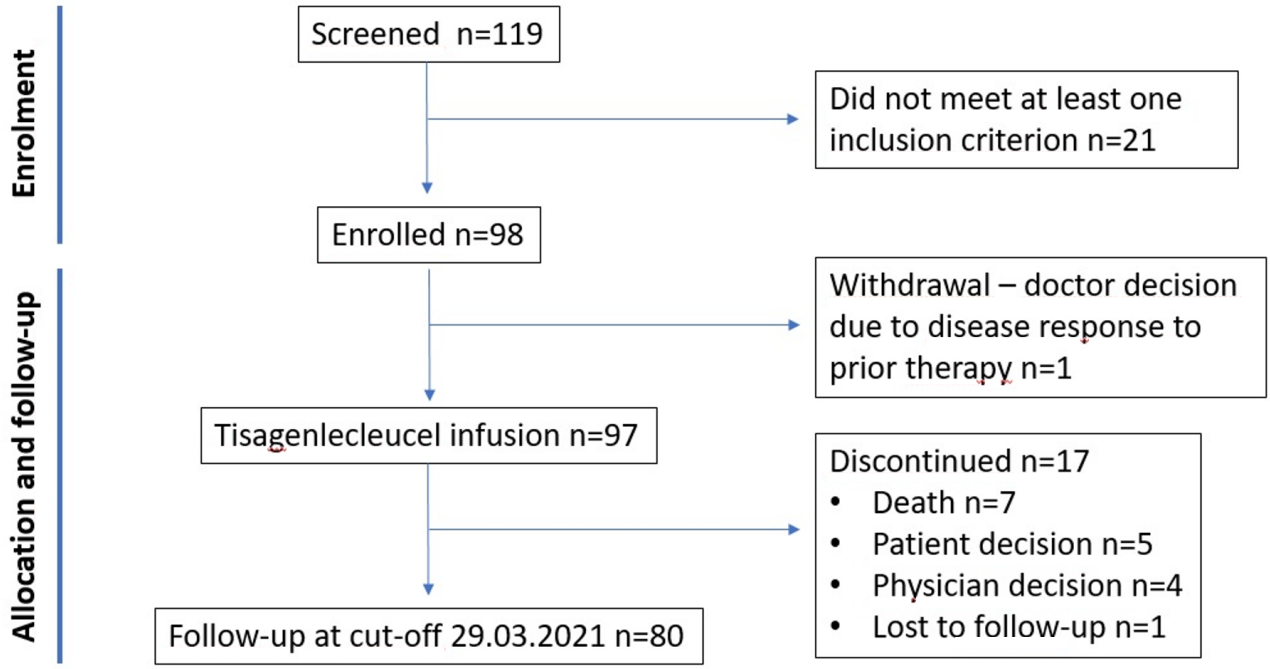


Figure 19: Participant flow in study E2202
* Withdrawal based on doctor decision due to disease response to prior therapy (copanlisib, a PI3K inhibitor)

Recruitment

Study E2202 was conducted in 32 sites, with patients enrolled and treated in 30 of these sites. The patients were enrolled across 12 countries, including Australia (3 centers), Austria (1), Belgium (1), Germany (3), Spain (2), France (2), United Kingdom (2), Italy (2), Japan (3), Netherlands (1), Norway (1), and United States of America (9). Infusion in an outpatient setting (i.e., day-care admission for infusion followed by ambulatory monitoring) was allowed as per Investigator's decision. The data provided is based on a follow up analysis when 97 patients were infused with tisagenlecleucel and 90 patients had either completed 12 months of follow-up from the time of infusion or had discontinued earlier.

Study initiation date: 12-Nov-2018 (first patient first visit).

DCO date for the main extended follow-up analysis: 29-Mar-2021 (median follow up in EAS:16.9 months, range: 10.3-25.7)
DCO date for subsequent extended follow-up analysis: 03-Aug-2021 (median follow up in EAS: 21 months, range: 14-30)
Database lock: 07-May-2021. The study was ongoing at the time of the CAT/CHMP opinion.

Conduct of the study

No substantial amendments were made to the original protocol, dated 29-Mar-2018.

During the study, the Independent Review Committee Charter was modified four times. These changes were to provide clarifying edits to the lesion location list, FGD-PET assessment guidance for timepoint by timepoint review, and to clarify CR and PR response assessments during global radiology review (Version 2); to add the Secondary Radiology Analysis review and the assessment window for bone marrow data was updated to align with the protocol language (Version 3); to add Secondary Analysis Oncology Review for patients receiving bridging therapy (Version 4).

In the Enrolled set (n=98), protocol deviations were reported in 58 patients (59.2%); however, these deviations were typically minor and were not considered to impact the overall conclusions of the study. The most common protocol deviations reported in ≥ 10 patients fell into the following categories:

- 'Other deviations', were reported in 50 patients (51.0%). The most common subcategories reported in ≥ 10 patients were:
  - 18.4% of the patients missed ≥ 3 consecutive PK timepoints (qPCR and/or flow cytometry)
  - In 17.3% of the patients, ≥ 3 consecutive PRO questionnaires were not collected as per protocol
  - In 14.3% of the patients (n=14), safety assessments were not performed as per protocol
  - In 13.3% of the patients (n=13), response assessments were not performed as per protocol
- Treatment deviations in 15 patients (15.3%) – the majority were due to 'influenza testing not performed within 10 days prior to planned tisagenlecleucel infusion'
- Any inclusion criteria deviation in 11 patients (11.3%) – of which, 3 patients were not r/r after ≥ 2 lines of systemic therapy (the patients had relapsed >6 months after completion of their second-line of therapy), in 3 patients oxygen saturation by pulse oximetry was not done, and in 2 patients, study procedures were performed prior to obtaining signed ICF (ECG was performed in 1 patient and ECG and viral test were performed in the second patient) and the other deviations were reported by one patient each.

There was no impact of COVID-19 pandemic on patient enrolment and study population.

Protocol deviations during the COVID-19 pandemic occurred mainly due to patient concern (23.7%), lockdown (11.3%), site issue (11.3%), and patient health status (2.1%). These deviations included:

- In 46 patients visits were not done at the study site due to patient concern (n=19), lockdown (n=10), other issues (n=10) and site issues (n=7).
- 11 patients missed visits due to patient concern (n=5), lockdown (n=2), other issues (n=2), health status (n=1) and site issues (n=1)
- In 9 patients assessment/procedure changed due to other reasons (n=5), site issues (n=3) and patient concern (n=1)
- 1 patient discontinued the study due to COVID-19 infection

Note: A patient could have multiple protocol deviations.

These deviations did not have an impact on the primary efficacy endpoint at the time of the main extended follow-up analysis (29-mar-2021).

Numbers analysed

The numbers of participants included in each analysis set are shown in Table 17.

Nine patients (9.6%) were excluded from the EAS (94 patients) to form the PPS (n=85):

- 5 patients with missing or incomplete documentation of disease at baseline - 4 patients did not have bone marrow assessment, but had complete radiological assessments at baseline, and 1 patient did not undergo a PET scan, but had a CT at baseline
- 4 patients received a dose lower than the recommended dose

Table 16: Analysis sets (enrolled set)

Analysis set	All Patients N=98 n (%)
Enrolled set	98 (100)
Tisagenlecleucel infused set	97 (99.0)
Safety set	97 (99.0)
Efficacy analysis set	94 (95.9)
Modified efficacy analysis set	90 (91.8)
Per-protocol set	85 (86.7)
Cellular kinetic analysis set	94 (95.9)
Tocilizumab cellular kinetic analysis set	11 (11.2)

Baseline data

The demographic variables and baseline characteristics for the Enrolled set and the EAS are shown in Table 18.

Table 17: Demographics and baseline characteristics (Enrolled set and EAS)

Demographic variable	Enrolled set N=98 n (%)	EAS N=94 n (%)
Age at study entry (years)		
Mean (SD)	56.5 (10.34)	56.4 (10.54)
Median	57.5	57.0
Q1-Q3	49.0-64.0	49.0-65.0
Min-Max	29-73	29-73
Age category - n (%)		
18-<65 years	74 (75.5)	70 (74.5)
65-<85 years	24 (24.5)	24 (25.5)
Sex - n (%)		
Male	65 (66.3)	64 (68.1)
Female	33 (33.7)	30 (31.9)
Race - n (%)		
White	74 (75.5)	72 (76.6)
Asian	13 (13.3)	11 (11.7)
Japanese	9 (9.2)	8 (8.5)
Indian	2 (2.0)	2 (2.1)
Missing	2 (2.0)	1 (1.1)
Black or African American	1 (1.0)	1 (1.1)
Missing	10 (10.2)	10 (10.6)
Ethnicity - n (%)		
Not Hispanic or Latino	84 (85.7)	81 (86.2)
Hispanic or Latino	3 (3.1)	2 (2.1)
Not reported	11 (11.2)	11 (11.7)
ECOG performance status - n (%)		
0	56 (57.1)	53 (56.4)
1	39 (39.8)	38 (40.4)
2[1]	3 (3.1)	3 (3.2)

[1] These three patients had ECOG status of 2 recorded just before receiving tisagenlecleucel infusion, and not at the time of signing the ICF.
SD: standard deviation

The primary disease history prior antineoplastic therapies in the Enrolled set and EAS are shown in Table 19. The demographics of the population in the EAS and mEAS were consistent with the Enrolled set.

The enrolled study population was heavily pre-treated as indicated by the median number of prior lines of antineoplastic therapies administered, i.e. 4.0 (range: 2 to 13), with 28.6% of the patients receiving ≥ 5 lines (Table 19).

Table 18: Primary disease history and prior antineoplastic therapies (Enrolled set and EAS)

Disease history	Enrolled set N=98 n (%)	EAS N=94 n (%)
Diagnosis of disease – n (%)		
Follicular lymphoma	98 (100)	94 (100)
Stage at initial diagnosis – n (%)		
Stage I	6 (6.1)	5 (5.3)
Stage II	13 (13.3)	13 (13.8)
Stage III	21 (21.4)	20 (21.3)
Stage IV	57 (58.2)	55 (58.5)
Missing	1 (1.0)	1 (1.1)
Stage at time of study entry – n (%)		
Stage I	3 (3.1)	2 (2.1)
Stage II	11 (11.2)	11 (11.7)
Stage III	26 (26.5)	25 (26.6)
Stage IV	58 (59.2)	56 (59.6)
Bone marrow involved at study entry – n (%)		
Yes	37 (37.8)	35 (37.2)
No	60 (61.2)	58 (61.7)
Missing	1 (1.0)	1 (1.1)
Histological grade at study entry – n (%)		
Grade 1-2 (low grade)	88 (89.8)	85 (90.4)
Grade 3A	10 (10.2)	9 (9.6)
Were any extralymphatic sites involved by lymphoma at study entry – n (%)		
Yes	30 (30.6)	30 (31.9)
No	68 (69.4)	64 (68.1)
FLIPI at study entry[1] – n (%)		
Low	18 (18.4)	17 (18.1)
Intermediate	21 (21.4)	20 (21.3)
High	59 (60.2)	57 (60.6)
Absolute lymphocyte count (ALC) at study entry (10^9/L)		
n	97	94
Mean (SD)	2.4 (1.51)	2.4 (1.53)
Median (min – max)	1.9 (0.2 – 7.0)	1.9 (0.2 - 7.0)
Number of prior lines of antineoplastic therapy		
Median (min – max)	4.0 (2.0 – 13.0)	4.0 (2.0 – 13.0)
Number of prior lines of antineoplastic therapy – n (%)		
2	24 (24.5)	24 (25.5)
3	21 (21.4)	19 (20.2)
4	25 (25.5)	24 (25.5)
≥5	28 (28.6)	27 (28.7)
6	7 (7.1)	7 (7.4)
7	5 (5.1)	5 (5.3)

9	1 (1.0)	1 (1.1)
13	1 (1.0)	1 (1.1)
Progression of disease within 24 months (POD24)[2] from first-line anti-CD20 mAb containing therapy - n (%)		
POD24 group	61 (62.2)	61 (64.9)
Non-POD24 group	36 (36.7)	33 (35.1)
Missing	1 (1.0)	0
Bulky disease at baseline [3] - n (%)		
Yes	62 (63.3)	61 (64.9)
No	36 (36.7)	33 (35.1)
Treatment density[4]		
Mean (SD)	1.73 (1.165)	1.67 (1.140)
Median (min – max)	1.40 (0.14 – 5.65)	1.37 (0.14 - 5.65)

[1] FLIPI includes 5 labelled prognostic factors; FLIPI = sum (where prognostic factor = 'Yes'); Low: 0-1 criteria met; intermediate: 2 criteria met; high: 3 or more met.
[2] POD24: subjects with primary refractory or experiencing progression of disease within 24 months from initiation of a first-line anti-CD20 mAb containing treatment.
[3] Bulky disease defined per IRC as imaging showing any nodal or extra nodal tumor mass that is >7 cm in diameter or involvement of at least 3 nodal sites, each with a diameter >3 cm.
[4] Treatment density: derived as time from initial diagnosis to study entry (year)/number of lines of prior therapy
SD: standard deviation

Refractory was defined as failure to respond to previous treatment (SD/PD as best response) or PD within 6 months of prior therapy completion. Of the enrolled patients, 76 (77.6%) of patients were refractory to their last line of therapy. Of which, 54 patients (55.1%) showed SD/PD as their best response to their most recent regimen and 22 patients (22.4%) had disease relapse within 6 months from completion of this last regimen. Thirty-six patients received prior HSCT, of whom 15 patients relapsed within 12 months from transplant.

Commonly used prior antineoplastic therapies, i.e. anti-CD20 mAbs, alkylating agents, PI3K inhibitors, and HSCT are summarized in Table 20. Commonly used prior antineoplastic medications by PT in >20% of the patients included rituximab (100%), cyclophosphamide (94.9%), doxorubicin (89.8%), vincristine (68.4%), bendamustine (67.3%) etoposide (54.1%), prednisone (51.0%), cytarabine (44.9%), prednisolone (42.9%), dexamethasone (30.6%), melphalan (31.6%), carmustine (30.6%), vincristine sulfate (27.6%), ifosfamide (26.5%), obinutuzumab (26.5%), cisplatin (25.5%), lenalidomide (22.4%), and carboplatin (21.4%). Twenty-seven patients (27.6%) in the Enrolled set received prior radiotherapy, mostly in therapeutic setting (n=23).

Concomitant medications administered were representative of those routinely prescribed for adult patients with FL, treatment and prophylaxis of AEs related to bridging/LD therapy, and treatment of CRS and associated events as recommended by the study protocol.

At the time of the current DCO:

- All patients in the Infused set with one exception received non-study concomitant medications
- The most commonly used concomitant medications (in >30% of patients) by ATC class included the below, presented in decreasing order:
    - Anti-infectives for systemic use in 93.8% of patients (primarily Bactrim (42.3%))
    - Alimentary tract and metabolism medications in 79.4% of patients (primarily ondansetron (32.0%))
    - Nervous system medications in 71.1% (primarily paracetamol (53.6%))
    - Blood and blood-forming organs medications in 58.8% (primarily enoxaparin/enoxaparin sodium (22.7%))
    - Dermatologicals in 50.5% (primarily aciclovir (27.8%))
    - Musculoskeletal system medications in 50.5% (primarily allopurinol (40.2%))

    - Antineoplastic and immunomodulating agents in 47.4% (primarily filgrastim (25.8%), which was given following the restrictions defined by the protocol with respect to permitted and prohibited concomitant medications.
    - Cardiovascular system medications in 37.1% of patients
- 17 patients (17.5%) in the Infused set received anti-cytokine medication for CRS. All 17 patients received tocilizumab and 4 of them received corticosteroids in addition.

Table 19: Key prior antineoplastic therapies (enrolled set)

Prior antineoplastic therapy and refractoriness/relapse	Enrolled set
Anti-CD20 mAb	98 (100)
Refractory to anti-CD20 mAb	85 (86.7)
POD24 from first-line anti-CD20 mAb containing therapy	61 (62.2)
Alkylating agents	98 (100)
Refractory to alkylating agent	70 (71.4)
PI3K inhibitors	21 (21.4)
Refractory to PI3K inhibitors	14 (14.3)
Refractory to anti-CD20 mAb (any regimen) + alkylating agent (any regimen)	67 (68.4)
Refractory to anti-CD20 mAb (any regimen) + alkylating agent (any regimen) + PI3K inhibitors (any regimen)	10 (10.2)
Refractory to anti-CD20 mAb (any regimen) + alkylating agent (any regimen) + lenalidomide (any regimen)	17 (17.3)
Prior HSCT	36 (36.7)
Relapsed ≤ 12 months after autologous HSCT	15 (15.3)

Bridging therapy

Of the 97 patients infused, 44 patients (45.4%) received optional antineoplastic bridging therapy prior to tisagenlecleucel infusion. The most commonly used agents (in ≥ 5% of patients) were rituximab (21.6%), dexamethasone (11.3%), gemcitabine (10.3%), oxaliplatin (7.2%), prednisolone (7.2%), etoposide (6.2%), cyclophosphamide (5.2%), and vincristine (5.2%). In 5 patients, only corticosteroids were administered as bridging therapy. Furthermore, two patients received bridging radiotherapy – one patient received only radiotherapy and the other patient received radiotherapy and corticosteroids.

Lymphadenopathy chemotherapy

All infused patients received LD chemotherapy prior to tisagenlecleucel infusion. Ninety-two (94.8%) of patients received fludarabine + cyclophosphamide, and the remaining 5 patients (5.2%) received bendamustine.

Patient exposure to tisagenlecleucel

The recommended tisagenlecleucel dose range in this study was 0.6 to 6.0×10^8 CAR-positive viable T-cells.

Table 20: Tisagenlecleucel dose administration (tisagenlecleucel infused set)

Description	All patients N=97
CAR-positive viable T cell dose categorized: n (%) [1]	
Below target dose range	4 (4.1)
Within target dose range	93 (95.9)
CAR-positive viable T cells count (10^8 cells)	
Mean	2.13
SD	0.981
Median (min – max)	2.06 (0.1 - 6.0)
Total viable cell count (10^8 cells)	
Mean	13.28
SD	6.628
Median (min – max)	12.00 (0.4 – 34.0)

[1] Recommended dose range is 0.6 to 6.0×10^8 CAR-positive viable T-cells
SD: standard deviation

Six patients were infused with a tisagenlecleucel batch provided upon the request of the Principal Investigator under the exceptional provision procedure for final product that did not meet all predefined release specifications (OOS).

- Four patients received tisagenlecleucel products that were OOS due to a lower dose than specified as per protocol (OOS range: 0.1 to 0.46×10^8 CAR-positive viable T-cells)
- One patient received tisagenlecleucel product that was OOS due to lower viability at 51.7% (specified: ≥ 70%) but with an overall dose of CAR-positive viable T-cells in the targeted dose range (dose received: 0.8×10^8 cells).
- One patient received tisagenlecleucel product that was OOS due to a higher dose; however, the site was instructed by Novartis to infuse 91% of the volume and the patient was administered a dose of 6.0×10^8 CAR-positive viable T-cells that was within specification

Note: one patient received only one of the two infusion bags; (actual dose received: 1.45×10^8 CAR-positive viable T-cells).

One patient was not enrolled due to a failure to obtain an apheresis.

The median time from screening to enrolment in study E2202 for all enrolled patients was 30 days (range: 14-72). The median time from enrolment to infusion was 46 days (range: 23-127). The median duration of follow-up from infusion to the DCO date of 29-mar-2021 was 16.59 months (range: 10.3-25.7) for the Enrolled set and 16.85 months (range: 10.3-25.7) for the EAS.

Outcomes and estimation

Primary endpoint

The primary endpoint was met at the interim analysis (corresponding to a DCO date of 26-May-2020), conducted when at least 50 patients had received tisagenlecleucel infusion and had either completed 6 months of follow-up or had discontinued earlier for any reason, with a CRR of 65.4% (34/52; 99.5% CI: 45.1, 82.4). This result was statistically significant at a 1-sided critical alpha level of 0.0025 to reject the null hypothesis (H_0) CRR ≤ 15%.

Furthermore, the results of the primary analysis (corresponding to a DCO date of 28-Sep-2020), conducted when 94 patients had either completed 6 months of follow-up or had discontinued for any reason, confirmed these findings, with a CRR per IRC in the EAS of 66.0% (95% CI: 55.5, 75.4).

Complete response rate

The CRR results of this analysis, with a median duration of follow-up of 16.85 months (range: 10.3 to 25.7) from the time of the infusion to the DCO date, were consistent with both the interim analysis and the primary analysis.

Table 21: BOR and ORR per IRC assessment (EAS), DCO 29-Mar-2021

	All patients N=94	
	n (%)	95% CI
Best overall response		
CR	**65 (69.1)**	**(58.8, 78.3)**
PR	16 (17.0)	
SD	3 (3.2)	
PD	9 (9.6)	
Unknown[1]	1 (1.1)	
Overall response rate (ORR: CR+PR)	**81 (86.2)**	**(77.5, 92.4)**

[1] This patient received a lower dose than the assigned range of CAR-positive viable T cells. The Investigator started a new anticancer treatment before Month 3.
For ORR the 95% exact Clopper-Pearson CIs are displayed.

The CRR per local Investigator assessment was 72.3% (95% CI: 62.2, 81.1), which is consistent with the IRC assessment. Similarly, the ORR 90.4% (95% CI:82.6, 95.5) compared to 86.2% (95% CI:77.5,92.4). Results consistent with that of the EAS were observed when CRR was analysed across the different analysis sets (Table 23).

Table 22: CRR and ORR per IRC and local investigator assessment (Enrolled set, Tisagenlecleucel infused set, mEAS and PPS), DCO 29-March-2021

	IRC assessment		Local assessment	
	n (%)	95% CI	n (%)	95% CI
CRR				
Enrolled set (N=98)	67 (68.4)	(58.2, 77.4)	70 (71.4)	(61.4, 80.1)
Tisagenlecleucel infused set (N=97)	67 (69.1)	(58.9, 78.1)	70 (72.2)	(62.1, 80.8)
mEAS (N=90)	62 (68.9)	(58.3, 78.2)	65 (72.2)	(61.8, 81.1)
PPS (N=85)	62 (72.9)	(62.2, 82.0)	64 (75.3)	(64.7, 84.0)
ORR				
Enrolled set (N=98)	84 (85.7)	(77.2, 92.0)	88 (89.8)	(82.0, 95.0)
Tisagenlecleucel infused set (N = 97)	84 (86.6)	(78.2, 92.7)	88 (90.7)	(83.1, 95.7)
mEAS (N=90)	77 (85.6)	(76.6, 92.1)	81 (90.0)	(81.9, 95.3)
PPS (N =85)	74 (87.1)	(78.0, 93.4)	78 (91.8)	(83.8, 96.6)

ORR: CR+PR

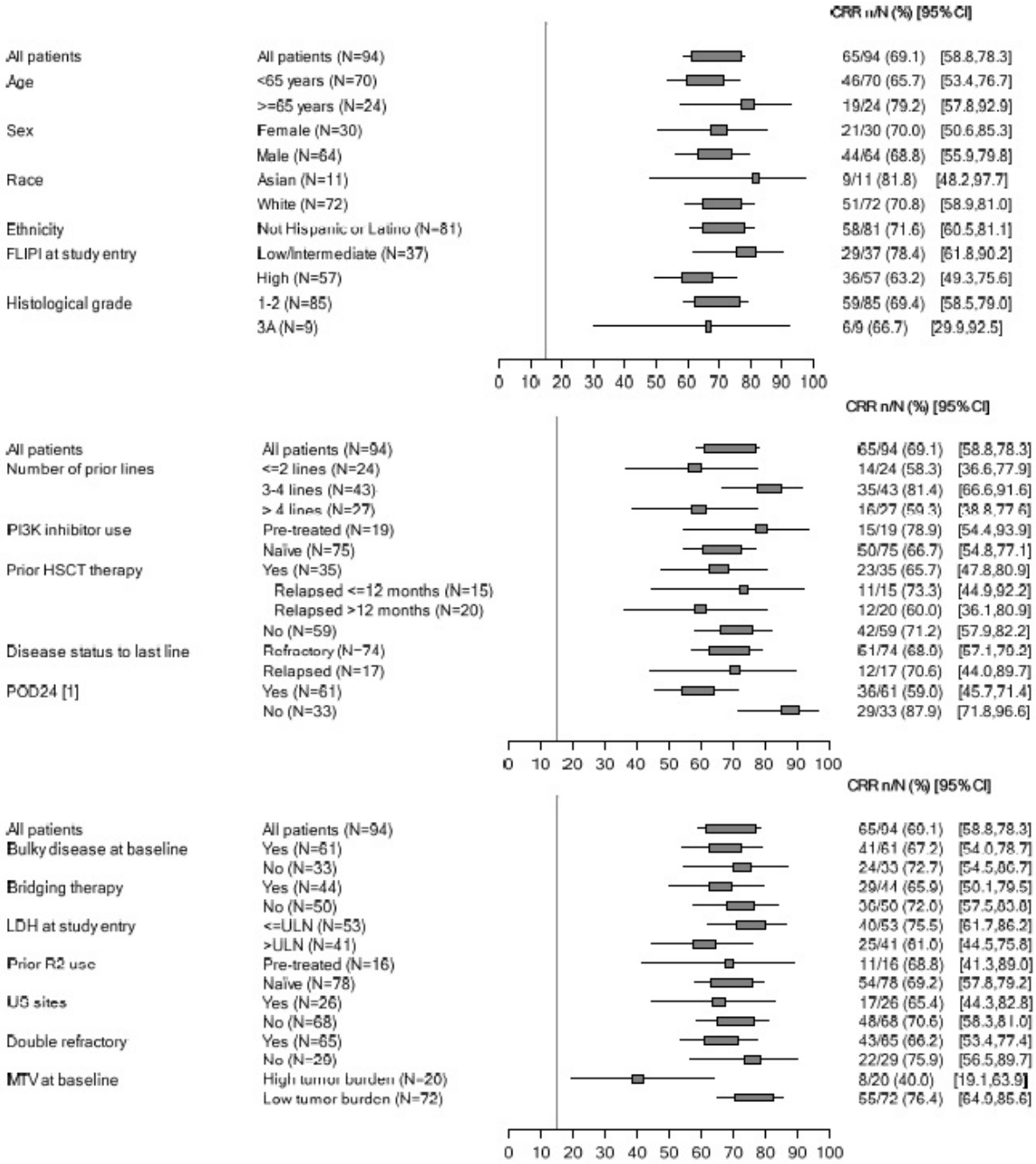
Subgroup analysis of CRR per IRC assessment

A homogeneous treatment effect was evident across all subgroups (Figure 20).

The CRRs in the subgroups ranged from 58.3 to 87.9% and were similar to the overall study population in the EAS, in particular for these high-risk subgroups:

- Patients refractory to last line of prior therapy (68.9%)
- Patients with bulky disease at baseline (67.2%)
- Patients who were double refractory (66.2%)
- Patients who received bridging therapy (65.9%)
- Patients who received prior HSCT (65.7%)
- Patients with high FLIPI (63.2%) and high LDH (61.0%)
- Patients who received >4 prior lines of treatment (59.3%)
- Patients belonging to POD24 group (59.0%)

Patients with high total metabolic tumour volume (TMTV) showed a decreased CRR (40%), although in this subgroup the ORR was less impacted (75%). These estimates should be interpreted with caution given the small number of patients (n=20). The TMTV is a quantitative tumour burden parameter, obtained from FDG-PET/CT. A TMTV value >510 cm^3 was used as threshold to define high TMTV (Delfau-Larue et al 2018).



The area of each box is proportional to the number of patients in the particular grouping.
The 95% CIs are exact Clopper-Pearson CIs calculated for each subgroup.

Figure 20: CRR treatment effect per IRC assessment – Forest plot for subgroups (EAS), DCO 29-Mar-2021

Secondary endpoints

ORR per IRC assessment.

The ORR in the EAS was 86.2% (81/94 patients, 95% CI: 77.5, 92.4) per IRC assessment and 90.4% (85 patients, 95% CI: 82.6, 95.5) per local Investigator assessment, demonstrating consistency in the results. Among 31 patients with initial PR per IRC assessment, 15 patients converted to CR (i.e. achieved BOR of CR) which occurred within approximately 6 months post-tisagenlecleucel infusion for the majority of these 15 patients.

The ORR results of this extended follow-up analysis (DCO: 29-Mar-2021) were consistent with the interim (82.7%) and primary analyses (86.2%). Data from a more recent DCO (03-Aug-2021) was provided in the second assessment round (see ancillary analyses section). No new responders were observed with longer follow-up. Therefore, ORR remained unchanged.

The ORR results were driven by high CRR, and the robustness of the ORR (per IRC assessment) was confirmed by the results of predefined sensitivity and supplemental analyses using the mEAS (85.6%), PPS (87.1%), and Tisagenlecleucel infused set (86.6%) (Table 23).

DOR

At the time of the main analysis (DCO: 29-Mar-2021), the median DOR per IRC was not reached.

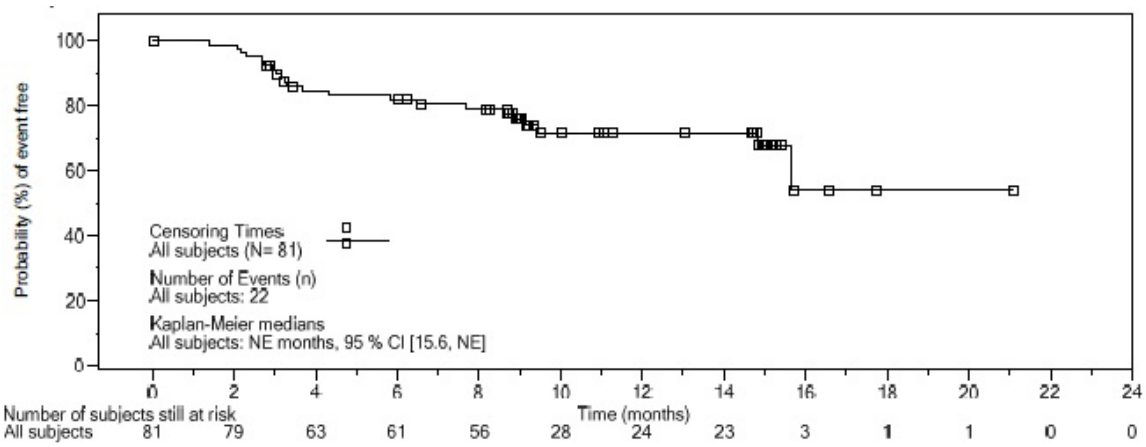
Responses (CR or PR) per IRC review in the EAS set were achieved in 81 patients, with the estimated probability of remaining in response for 9 months being 76.0% (95% CI: 64.6, 84.2) (Table 24). Out of the 81 responders, 59 patients were censored. The reasons for censoring in these 59 patients were as follows: 56 patients were ongoing without an event, 1 patient withdrew consent, 1 patient was lost to follow-up, and 1 patient was censored for starting new anticancer therapy other than HSCT.

Table 23: DOR per IRC and local investigator assessment (EAS), DCO 29-Mar-2021

	Patients with BOR of CR or PR	
	All patients N=94	
	IRC assessment	Local assessment
Events/Responders (%)	22/81 (27.2)	24/85 (28.2)
Percentiles (95% CI)[1]		
25th	9.1 (3.7, NE)	8.9 (3.3, 15.6)
50th	NE (15.6, NE)	15.6 (15.3, NE)
75th	NE	NE (15.6, NE)
% Event-free probability estimates (95% CI)[2]		
Month 3	91.2 (82.5, 95.7)	91.5 (83.1, 95.9)
Month 6	82.0 (71.4, 88.9)	79.2 (68.7, 86.5)
Month 9	76.0 (64.6, 84.2)	74.8 (63.6, 83.0)
Month 12	71.6 (58.9, 80.9)	72.9 (61.3, 81.5)
Month 15	67.8 (53.4, 78.6)	70.1 (57.4, 79.6)

[1] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
[2] % Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the KM survival estimates; Greenwood's formula is used for CIs of KM estimates.

The KM plot of DOR per IRC assessment is presented in Figure 21. DOR results per local Investigator assessment were consistent with the IRC assessment.



Responders: Patients with BOR of CR or PR.

Figure 21: Kaplan-Meier plot of DOR per IRC assessment (EAS), DCO 29-Mar-2021

DOR for CR only, based on IRC

Of the 65 patients who achieved CR, 11 patients experienced disease relapse (occurring 83 to 476 days after the onset of response). Of the 16 patients who achieved PR, 11 patients experienced disease relapse. The estimated probability of remaining in response for patients achieving CR was 86.5% at Month 9 vs 25.9% for patients achieving PR as BOR. The median DOR for patients with CR was not reached Figure 22. These results demonstrate that CR translates to prolonged DOR, when compared to the DOR of patients achieving only PR as BOR.

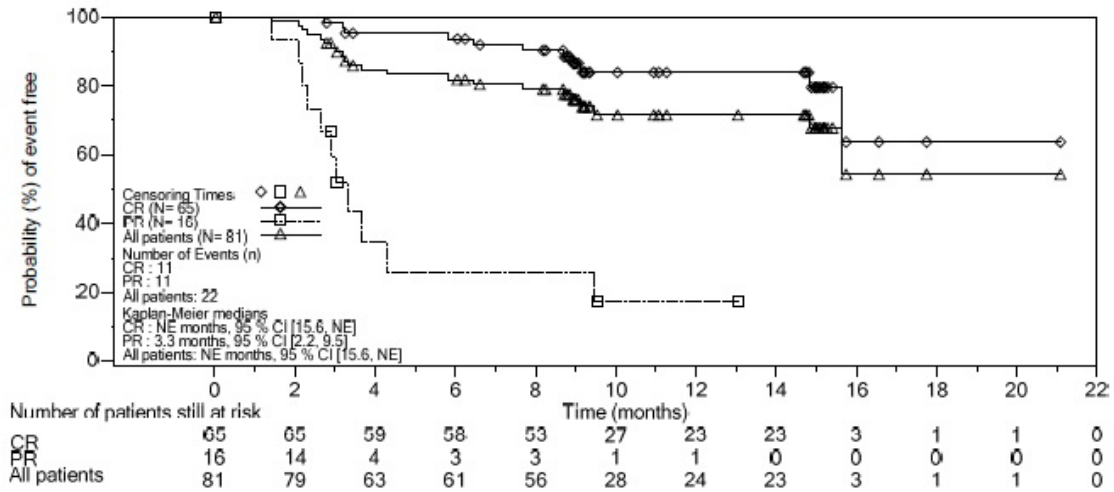


Figure 22: Kaplan-Meier plot of DOR by BOR per IRC assessment (EAS), DCO 29-Mar-2021

PFS based on IRC

At the time of the DCO of 29-Mar-2021, the median PFS per IRC in the EAS was 18.4 months (95% CI: 12.3, NE); however, this should be interpreted with caution since there were limited numbers of patients remaining at risk after Month 18.

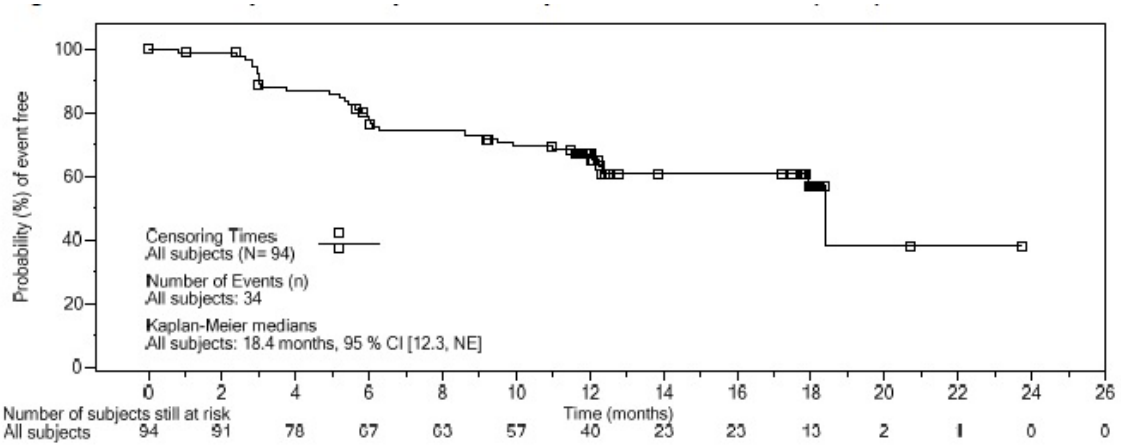
There were 34 PFS events in total (disease progression or death). The estimated progression-free probability was 67.0% (95% CI: 56.0, 75.8) at Month 12 (Table 25). The KM plot for PFS per IRC assessment is presented in Figure 23.

Sixty patients were censored from the analysis for the following reasons: 55 patients were ongoing without an event, 3 patients started new anticancer therapy other than HSCT, 1 patient withdrew their consent, and 1 patient was lost to follow-up

Table 24: PFS per IRC and local investigator assessment (EAS), DCO 29-Mar-2021

	All patients N=94	
	IRC assessment	**Local assessment**
Events/Responders (%)	34/94 (36.2)	34/94 (36.2)
Percentiles (95% CI)[1]		
25th	6.3 (5.3, 12.1)	6.2 (5.7, 12.1)
50th	18.4 (12.3, NE)	18.4 (15.6, NE)
75th	NE (18.4, NE)	NE (18.4, NE)
% Event-free probability estimates (95% CI)[2]		
Month 3	89.0 (80.6, 93.9)	91.2 (83.2, 95.5)
Month 6	77.8 (67.7, 85.1)	78.0 (68.0, 85.2)
Month 9	73.1 (62.6, 81.1)	73.5 (63.1, 81.4)
Month 12	67.0 (56.0, 75.8)	67.6 (56.8, 76.3)
Month 15	61.1 (49.1, 71.1)	64.0 (52.5, 73.3)
Month 18	57.0 (43.2, 68.7)	61.4 (49.3, 71.5)

[1] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
[2] % Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the KM survival estimates; Greenwood's formula is used for CIs of KM estimates.
*From infusion to disease progression/death



Time is relative to onset of response, 1 month=30.4375 days.

Figure 23: Kaplan-Meier plot of PFS per IRC assessment (EAS), DCO 29-Mar-2021

The estimated PFS for patients achieving CR was 85.5% at Month 12 vs 25.7% for patients achieving PR as BOR; the median PFS for patients achieving PR was 6.0 months (Figure 24). These results demonstrate that CR translates also into prolonged PFS, when compared with PFS of patients achieving PR as BOR.

PFS results as assessed by local Investigator were consistent with IRC assessment. PFS in the Enrolled set were consistent with the EAS; however, in the Enrolled set, the median PFS per IRC was not reached.

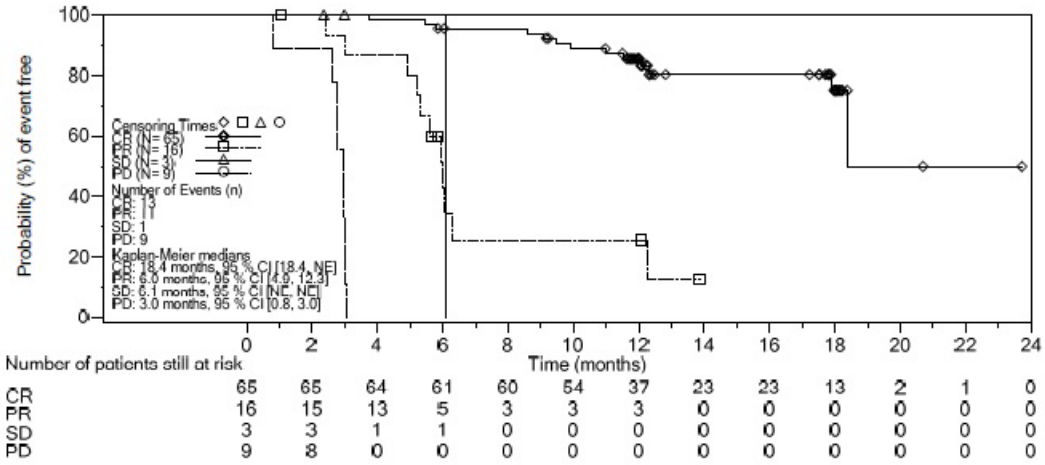


Figure 24: Kaplan-Meier plot for PFS per IRC assessment by BOR (EAS), DCO 29-Mar-2021

During the procedure, data from a subsequent DCO (03-Aug-2021) was provided. 12-month PFS remained unchanged from the Mar-29-2021 DCO. Median PFS increased from 18.4 months to 29.5 months at this later DCO, although a low number of patients remained at risk after month 25. For further details, see the ancillary analyses section.

OS

The median OS was not reached at the time of the 29-Mar-2021 DCO. Seven deaths had occurred in the study (Table 26). (See section on Safety)

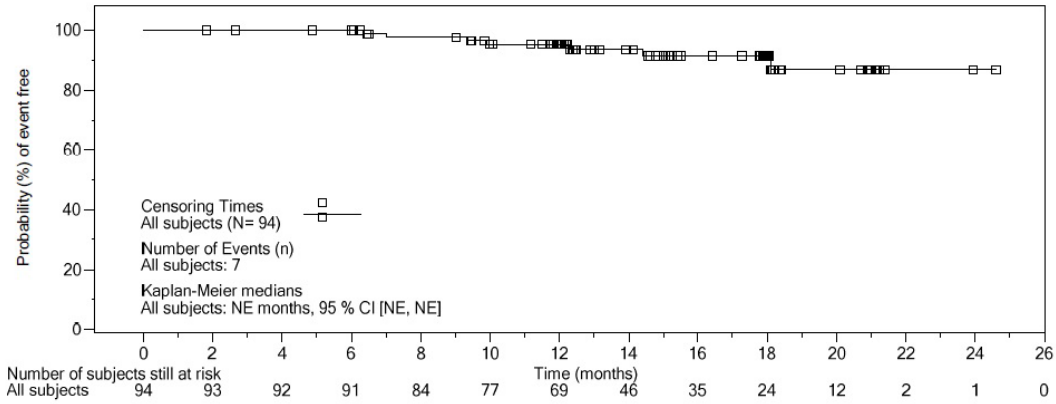
In the EAS, the estimated probability of survival was 95.3% (95% CI: 88.0, 98.2) at Month 12 and 91.6% (95% CI: 81.7, 96.2) at Month 18 (Table 26).

Table 25: Overall survival – Study E2202 (EAS), DCO 29-Mar-2021

	EAS N=94
Events/Responders (%)	7/94 (7.4)
Percentiles (95% CI)[1]	
25th	NE (18.1, NE)
50th	NE
75th	NE
% Event-free probability estimates (95% CI)[2]	
Month 3	100 (100, 100)
Month 6	100 (100, 100)
Month 9	97.7 (91.1, 99.4)
Month 12	95.3 (88.0, 98.2)
Month 15	91.6 (81.7, 96.2)
Month 18	91.6 (81.7, 96.2)

[1] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
[2] % Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.

The KM plot for OS is presented in Figure 25.



Time is relative to tisagenlecleucel infusion, 1 month=30.4375 days.

Figure 25: Kaplan-Meier plot of OS – Study E2202 (EAS), DCO 29-Mar-2021

Overall survival was also analyzed in the Enrolled set (from enrollment), the Tisagenlecleucel infused set, and the mEAS, all of which yielded similar results.

During the procedure, data from a subsequent DCO (03-Aug-2021) was provided. In the EAS, 12-month OS remained unchanged compared to the previous DCO. Please see ancillary analyses section.

Summary of primary and secondary endpoints for the mEAS.

The mEAS comprised of the first 90 consecutively infused patients who received tisagenlecleucel and had measurable disease at baseline per IRC. These 90 patients were followed for 12 months after infusion or have discontinued earlier. Efficacy analyses are additionally provided on the mEAS. The demographics and baseline disease characteristics of the population in the mEAS were consistent with the EAS and Enrolled set.

In summary:

- CR per IRC in the mEAS was 68.9% (62 patients: 95% CI: 58.3, 78.2). There were 15 patients (16.7%) who achieved PR as best response.
- ORR per IRC was 85.6% (77 patients) (95% CI: 76.6, 92.1).
- Median DOR was not reached. The estimated event-free probability among responders per IRC was 76.4% (95% CI: 64.7, 84.6) at Month 9.
- Median PFS per IRC was 18.4 months (95% CI: 12.3, NE); however, this should be interpreted with caution since there were limited numbers of patients remaining at risk after Month 18. The estimated event-free probability was 68.0% (95% CI: 56.8, 76.8) at Month 12.
- Median OS was not reached at the time of the data cut-off. The estimated probability of survival was 96.4% (95% CI: 89.1, 98.8) at Month 12 and 92.6% (95% CI: 82.6, 96.9) at Month 18.

Treatment post tisagenlecleucel

Seventeen patients (17.5%) in the Tisagenlecleucel infused set received at least one new antineoplastic medication post-tisagenlecleucel infusion, mostly due to stable disease or progressive disease.

The majority of the patients (n=14) received antineoplastic and immunomodulating agents like lenalidomide (n=9), rituximab (n=8), idelalisib (n=4) and etoposide (n=3). In three patients, corticosteroids were administered.

Two patients (2.1%) received allogeneic HSCT.

The effect of tisagenlecleucel therapy on patient reported outcomes (PRO)

The results of patient report outcomes (PRO) were assessed in the EAS to further evaluate the impact of tisagenlecleucel on patients' health-related quality of life (QoL). The results in this section summarize the PRO results from the patients who completed the PRO assessment from the FAS (tisagenlecleucel infused population (n=97).

Three questionnaires were used in this study to capture patient reported outcomes (PROs) at Screening, and months 3, 6, 9,1 2, 18, 24 and the end of study for each patient. These were SF-36 version 2, FACT-Lym and EQ-5D-3L. For patients who relapse or progress, assessments of patient-reported outcomes (SF-36 version 2; EQ-5D-3L; FACT-Lym) were continued for the subsequent two visits. PRO data was collected by electronic devices (i.e. tablet) and the questionnaires were administered by the patient themselves.

FACT-Lym, SF-36v2 and EQ-5D-3L questionnaires:

The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) is a questionnaire to assess the quality of life in patients with Lymphoma. It consists of a general quality of life questionnaire (FACT-G) and a condition specific module called Lym. The FACT-Lym is QOL questionnaire which is validated in patients with lymphoma. It includes a module which assesses specific concerns of patients with lymphoma. The FACT-G has 27 items that patients are asked to respond to on a Likert-scale by choosing one of five standardised response options, (not at all, a little, somewhat, quite a bit, very much). The general module consists of five domains (Physical Well-Being, Social/Family Well- Being, Emotional Well-Being, Functional Well-Being and Additional Concerns). The Lym module consists of 15 items that patients are asked to respond to on the same five-point Likert-scale.

The Short Form Health Survey (SF-36) is a widely used and extensively studied questionnaire to measure health-related quality of life among healthy patients and patients with acute and chronic conditions. It consists of eight domains that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role- Emotional, and Mental Health. Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) can also be computed.

The EQ-5D-3L is a widely used, self-administered questionnaire designed to assess health status in adults. The questionnaire is divided into two distinct sections. The first section is a questionnaire that assesses five dimensions, by one item each (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). The patients respond to each of these items by choosing one of the following response options "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension.

The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale (VAS) where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum.

The minimal clinically important difference (MID) is defined as the smallest difference in quality of life (QoL) that patients perceive as beneficial and that mandates a change in management.

Minimally clinically important differences (MID) ranged from 5.5 to 11 for the FACT-Lym TOI, 6.5 to 11.2 for the FACT-Lym total score, 3 to 7 for FACT-G, and 2.9-5.4 for FACT-Lym-S.

For the SF-36, MIDs were 3 for both PCS (physical component score) and MCS (mental component score).

The FACT Lym scores showed improvement in QoL over time in the majority of patients post-tisagenlecleucel infusion. Similar results were observed for the SF-36 questionnaire results (Figure 26).

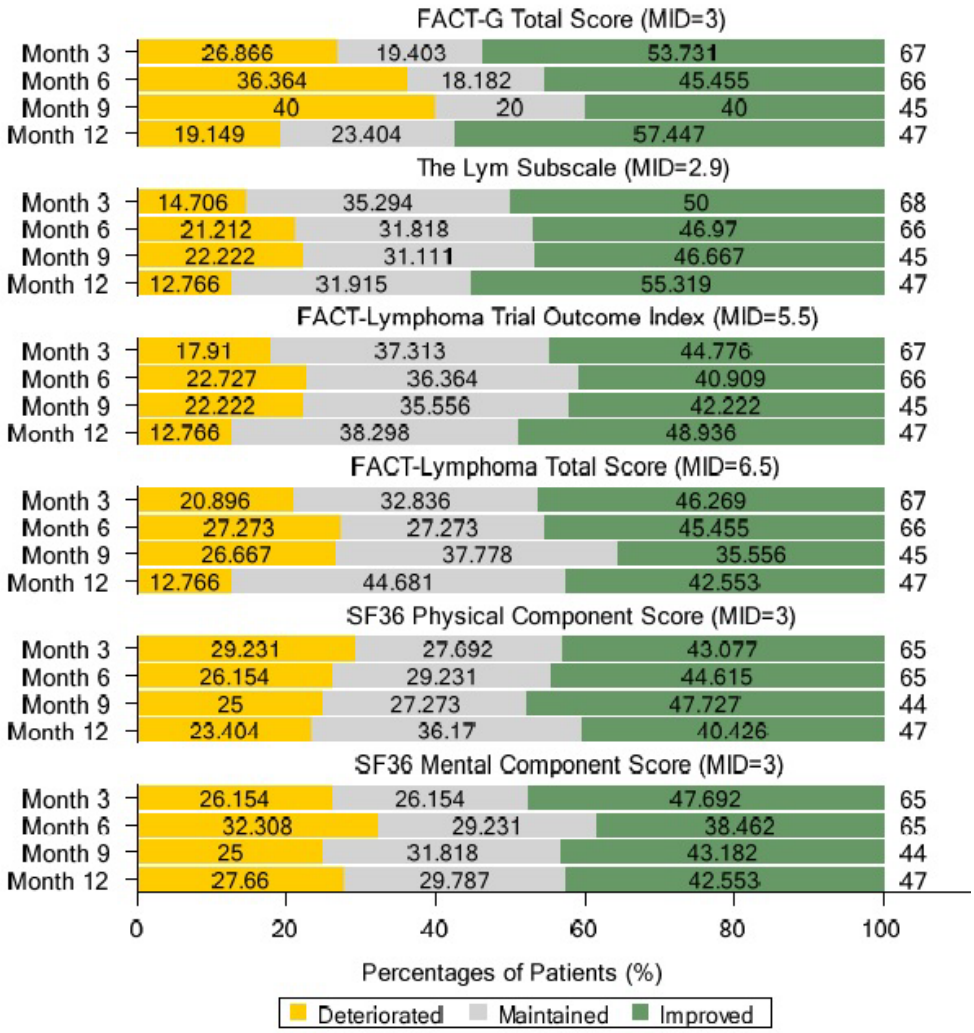


Figure 26: Proportion of subjects who deteriorated, improved, or with no change for FACT lymphoma and SF-36 questionnaires by time point – Study E2203 (EAS).

The Y-axis on the right panel indicates the number of patients.

EQ-5D-3L questionnaire

At Month 12, the EQ-5D-3L scores were similar to Baseline, with no evidence of deterioration (Figure 27).

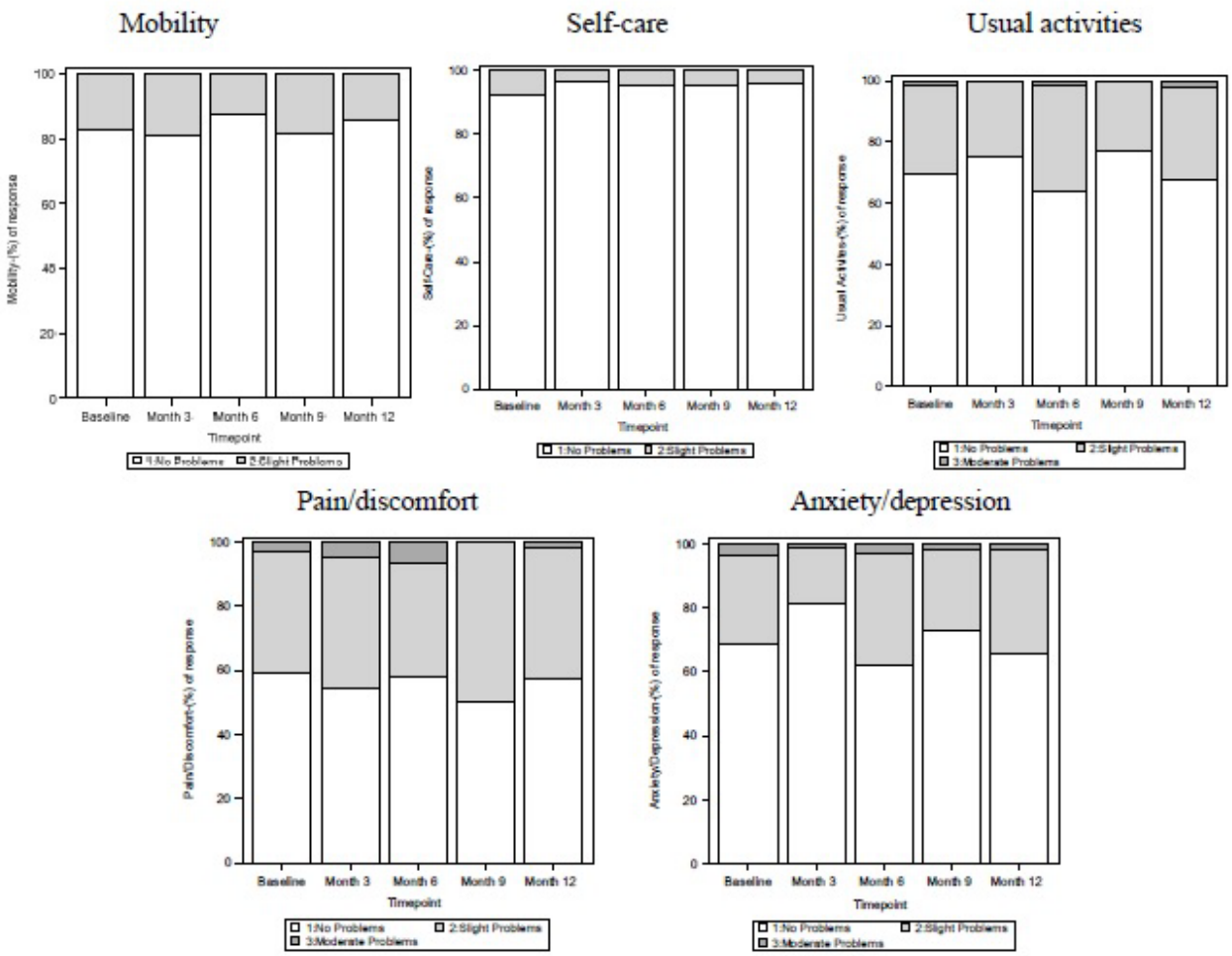


Figure 27: Distribution of response by dimension and timepoint for EQ-5D-3L questionnaire – study E2202 (EAS)

Baseline = the most current assessment on or prior to the date of enrolment.
The percentages are based on number of patients with non-missing value for that dimension at the corresponding time point.

The mean EQ-VAS score (visual analog scale) was 69.4 at baseline, which increased to 72.9 at Month 6, and 75.3 at Month 12, indicating an overall improvement in health-related QoL after tisagenlecleucel infusion (Table 27).

Table 26: EQ-VAS score and change from baseline by visit (EAS)

Time point	Statistics	EQ-VAS score	Change from baseline
Baseline	n	76	-
	Mean	69.4	-
	SD	20.97	-
	Median (min – max)	74.5 (10.0 – 100.0)	-
Month 3	n	64	60
	Mean	75.5	3.4
	SD	20.41	23.70
	Median (min – max)	80.0 (8 – 100)	5.5 (-83 – 69)
Month 6	n	62	57
	Mean	72.9	3.3
	SD	19.75	18.43
	Median (min – max)	74.5 (21 – 100)	3.0 (-60.0 – 50.0)
Month 9	n	44	39
	Mean	76.4	6.1
	SD	14.30	14.72
	Median (min – max)	80.0 (30 – 100)	2.0 (-20 - 44)
Month 12	n	47	41
	Mean	75.3	6.3
	SD	19.04	13.81
	Median (min – max)	80.0 (19 – 100)	6.0 (-29 – 50)
Month 18	n	19	18
	Mean	79.7	8.2
	SD	18.39	15.04
	Median (min – max)	83.0 (38 – 100)	8.0 (-15 – 58)

Ancillary analyses

Updated Efficacy Results in E2202 (DCO 03-Aug-2021):

Further efficacy data from a subsequent DCO of 03-Aug-2021, corresponding to additional 4 months of median follow-up (median follow up: 21 months in the EAS, range: 14-30), were submitted during the procedure.

No new responders and no new conversions from PR to CR were observed with longer follow-up. Therefore, CRR and ORR remain unchanged with the DCO of 03-Aug-2021 for the EAS, infused set and enrolled set. CRR and ORR by local assessment were consistent with the IRC assessment (Table 28, Table 29: CRR for EAS, infused set and enrolled set at the DCO of 29-Mar-2021 and 03-Aug-2021.Table 29).

Table 27: ORR for EAS, infused set and enrolled set at the DCO of 29-Mar-2021 and 03-Aug-2021.

	IRC Assessment n(%) 95% CI	Local Assessment n(%) 95% CI
ORR (CR+PR) **DCO 03-Aug-2021**		
Efficacy Analysis set (EAS) (n=94)	81(86.2%) (75.5, 92.4)	85(90.4%) (82.6, 95.5)
Infused set (n=97)	84 (86.6%) (78.2, 92.7)	88(90.7%) (83.1, 95.7)
Enrolled set (n=98)	84(85.7%) (78.2, 92.7)	88(89.8%) (83.1, 95.7)

ORR (CR+PR) **DCO 29-Mar-2021**		
Efficacy Analysis set (EAS) (n=94)	81 (86.2%) (77.5,92.4).	85 (90.4%) (82.6, 95.5)
Infused set (n=97)	84 (86.6%) (78.2, 92.7)	88(90.7%) (83.1, 95.7)
Enrolled set (n=98)	84(85.7%) (77.2, 92.0)	88(89.8%) (82.9, 95.0)

Table 28: CRR for EAS, infused set and enrolled set at the DCO of 29-Mar-2021 and 03-Aug-2021.

	IRC Assessment n(%) 95% CI	Local Assessment n(%) 95% CI
CRR **DCO 03-Aug-2021**		
Efficacy Analysis set (EAS) (n=94)	65 (69.1%) (58.8, 78.3)	68 (72.3%) (62.2, 81.1)
Infused set (n=97)	67 (69.1%) (58.9, 78.1)	70 (72.2%) (62.1, 80.8)
Enrolled set (n=98)	67(68.4%) (58.2, 77.4)	70(71.4%) (61.4, 80.1)
CRR **DCO 29-Mar-2021**		
Efficacy Analysis set (EAS) (n=94)	65(69.1%) (58.8, 78.3)	68(72.3%) (62.2, 81.1)
Infused set (n=97)	67 (69.1%) (58.9, 78.1)	70 (72.2%) (62.1, 80.8)
Enrolled set (n=98)	67(68.4%) (58.9, 78.1)	70 (71.4%) (62.1, 80.8)

In terms of time-to-event endpoints, the data from the DCO of 03-Aug-2021 was similar to that from the 29-Mar-2021 DCO (Table 30). In the EAS, 9-month DOR, 12-month PFS and OS remained unchanged from the previous DCO. Median PFS increased from 18.4 months to 29.5 months, with the caveat of a low number of patients at risk after month 25.

Table 29: Summary of time-to-event efficacy endpoints at 17 and 21 months of median follow-up (Enrolled set and EAS)

	Date cut-off 29-Mar-2021 Median follow up 17 months for EAS		Date cut-off 03-Aug-2021 Median follow up 21 months for EAS		
	DOR				
	No of events/responders	% 9 month DOR	No of events/responders	% 9 month DOR	%12 month DOR
EAS (N =94)	22/81	76	24/81	76	73
	PFS				
	No of events	% 12 month PFS	No of events	% 12 month PFS	% 15 month PFS
Enrolled set (N=98)	35	72	38	72	63
EAS (N =94)	34	67	37	67	63
	OS				
	No of events	% 12 month OS	No of events	% 12 month OS	% 15 month OS
Enrolled set (N=98)	7	96.7	10	96.7	94.4
EAS (N =94)	7	95.3	10	95.4	93.0

Sources: Study E2202 CSR -Table 14.2-2.1, Table 14.2-3.1, Table 14.2-3.2, Table 14.2-4.3, [D120-Table 14.2-3.4], [EMA_Table 2-3.4], [EMA_Table 2-4.4], [D120-Table 14.2-4.2], [D120-Table 14.2-2.1]

DOR was defined as time from achievement of CR or PR to relapse or death due to FL, whichever occurs first.

PFS was defined as the time from the date of first tisagenlecleucel infusion to the date of event defined as the first documented progression or death due to any cause for EAS (N=94) and time from date of enrolment to the date of event defined as the first documented progression or death due to any cause for enrolled set (N=98).

OS was defined as the time from date of first tisagenlecleucel infusion to date of death due to any reason for EAS (N=94) and time from date of enrolment to the date of death due to any cause for enrolled set (N=98).

Table 30: DOR in EAS for patients with BOR of CR or PR (DCO: 03-Aug-2021)

	All Subjects N=94	
	Local assessment	**IRC assessment**
Events/Responders (%)	26/85 (30.6)	24/81 (29.6)
Maximum follow-up (months)	22.0	22.0
Median follow-up (months)	14.23	14.23
Percentiles (95% CI) [1]		
25th	9.1 (3.5, 15.6)	9.1 (3.7, 20.9)
50th	NE (15.6, NE)	NE (15.6, NE)
75th	NE	NE
% Event-free probability estimates (95% CI) [2]		
Month 3	91.4 (82.9, 95.8)	91.1 (82.2, 95.7)
Month 6	80.2 (69.7, 87.4)	81.9 (71.3, 88.8)
Month 9	76.1 (65.1, 84.0)	76.2 (64.9, 84.3)
Month 12	73.2 (61.9, 81.7)	73.1 (61.3, 81.8)
Month 15	71.5 (59.9, 80.3)	71.0 (58.8, 80.2)
Month 18	62.2 (47.6, 73.8)	64.2 (49.5, 75.7)
Month 21	57.0 (40.1, 70.8)	58.4 (40.6, 72.5)
Month 24	NE	NE

1 Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
2 % Event-free probability estimate is the estimated probability that a subject will remain event-free up to the specified time point.
% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.

Table 31: PFS for patients with BOR of CR, PR, SD, PD or unknown, in EAS (DCO: 03-Aug-2021)

	All subjects N=94	
	Local assessment	IRC assessment
Event/Responders	37/94 (39.4)	37/94 (39.4)
Maximum follow-up	29.5	29.5
Median follow-up	12.32	12.16
Percentiles (95% CI)[1]		
25%	8.6 (5.7, 12.3)	6.3 (5.3, 12.1)
50%	29.5 (18.0, NE)	29.5 (17.9, NE)
75%	29.5 (NE, NE)	29.5 (NE, NE)
% Event-free probability estimates (95% CI)[2]		
Month 3	91.2 (83.1, 95.5)	89.0 (80.5, 93.9)
Month 6	78.9 (69.0, 86.0)	77.6 (67.5, 84.9)
Month 9	74.4 (64.0, 82.2)	72.9 (62.4, 81.0)
Month 12	68.6 (57.8, 77.1)	67.0 (56.1, 75.8)
Month 15	64.6 (53.5, 73.7)	62.8 (51.5, 72.1)
Month 18	63.1 (51.9, 72.4)	58.7 (46.7, 68.8)
Month 21	54.6 (41.1, 66.3)	55.2 (42.1, 66.5)
Month 24	50.1 (35.0, 63.4)	50.2 (34.9, 63.7)

[1] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
[2] % Event-free probability estimate is the estimated probability that a subject will remain event-free up to the speci
% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates;
Greenwood formula is used for CIs of KM estimates.

Table 32: Overall Survival (OS) in EAS (DCO: 03-Aug-2021)

	All Subjects N=94
Events/Total (%)	10/ 94 (10.6)
Maximum follow-up (months)	29.5
Median follow-up (months)	18.00
Percentiles (95% CI) [1]	
25th	29.5 (23.7, NE)
50th	29.5 (NE, NE)
75th	29.5 (NE, NE)
% Event-free probability estimates (95% CI) [2]	
Month 3	100 (100 , 100)
Month 6	100 (100 , 100)
Month 9	97.7 (91.2, 99.4)
Month 12	95.4 (88.2, 98.2)
Month 15	93.0 (85.0, 96.8)
Month 18	93.0 (85.0, 96.8)
Month 21	88.4 (77.3, 94.3)
Month 24	84.0 (68.4, 92.3)
Month 27	84.0 (68.4, 92.3)
Month 30	0.0 (NE, NE)

1 Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
2 % Event-free probability estimate is the estimated probability that a subject will remain event-free up to the specified time point.
% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.

In the Enrolled set (N=98), the 12 months PFS estimate increased by 1% between the Mar-29-2021 DCO and 03-Aug-DCO. In the infused set (N=97), 9 month DOR, 12 months PFS and OS estimates at the 03-Aug-2021 DCO remained similar to the EAS.

Real world data:

To contextualise the findings presented in the pivotal clinical study E2202, the MAH carried out two analyses of real-world data, ReCORD and Flatiron in addition to a systematic literature review.

ReCORD

The non-interventional retrospective cohort study of treatment outcomes among adult patients with refractory or relapsed FL (ReCORD-FL) based on current standard of care, aimed to provide patient-level data for an indirect comparison with the single-arm tisagenlecleucel E2202 clinical trial. ReCORD (*A Retrospective Cohort Study of Treatment Outcomes Among Adult Patients with Refractory or Relapsed Follicular Lymphoma).* ReCORD included patient level data from centres in Europe and North America where 70% of the centres also participated in study E2202.

Methods:

ReCORD is a retrospective medical record review in a cohort of patients from multiple centers in Europe and North America. To obtain an adequate sample size and to include patients treated with different regimens reflecting evolving management strategies in clinical practice over the years (e.g., chemo-immunotherapy and PI3K inhibitors), data was collected from patients with r/r FL treated between 1998 and 2020. No initial diagnoses of FL before January 1, 1998 were permitted as a key treatment in the FL landscape, rituximab, was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 1997 and 1998, respectively, for r/r FL. Based on the study design, patients diagnosed and managed before the availability of rituximab were excluded.

Patient-level data was abstracted and provided by physicians or their designated clinical staff from Europe and North America (10 sites across France, Germany, Spain, UK, Canada and USA), who have been/are treating patients with FL and have agreed to participate in the ReCORD study.

Wherever feasible, the ReCORD study adopted the same inclusion and exclusion (I/E) criteria as study E2202. The index date must have occurred during the period between January 1, 2000 and December 31, 2018; initial FL diagnosis must have occurred before the index date but not earlier than January 1, 1998. Patients could be living or deceased at the time of record abstraction.

Statistical Methods

A model for the propensity score, the probability of enrollment into the E2202 study conditional on observed baseline covariates, was estimated using a Generalized Estimating Equation (GEE) approach to fitting a logistic regression to the outcome data, employing a robust sandwich variance estimator to account for the correlation between repeated observations on the same patient. This was done since each patient may be eligible for inclusion at the start of more than one line of therapy and contribute multiple correlated observations. The fitted logistic regression was be used to derive a point estimate of the propensity score (PS) for each patient in ReCORD at each eligible line of therapy. The potential confounders that were considered for inclusion in the PS-model at each line of therapy were:

- Age at treatment initiation
- Region (Europe or North America)
- Gender
- History of autologous stem cell transplant
- Number of previous lines of systemic treatment
- Group stage at initial FL diagnosis
- Number of months between initial FL diagnosis and initiation of index treatment
- Sites of nodal involvement at treatment initiation
- Refractory to systemic therapies
- Progression of disease within 24 months (POD24) of initiation of first line of treatment

For each patient the eligible line of therapy (LoT) associated with the highest PS was to be selected, and the PS model recalculated based on this using a logististic regression adjusting for the above variables to balance the baseline covariates across the two cohorts. A PS was then to be estimated for each patient in the ReCORD study, an estimate of their probability of being included in the E2202 study given their baseline covariates at the selected LoT. A complete case analysis that only includes observations without missing data on the prognostic factors as listed above was to be conducted as a sensitivity analysis to address the potential issue of missing data. A conservative 'worst-case' scenario might also be considered according to the analysis plan.

Estimates of the causal treatment effect of interest, outcomes across groups were to be compared using weighting by odds approach to adjust for potential confounding. This method allowed for the use of all patients' data from ReCORD and study E2202. The method maintains the composition of patients

in the study E2202 (assigning each patient a weight of 1), while patients in ReCORD were assigned weights by the odds of being in the trial cohort, $\widehat{PS}/(1-\widehat{PS})$, to reflect the trial population characteristics. To assess covariate balance, the distributions of baseline covariates pre- and post-weighting was to be summarized, standardized mean differences (SMD) reported, and an SMD value of <.25 for all the covariates listed was to be considered as balanced. If an imbalance was detected additional analyses, such as using trimming or weight truncation, was planned to be mitigate the impact of patients with extreme weights on the variability of the treatment effect estimates.

All time-to-event endpoints was to be evaluated from the start of enrollment in E2202 study and from the start date of SOC in ReCORD which was expected to be an adequate approximation of the date of prescription. The distribution of each time-to-event endpoint was to be estimated using a weighted Kaplan-Meier estimator, and a weighted Cox proportional hazards regression used to estimate the hazard ratio. The median survival, proportion of patients without event and corresponding hazard ratios were to be calculated at certain timepoints (3, 6, 12 months), and the bootstrap 95% confidence intervals provided.

PFS, defined as time to first documented disease progression or death due to any cause, was to be censored, at the date of the starting new anticancer therapy, if the patient did not have disease progression before the start of new anticancer therapy. A sensitivity analysis for PFS considering new anti-cancer therapy as a PFS event was to be performed. However, progression dates were not available for many patients in ReCORD, so the comparison analysis of PFS was performed by considering new anticancer therapy as an event for patients in both ReCORD and Study E2202.

TTNT, defined as time to the start of a new anti-lymphoma treatment (including HSCT) or death due to any cause, was to be censored on the last contact date, if the patient did not experience the event.

The weighted proportion of patients who achieved complete response and any response (partial response or complete response) before disease progression or start of new anticancer therapy, whichever comes first, was to be evaluated, differences in proportions summarized, and 95% confidence intervals was to be calculated using bootstrapping. Patients with unknown clinical response was to be treated as non-responders.

A subgroup analysis of patients with a selected LoT with treatment initiation date in or after 2014 (coinciding with the introduction of the Lugano criteria as well as the EMA approval of idelalisib) was to be performed.

A comparison of baseline variables between ReCORD patients (at their selected LoT) and Study E2202 patients before and after ReCORD patients are weighted by their odds of being in Study E2202 are shown in

Table **34**. Standardized mean differences between the two cohorts were assessed for pre-weighted and post-weighted data. Success of the weighting process was evaluated based on the SMD; an absolute SMD of <25% for a particular variable was considered balanced [Study E2202 versus ReCORD RWE report-Section 6.3].

Imbalances between Study E2202 and the pre-weighted ReCORD dataset in selected LoT have been reduced by weighting. Since all of the important baseline prognostic variables achieved balance using the criterion of absolute SMDs < 25%, the weighting by odds analysis appears to be reasonable to adjust for imbalances of measured baseline variables between groups.

Table 33: Baseline characteristics for ReCORD and E2202 before and after weighting at selected LoT

		Before weighting		After weighting	
Baseline variable Statistics	Study E2202 N=97	ReCORD N=143	|SMD|	ReCORD N=99[a]	|SMD|
Prognostic factors included in PS modeling					
Age at treatment initiation (years)					
n	97	143	0.326	99	0.038
Mean(SD)	56.5 (10.40)	60.1 (11.72)		56.1 (11.52)	
Median	58	60		56.3	
Min-Max	29-73	25-86		25-86	
Age at treatment initiation category – n (%)					
<65 years	73 (75.3)	89 (62.2)	0.284	76 (76.7)	0.034
≥65 years	24 (24.7)	54 (37.8)	0.284	23 (23.3)	0.034
Gender – n (%)					
Female	33 (34.0)	61 (42.7)	0.178	30.8 (31.1)	0.063
Male	64 (66.0)	82 (57.3)	0.178	68.3 (68.9)	0.063
Region – n (%)					
Europe	44 (45.4)	90 (62.9)	0.358	41.4 (41.8)	0.072
RoW	53 (54.6)	53 (37.1)	0.358	57.6 (58.2)	0.072
Prior Auto-HSCT – n (%)					
Yes	36 (37.1)	53 (37.1)	0.001	36.1 (36.5)	0.013
No	61(62.9)	90 (62.9)	0.001	62.9 (63.5)	0.013
Number of previous lines of systemic treatment					
n	97	143	0.117	99	0.104
Mean (SD)	3.9 (1.78)	3.7 (2.05)		4.1 (2.25)	
Median	4	3		4	
Min-Max	2-13	2-10		2-10	
Number of previous lines of systemic treatment N (%)					
2-4	69 (71.1)	110 (76.9)	0.132	69.9 (70.6)	0.011
>4	28 (28.9)	33 (23.1)	0.132	29.1 (29.4)	0.011
Disease stage at initial FL diagnosis –n (%)					
Stage I	6 (6.2)	10 (7.0)	0.033	4.7 (4.7)	0.064
Stage II	13 (13.4)	13 (9.1)	0.137	9.5 (9.6)	0.12
Stage III	21 (21.6)	26 (18.2)	0.087	25.4 (25.7)	0.095
Stage IV	57 (58.8)	94 (65.7)	0.144	59.4 (60.0)	0.026
Months between initial FL diagnosis and initiation of treatment					
n	98	143	0.099	99	0.005
Mean (SD)	77.3 (56.33)	72.1 (48.53)		77.1 (49.21)	
Median	66.2	61.7		69.7	
Min-Max	6.4-355.4	2.8-255		2.8-255	
Number of nodal involvement at treatment initiation –n (%)					
≤4	39 (40.2)	74 (51.7)	0.233	38.1 (38.5)	0.035
>4	58 (59.8)	69 (48.3)	0.233	60.9 (61.5)	0.035
Double refractory–n (%)					
Yes	66 (68.0)	97 (67.8)	0.004	67.8 (68.5)	0.01
No	31 (32.0)	46 (32.2)	0.004	31.2 (31.5)	0.01
POD24– n (%)					
Yes	61 (62.9)	86 (60.1)	0.056	62.7 (63.3)	0.009
No	36 (37.1)	57(39.9)	0.056	36.3 (36.7)	0.009
Other baseline characteristics not included in PS modeling					
Refractory status to last prior therapy–n (%)					
Yes	75 (77.3)	112 (78.3)	0.024	79.2 (80.0)	0.066
No	21 (21.6)	31 (21.7)	0.001	19.8 (20.0)	0.041
Missing	1 (1.0)	0	0.144	0	0.144
FLIPI-n (%)					
High	59 (60.8)	80 (55.9)	0.099	56.6 (57.2)	0.074
Intermediate	20 (20.6)	21 (14.7)	0.156	14.3 (14.5)	0.162
Low	18 (18.6)	15 (10.5)	0.23	9.7 (9.8)	0.252
Missing	0	27 (18.9)	0.682	18.3 (18.5)	0.673

SMD: standard mean difference; FLIPI: Follicular Lymphoma International Prognostic Index
[a]Sample size after weighting (i.e., sum of weights) was 99 for the ReCORD study and effective sample size was 95.

The key question of interest is the effect of prescribing tisagenlecleucel vs. SOC in patients who participated in Study E2202. As a consequence, weight of 1 is assigned to patients in Study E2202 and

the results of Study E2202 do not change after weighting. The changes in ReCORD study results after weighting reflect the adjustment of the population to address the question of interest.

The median study follow-up time (defined as time to death or last follow-up date) was 15 months for Study E2202, and 22 months in the weighted sample for ReCORD (at the selected LoTs). The median survival and corresponding HRs for tisagenlecleucel from Study E2202 compared to standard treatments from ReCORD were calculated for OS, PFS and TTNT (time to start new therapy) based on all patients. The bootstrap 95% confidence intervals were provided. A clinically meaningful and consistent improvement for all endpoints was observed before and after weighting in Study E2202 vs. ReCORD (Table 35).

Table 34: Efficacy comparison of study E2202 and ReCORD before and after weighting

	E2202 Enrolled	Before weighting ReCORD	After weighting ReCORD
Response rate	**N=97**	**N=143**	**N=99[a]**
CR, 95% CI	69.1 (59.8, 78.3)	39.2 (31.1, 47.2)	37.3 (26.4, 48.3)
ORR, 95% CI	85.6 (78.7, 92.5)	68.5 (61.0, 76.1)	63.6 (52.5, 74.7)
Difference in CR, 95% CI		29.9 (17.7, 42.1)	31.8 (18.1, 45.3)
Difference in ORR, 95% CI		17.1 (6.7, 27.4)	22.0 (9.4, 34.5)
OS			
Kaplan-Meier analysis	**N=97**	**N=143**	**N=99**
Events/Total (%)	7/97	39/143	31.3/99
Median, 95% CI (months)	NA	NA	NA
6 months	100 (100,100)	88.4 (83.0, 93.7)	85.6 (77.0, 94.2)
12 months	96.6 (92.9, 100)	75.7 (68.3, 83.0)	71.7 (61.2, 82.2)
18 months	91.4 (84.6, 98.3)	71.5 (63.7, 79.3)	65.8 (54.3, 77.2)
24 months	87.8 (78.0, 97.6)	69.7 (61.8, 77.7)	64.8 (53.3, 76.2)
Cox proportional hazard model			
HR, 95% CI		0.25 (0.03, 0.46)	0.20 (0.02, 0.38)
PFS considering new anti-cancer therapy as event			
Kaplan-Meier analysis	**N=97**	**N=143**	**N=99**
Events/Total (%)	37/97	72/143	54.1/99
Median, 95% CI (months)	NA (18.8, NA)	17.6 (11.2, NA)	13.1 (8.1, NA)
6 months	85.3 (78.3, 92.3)	70.7 (63.1, 78.2)	66.5 (55.6, 77.3)
12 months	70.5 (61.4,79.7)	56.2 (47.9, 64.6)	51.9 (40.6, 63.3)
18 months	60.9 (50.4, 71.4)	48.4 (39.9, 56.9)	44.6 (33.3, 55.9)
24 months	54.1 (41.2, 66.9)	46.7 (38.3, 55.2)	42.2 (31.0, 53.5)
Cox proportional hazard model			
HR, 95% CI		0.69(0.41,0.97)	0.60(0.34, 0.86)
TTNT			
Kaplan-Meier analysis	**N=97**	**N=143**	**N=99**
Events/Total (%)	19/97	68/143	51.3/99
Median, 95% CI (months)	NA (20.1, NA)	20.8 (11.6, NA)	14.4 (9, NA)
6 months	94.7 (90.2, 99.2)	76.2 (69.1, 83.2)	71.5 (60.9, 82.0)
12 months	85.9 (78.8, 92.9)	57.7 (49.4, 66.1)	53.9 (42.5,65.2)
18 months	79.9 (71.1, 88.7)	50.5 (41.9, 59.1)	46.6 (35.2, 58.0)
24 months	68.4 (50.6, 86.2)	48.8 (40.2, 57.4)	44.2 (32.8, 55.6)
Cox proportional hazard model			
HR, 95% CI		0.36 (0.17, 0.55)	0.31 (0.14, 0.49)

OS, PFS and TTNT is measured relative to enrollment date/treatment start date. All Kaplan-Meier and Cox regression results are based on survival data within the first 24 months (patients with survival data beyond 24 months were censored at Month 24).
[a]Sample size after weighting (i.e., sum of weights) was 99 for the ReCORD study and effective sample size was 95.

A subgroup analysis of patients with at least one eligible line of therapy beginning in or after 2014, to coincide with the introduction of the new Lugano response criteria as well as the EMA approval of idelalisib, was conducted. The results from this subset of patients treated in or after 2014 are generally consistent with results observed in the main analysis presented above. As a sensitivity analysis to address the potential issue of missing data in key prognostic factors, a conservative 'worst-case' scenario was conducted. The results suggest a strong benefit of tisagenlecleucel in increasing patients' response rate and in reducing the risk of death, disease progression and taking additional new anti-cancer therapy compared to standard treatments.

Flatiron Health Research Database.

This non-interventional study utilizing electronic health records was conducted to provide comparative, contextual evidence to the existing data on the efficacy of tisagenlecleucel from E2202 based on current standard of care. Patient-level data collected from the US Flatiron Health Research Database (Flatiron), which covers community cancer practices, was analyzed following a pre-specified analysis plan. The study design is shown in Figure 28.

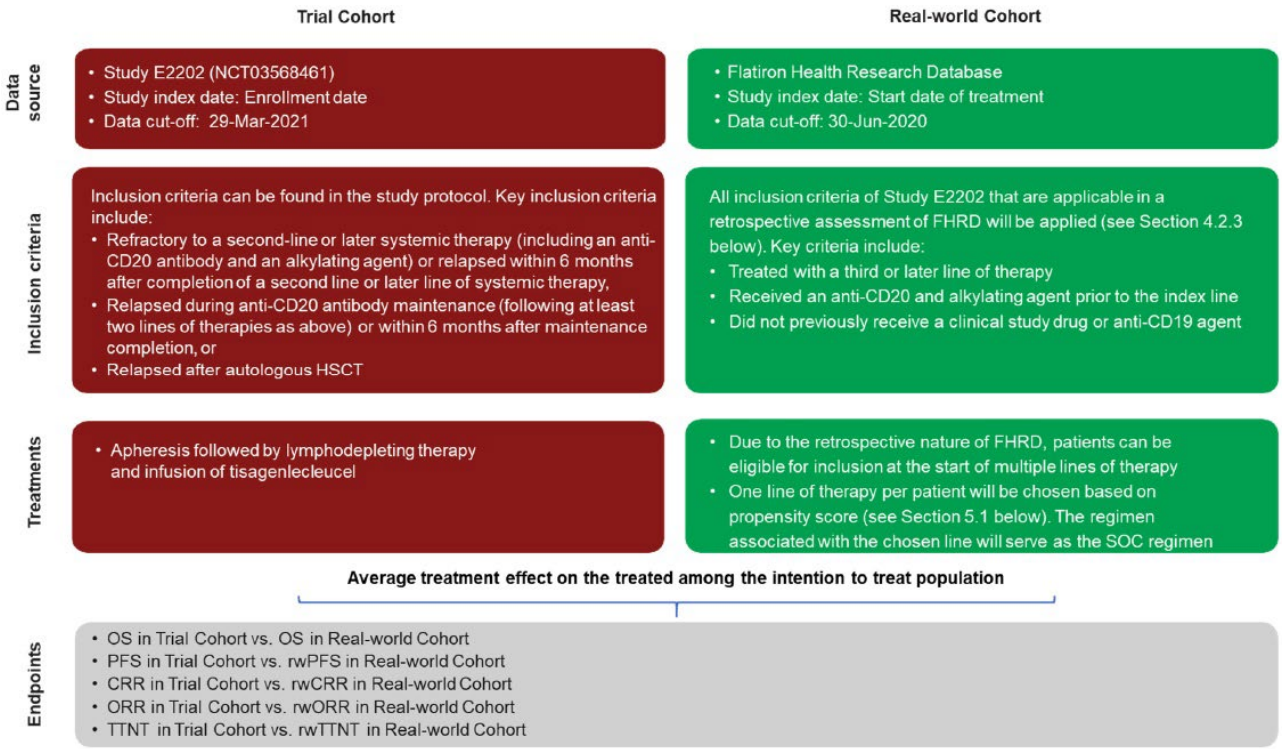


Figure 28: Study design of Flatiron Non-interventional study for comparison with study E2202

Methodology:

Of note, not all Study E2202 inclusion/exclusion criteria were adopted in Flatiron.

Main inclusion criteria:

1. Two or more visits in the Flatiron Health network on or after 01-Jan-2011
2. Diagnosed with Non-Hodgkin's Lymphoma (International Classification of Diseases 9th revision [ICD 9]: 200x, 202x or ICD 10th revision [ICD 10]: C82x, C83x, C84x, C85x, C86x, C88x, C96x), as captured in structured data.
3. Has a diagnosis of FL with an initial diagnosis date on or after Jan 2011

4. Has a tumor grade of I, II, or IIIA, or low grade not otherwise specified at time of initial FL diagnosis
5. Has evidence of medication exposure to at least three lines of systemic therapy for treatment of FL
6. Exposed to an anti-CD20 therapy (rituximab, obinutuzmab, or ofatumamab) after FL diagnosis
7. Exposed to an alkylating agent (cyclophosphamide, carmustine, bendamustine, ifosfamide, carboplatin, oxaliplatin, cisplatin, melphalan, chlorambucil, busulfan, dacarbazine, or procarbazine) after FL diagnosis.
8. Upon applying #6 and #7 above, all lines of therapy after line 2, and after the exposure to an anti-CD20 and alkylating agent for each patient were selected. The start date of each line was considered as the index date. The regimen associated with this line was defined as index regimen. After applying the remaining inclusion and exclusion criteria below, each patient in the Real-world Cohort may have multiple index dates and index regimens.
9. Aged at least 18 years old at index date.
10. ECOG performance status that was either 0 or 1 within 30 days prior to and including index date. For patients with multiple ECOG assessments within this period, the closest assessment to the index date was chosen. Patients with a missing or unknown ECOG status during this period were included in the study. Internal research by Flatiron has revealed that ECOG is more likely to be documented among patients with worse prognosis. As such, it was anticipated that exclusion of patients with missing ECOG status at baseline would result in a biased sample.
11. Index date was on or prior to 31-Mar-2020. Assuming a DCO date of 30-Jun-2020, this criteria allowed for a potential minimum follow-up time of 3 months.
12. Confirmation of index line of therapy via abstraction
13. Predicted to be FL 3L+ according to the machine learning model.
14. Index date was on or after 01-Jan-2014.

Main exclusion criteria (assessed at or before study index date)

1. Evidence of histologic transformation prior to and including index date
2. Evidence of any of the following prior to index date
    - Anti-CD19 therapy administration
    - Gene therapy or adoptive T-cell therapy
    - Allogeneic HSCT
    - Document receipt of clinical study drug
3. Index regimen includes a clinical trial study drug, anti-CD19 therapy, or gene therapy.
4. Evidence of active CNS involvement by malignancy at initial diagnosis or 1L treatment initiation.
    - This criterion was applied as documented by Flatiron in their analytic guide. Because site of involvement was only available at initial diagnosis or 1L treatment initiation, we are unable to apply the criteria in the protocol and briefing book, which is excluding active CNS involvement by malignancy within 30 days prior to index date.
5. Documented tumor grade IIIB at time of initial diagnosis date
6. Evidence of a non-FL primary malignancy with a diagnosis date, treatment date, or first documentation date occurring on or prior to the index line start date.
    - This criterion was applied by Flatiron even though it was listed as one of the infeasible criteria in the briefing book.

Statistical methods

A model for the propensity score, the probability of enrolment into the E2202 study conditional on observed baseline covariates, was estimated using a Generalized Estimating Equation (GEE) approach to fitting a logistic regression to the outcome data, employing a robust sandwich variance estimator to account for the correlation between repeated observations on the same patient. This was done since

each patient may be eligible for inclusion at the start of more than one line of therapy and contribute multiple correlated observations. The fitted logistic regression was to be used to derive a point estimate of the propensity score for each patient in the Flatiron data at each eligible line of therapy. The potential confounders that were considered for inclusion in the propensity score model at each line of therapy were:

- Age at treatment initiation
- Race
- Gender
- History of autologous stem cell transplant
- Number of previous lines of systemic treatment
- Group stage at initial FL diagnosis
- Number of months between initial FL diagnosis and initiation of index treatment
- Sites of nodal involvement at initial diagnosis
- Double refractory to systemic therapies
- Progression of disease within 24 months (POD24) of initiation of first line of treatment

For each patient the eligible LoT associated with the highest propensity score was to be selected, and the propensity score model recalculated based on this using a logististic regression adjusting for the above variables to balance the baseline covariates across the two cohorts. A propensity score was then to be estimated for each patient in the Real-World cohort, an estimate of their probability of being included in the E2202 study given their baseline covariates at the selected LoT.

Estimates of the causal treatment effect of interest, outcomes across groups were to be compared using weighting by odds approach to adjust for potential confounding. This method allowed for the use of all patients' data from the Real-World cohort and study E2202. The method maintains the composition of patients in the study E2202 (assigning each patient a weight of 1), while patients in the Real-world cohort were assigned weights by the odds of being in the trial cohort, $\widehat{PS}/(1-\widehat{PS})$, to reflect the trial population characteristics. To assess covariate balance, the distributions of baseline covariates pre- and post-weighting was to be summarized, standardized mean differences (SMD) reported, and an SMD value of <.25 for all the covariates listed was to be considered as balanced. If an imbalance was detected additional analyses were carried out, specifically first exploring if inclusion of interaction, alternate functional forms, or categorization of variables would sufficiently reduce imbalance. Sensitivity analyses using trimming or weight truncation approaches may be implemented to mitigate the impact of patients with extreme weights on the variability of the treatment effect estimate.

All time-to-event endpoints were to be evaluated from the start of enrollment in E2202 study and from the start date of SOC in Flatirion which was expected to be an adequate approximation of the date of prescription. The evaluation was to include all patients that satisfy inclusion/exclusion criteria. The distribution of each time-to-event endpoint was to be estimated using a weighted Kaplan-Meier estimator, and a weighted Cox proportionalhazards regression used to estimate the hazard ratio. The median survival, proportion of patients without event and corresponding hazard ratios were to be calculated at certain timepoints (3, 6, 12 mth), and the bootstrap 95% confidence intervals provided. The proportionality assumption was to be examined by Schoenfeld residuals and visual inspection of a plot of the log cumulative hazard curves by log of time.

OS, defined as time to death due to any cause, with the death date being the event date. If a death had not been observed, then OS was censored at the patient's last activity date.

PFS, defined as time to first documented disease progression or death due to any cause, was to be censored, at the date of the starting new anticancer therapy, if the patient did not have disease progression before the start of new anticancer therapy.

TTNT, defined as time to the start of a new line of therapy (including HSCT) or death due to any cause, whichever occurred earlier, was to be censored on the last contact date, if the patient did not experience the event.

For CRR and Over All Response Rate All enrolled patients in the Trial Cohort were to be considered. As some patients in the Real-world Cohort may not have had any response evaluations during treatment, patients from this Cohort with at least one evaluation for response or a documented death during treatment were to be considered for the analysis. Weighting by odds was to be carried out to balance on baseline characteristics, and proportions and differences in proportions and 95% bootstrapping confidence intervals calculated. Patients in the Trial Cohort who discontinued (death or due to other reasons) Study E2202 prior to infusion tisagenlecleucel were to be considered as non-responders.

Several sensitivity analyses were planned, including ones aimed at examining the impact of missing data. A presentation of patient characteristics by missingness of ECOG status in the Realworld cohort to examine if there were meaningful difference between patients with and without ECOG status was to be performed.

A within-patient analysis comparing time to progression (TTP) on the last prior therapy to the PFS on experimental therapy was to be conducted for both the Trial Cohort and the Real-world Cohort. The experimental therapy refers to tisagenlecleucel for the Trial Cohort and the selected LoT for the Real-world Cohort.

A complete case analysis including only patients with complete data for the covariates considered for balancing was planned as a sensitivity analysis, and additionally a conservative 'worst-case' scenario was to be considered.

For PFS, a sensitivity analysis considering new anti-cancer therapy as a PFS event was to be performed.

Results:

A comparison of baseline variables between Flatiron patients and Study E2202 patients before and after Flatiron patients are weighted by their odds of being in Study E2202 are shown in Table 19. Standardized mean differences between the two cohorts were assessed for preweighted and post-weighted data. Success of the weighting process was evaluated based on the SMD; an absolute SMD value of <25% for a particular variable was considered balanced.

History of autologous HSCT and sites of nodal involvement at initial diagnosis were removed from the propensity score model due to extreme imbalance (standardized mean difference: 0.98 and 0.70, respectively) before weighting in order to achieve better overall balance for all other remaining variables. This was considered acceptable as more patients with history of autologous HSCT and nodal sites are present in Study E2202, i.e., not adjusting for these variables can be considered as conservative. The large imbalances between Study E2202 and the pre-weighted Flatiron dataset were greatly reduced by weighting (

Table **36**); excellent balance was achieved with regards to important prognostic factors between Flatiron and Study E2202. Since the majority of the SMDs are < 25%, the weighting by odds analysis appears to be reasonable to adjust for imbalances of measured baseline covariates between groups.

Table 35: Baseline characteristics for Flatiron and Study E2202 before and after weighting

Baseline variable Statistics	Study E2202[1] n=97	Before Weighting[2] Flatiron n=98	SMD	After Weighting[2] Flatiron n=88[5]	SMD
Included in Propensity Score Modeling					
Age at treatment initiation category (years)					
Mean (SD)	56.49 (10.40)	62.69 (12.56)	-0.54	54.49 (11.88)	0.17
Median (q1-q3)	58 (49.00-64.00)	63.5 (55.00-72.00)		55 (48.00-60.00)	
Min-Max	29-73	30-85		30-85	
Gender - n (%)					
Female	33 (34.0%)	45 (45.9)	-0.24	25.1 (28.5)	0.11
Male	64 (66.0%)	53 (54.1)	0.24	62.9 (71.5)	-0.11
Race - n (%)					
White	73 (75.3)	71 (72.5)	0.06	58.6 (66.6)	0.20
Non-White	24 (24.7)	27 (27.6)	-0.06	29.4 (33.4)	-0.20
Number of previous lines of systemic treatment - n (%)					
≤4	69 (71.1)	92 (93.9)	-0.62	64.3 (73.0)	-0.05
>4	28 (28.9)	6 (6.1)	0.62	23.7 (27.0)	0.05
Stage at initial FL diagnosis – n (%)					
Stage ≤II	19 (19.6)	19 (19.4)	0.01	12 (13.7)	0.15
Stage ≥III	78 (80.4)	79 (80.6)	-0.01	76 (86.3)	-0.15
Duration between initial diagnosis and index date, months					
Mean (SD)	77.29 (56.33)	43.15 (23.90)	0.79	61.23 (29.31)	0.37
Median (q1-q3)	66.2 (36.20-106.60)	41.07 (24.44-60.35)		67.48 (39.13-77.80)	
Min-Max	6.4-355.4	2.83-100.30		2.83-100.30	
Double Refractory					

Yes	66 (68.0)	62 (63.3)	0.10	67.2 (76.4)	-0.17
No	31 (32.0)	36 (36.7)	-0.10	20.8 (23.6)	0.17
Progression of disease within 24 months (POD24) of initiation of first line of treatment – n (%)					
Yes	61 (62.9)	78 (79.6)	-0.37	60.7 (68.9)	-0.13
No	36 (37.1)	20 (20.4)	0.37	27.4 (31.1)	0.13
Other baseline characteristics not included in Propensity Score Modeling					
Prior Auto-HSCT – n(%)					
Yes	36 (37.1)	2 (2.0)	0.98	3.7 (4.2)	0.92
No	61 (62.9)	96 (98.0)	-0.98	84.3 (95.8)	-0.92
Number of nodal involvement at initial diagnosis[4] – n (%)					
>4	43 (44.3)	14 (14.3)	0.70	6.3 (7.2)	0.86
≤4	27 (27.8)	82 (83.7)	-1.35	76.5 (86.9)	-1.43
Unknown	27 (27.8)	2 (2.0)	0.77	5.3 (6.0)	0.65
Age at initial FL diagnosis (years)					
Mean (SD)	50.59 (9.94)	59.12 (12.5)	-0.76	49.52 (11.06)	0.10
Median (q1-q3)	50 (43.94-57.00)	60 (50.00-69.00)		51 (43.00-55.00)	
Min-Max	22.38-71	29-81		29-81	
Age at initial FL diagnosis - n (%)					
<65 years	89 (91.8)	60 (61.2)	0.77	82.2 (93.4)	-0.04
≥65 years	8 (8.3)	38 (38.8)	-0.77	5.9 (6.7)	0.04
ECOG status at baseline[3] - n (%)					
0	56 (57.7)	27 (27.6)	0.64	25.7 (29.3)	0.60
1	38 (39.2)	29 (29.6)	0.20	26.6 (30.2)	0.19
2	3 (3.1)	0 (0.0)	0.25	0 (0.0)	0.25
Missing	0 (0.0)	42 (42.9)	-1.22	35.7 (40.6)	-1.15
Stage at treatment initiation – n (%)					
Stage I	3 (3.1)	0 (0.0)	-	0 (0.0)	-
Stage II	11 (11.3)	0 (0.0)	-	0 (0.0)	-
Stage III	26 (26.8)	0 (0.0)	-	0 (0.0)	-
Stage IV	57 (58.8)	0 (0.0)	-	0 (0.0)	-
Not applicable	0 (0.0)	98 (100.0)	-	88 (100.0)	-
Lactic acid dehydrogenase (LDH) lab values at baseline[3] – n (%)					
Elevated	41 (42.3)	11 (11.2)	0.75	10.9 (12.4)	0.72
Normal	56 (57.7)	30 (30.6)	0.56	25.4 (28.9)	0.60
Missing	0 (0.0)	57 (58.2)	-1.66	51.7 (58.7)	-1.68
Hemoglobin lab values at baseline[3] – n (%)					
<12 g/L	36 (37.1)	27 (27.6)	0.20	31.9 (36.2)	0.02
≥12 g/L	61 (62.9)	47 (48.0)	0.30	34.9 (39.7)	0.47
Missing	0 (0.0)	24 (24.5)	-0.80	21.2 (24.1)	-0.79
Follow-up period (months)					
Mean (SD)	15.69 (4.72)	16.55 (15.31)	-0.08	15.58 (15.14)	0.01
Median (q1-q3)	15.11 (13.50-19.29)	12.24 (4.86-24.41)		13.6 (6.18-19.58)	
Min-Max	0.66-26.15	0.03-70.67		0.07-70.67	
Number of nodal involvement at index treatment – n (%)					
>4	58 (59.8)	0 (0.0)	-	0 (0.0)	-
≤4	39 (40.2)	0 (0.0)	-	0 (0.0)	-
Not applicable	0 (0.0)	98 (100.0)	-	88 (100.0)	-
Refractory to last line – n (%)					
Yes	75 (77.3)	62 (63.3)	0.31	58.7 (66.6)	0.24
No	21 (21.7)	36 (36.7)	-0.33	29.4 (33.4)	-0.26
Missing	1 (1.0)	0 (0.0)	0.14	0 (0.0)	0.14

Note: the format presented are based on the format included in the weighting model. Number of nodal sites at initial diagnosis and history of autologous HSCT were not included as removing them achieved better overall balance.
[1] One patient from Study E2202 with missing for stage at initial diagnosis was excluded
[2] The index line was selected from a GEE model including all the pre-specified prognostics variables in the suggest format/categorization.
[3] The most recent result within 30 days prior to index date (inclusive). If more than one assessment was available on the most recent date, result indicating abnormal/worse prognosis was used.
[4] Categories between Study E2202 and Flatiron were standardized.
[5] Sample size after weighting (i.e., sum of weights) was 88 for the Flatiron study and effective sample size was 29.

The key question of interest is the effect of prescribing tisagenlecleucel vs. SOC in patients who participated in Study E2202. As a consequence, weight of 1 is assigned to patients in Study E2202 and the results of Study E2202 do not change after weighting. The changes in Flatiron study results after weighting reflect the adjustment of the population to address the question of interest. The median study follow-up time for patients in Study E2202 was 15 months, and the median follow-up time for Flatiron (at the selected LoTs) was 14 months in the weighted sample. The median survival and corresponding HRs for tisagenlecleucel from Study E2202 compared to standard treatments from Flatiron were calculated for OS, PFS, and TTNT (time to start new therapy) based on all patients. The bootstrap 95% CIs were provided. An improvement for all endpoints was observed before and after weighting in Study E2202 vs. Flatiron (Table 37).

Table 36: Efficacy comparison of study E2202 and Flatiron before and after weighting

	Study E2202 Enrolled	Before Weighting Flatiron	After Weighting[1] Flatiron
Response Rate	**n=97**	**n=72**	**n=89**
CRR (95% CI)	69.1 (59.8-78.4)	27.8 (18.1-37.5)	17.7 (3.8-46.9)
ORR (95% CI)	85.6 (78.4-91.8)	62.5 (51.4-73.6)	58.1 (21.3-88.2)
Difference in CRR (95% CI)		41.3 (27.1-55.1)	51.4 (21.2-68.8)
Difference in ORR (95% CI)		23.1 (9.9-35.9)	27.4 (-3-65)
OS			
Kaplan-Meier Analysis	**n=97**	**n=98**	**n=88**
Events/Total (%)	7/97 (7.2%)	24/98 (24.5%)	12.8/88 (14.5%)
Median, 95% CI (months)	NR	NR	NR
6 months	100.0 (100.0-100.0)	86.7 (79.3-93.4)	95.7 (88.7-99.2)
12 months	96.6 (92.3-100.0)	77.0 (67.5-86)	84.5 (64.9-95.9)
18 months	91.4 (84.1-97.6)	71.8 (61.4-81.6)	82.7 (62.6-94.6)
24 months	87.8 (77.3-96.2)	67.7 (56.5-78.5)	79.1 (58.8-92.5)
Cox proportional hazard model			
HR, 95% CI, Study E2202 vs Flatiron (Ref)		0.24 (0.08-0.51)	0.41 (0.11-1.47)
PFS			
Kaplan-Meier Analysis	**n=97**	**n=98**	**n=88**
Events/Total (%)	34/97 (35.1%)	52/98 (53.1%)	48.3/88 (54.8%)
Median, 95% CI (months)	NR	9.9 (6.8-19.3)	9.9 (8-19.3)
6 months	87.2 (80.2-93.6)	63.7 (53.6-73.7)	77 (60.5-88.5)
12 months	73.2 (64.1-82.1)	45.2 (34.1-56.5)	41.8 (20-67.2)
18 months	63.2 (52.4-73.5)	39.0 (27.4-50.6)	29.8 (11.6-56.2)
24 months	56.1 (41.8-68.9)	32.6 (20.9-44.4)	26.2 (8.1-52.0)
Cox proportional hazard model			
HR, 95% CI		0.45 (0.29-0.69)	0.45 (0.26-0.88)
PFS considering new anti-cancer therapy as event			
Kaplan-Meier Analysis	**n=97**	**n=98**	**n=88**
Events/Total (%)	37/97 (38.1%)	58/98 (59.2%)	52.8/88 (60.0%)
Median, 95% CI (months)	NR	9.6 (5.8-15.9)	9.9 (8-17.3)
6 months	85.3 (77.9-91.8)	59.7 (49.7-69.7)	72.5 (55.4-85.0)
12 months	70.5 (61.1-79.8)	42.3 (31.7-53.2)	39.4 (18.7-63.4)
18 months	60.9 (50.2-71.3)	35.0 (24.1-46.0)	28.1 (10.8-52.4)
24 months	54.1 (40.2-66.7)	29.2 (18.5-40.3)	24.6 (7.6-48.4)
Cox proportional hazard model			
HR, 95% CI		0.44 (0.29-0.67)	0.45 (0.27-0.83)
TTNT			
Kaplan-Meier Analysis	**n=97**	**n=98**	**n=88**
Events/Total (%)	19/97 (19.6%)	51/98 (52.0%)	36.5/88 (41.5%)
Median, 95% CI (months)	NR	11.6 (8.0-19.0)	19.0 (8.3-22.1)
6 months	94.7 (89.5-98.9)	68.4 (58.6-77.8)	82.9 (70.7-91.5)

12 months	85.9 (78.2-92.5)	47.6 (36.5-58.7)	54.2 (29.2-75.5)
18 months	79.9 (70.5-88.2)	40.7 (29.4-52.1)	52.4 (26.9-74.3)
24 months	68.4 (47.0-84.1)	34.5 (23.0-46.2)	45.5 (18.9-68.1)
Cox proportional hazard model			
HR, 95% CI		0.25 (0.15-0.41)	0.34 (0.15-0.78)

*10,000 bootstrap samples were randomly drawn to calculate the percentile-based 95% CI
*All K-M and cox regression results are based on survival data within the first 24 months (patients with survival data beyond 24 months were censored at Month 24).
[1] Only patients with at least one evaluation for response or a documented death during treatment were considered for this analysis. Because the model would upweigh/downweigh each individual patient differently depending on the propensity score, the final sample size may not necessarily be proportionate to the sample size before weighting.

A number of limitations have been described by the MAH.

- Not all inclusion and exclusion criteria of Study E2202 were able to be replicated.
- Some prognostic factors captured in Study E2202 were either incomplete or not available in Flatiron.
- There may be inherent, unobservable differences between patients in the Flatiron receiving standard of care and patients choosing to enroll in Study E2202 who are seeking gene therapy. For example, one observed difference was a lower rate of autologous HSCT among patients in the real-world cohort. Other unobservable differences may include patient characteristics, such as higher socioeconomic status or better access to healthcare, among patients enrolled in Study E2202 compared to those in Flatiron.
- Flatiron did not explicitly abstract relapsed/refractory (r/r) status for the Real-world Cohort. This differs from the Study E2202 inclusion criteria, which required patient to be refractory to second line or later of systemic therapy, relapse within 6 months of completion of second line or later systemic therapy, relapse during anti-CD20 antibody maintenance (following at least two lines of therapies as above), or within 6 months after maintenance completion.
- The rwR and rwP variables were extracted from RWD collected in the EHR as part of routine clinical care, and information about response and progression event(s) were retrospectively abstracted from the available clinician documentation. rwR captures a clinician's assessment of change in disease burden following radiographic imaging during a line of therapy, and rwP captures each distinct episode in which the treating clinician concludes that there has been growth or worsening of disease. This method of data collection, while clinically meaningful, differs from prospective collection of progression and response data within the context of a clinical trial. Analysis of response and progression-related endpoints when using RWD may involve by missing data, absence or lag in routine scanning, imprecise time estimates, and imprecise assessments of change in disease status; this may lead to biased, but conservative, time-to-event estimates if the assessments were less frequent. However, the scan frequency for rwR in the Flatiron study was comparable to that in Study E2202, so potential biases were likely mitigated.
- The presence of potential confounding and selection bias necessitated the performance of robust statistical analyses in the absence of a randomized controlled clinical trial. More specifically, analyses that adjust for differences in key prognostic and confounding factors were warranted. It should be acknowledged that despite best attempts, the potential for selection bias and unmeasured and residual confounding cannot fully be ruled out.
- Flatiron may contain the inherent limitations of non-interventional RWD. The quality of information extracted from RWD depends on the quality of information available in the data source. While the dataset has the potential for missing, inaccurate, or incomplete data, technology-enabled abstraction by specially-trained human abstractors using documented

policies and procedures and defined QA and QC activities aim to reduce data issues and increase completeness.

Systematic literature review

The objective of the systematic literature review was two-fold:

- To identify evidence on the clinical efficacy, safety, and patients reported outcomes (PRO) of third-line and later (3L+) treatments for FL in the adult (≥18 years) population
- To assess the incidence, prevalence, and mortality of r/r 3L+ FL patients

Methodology:

The key biomedical databases including Medical Literature Analysis and Retrieval System Online (MEDLINE®), Excerpta Medica Database (Embase®), MEDLINE® In-Process, and Cochrane Central Register of Controlled Trials [CENTRAL] and Cochrane Database of Systematic Reviews [CDSR] were searched from January 1998 to 08 April 2021. In addition to these databases, abstracts from five relevant conference proceedings were hand-searched for the past three years (2018 to 2021). Furthermore, bibliographic screening of previously published SLRs and meta-analysis was conducted to identify any data gaps.

- The review was conducted according to a pre-defined study protocol including (i) randomized controlled trials (RCTs), single-arm trials, and observational studies reporting efficacy, safety and PRO of 3L+ treatments for adults FL patients, who have received at least two prior therapies (ii) epidemiology studies reporting fraction of patients who needs a 3L+ treatment for FL. To be included for the SLR evidence, the study had to meet the following two key criteria:
    - Reporting FL specific data (either FL alone or iNHL study including FL subgroup)
        - For studies including multiple indolent NHL histology, a subgroup data of FL was reported
        - For studies including multiple indolent NHL histology, ≥75% of FL patients contributing to the study population was considered acceptable for this SLR
    - 3L+ lines of therapy data
- Majority of patients (≥75%) must have at least 2 prior lines of therapy or prior two regimen treated including an anti-CD20 antibody and an alkylating agent.
- A two-stage screening of the references that were retrieved was undertaken based on the abstracts and full-text publications. Screening of relevant studies was conducted by two independent reviewers and any discrepancies between reviewers were reconciled by a third independent reviewer. Data from trials were extracted by a single reviewer with quality check undertaken by an independent reviewer. Studies with multiple publications were linked together.

Results:

The SLR time-frame was determined based on approval for rituximab in the FL indication (1998-April 2021). However, this extended time interval may introduce chronology bias due to modifications in diagnostic criteria/classifications (FLIPI introduction), clinical management, and response criteria assessment (Lugano) of FL. The 36 studies identified were further narrowed down to include evidence published from 2014 onwards resulting in the inclusion of 24 studies. Of the 24 studies, nine were clinical trials (single arm: 6, RCTs: 2, non-RCTs: 1) and 15 were retrospective observational studies. Overall, the interventions assessed across this evidence included CAR-T therapies (Tisa-cel; Axi-cel); Pi3K inhibitors (Idelalisib; Copanlisib; Duvelisib), lenalidomide + rituximab [R2], tazemetostat, mixed interventions for 3L+, auto-SCT, allo-SCT, and salvage therapy post auto-SCT relapse. The efficacy outcomes are shown in Table 38.

Table 37: Summary of efficacy outcomes across conventional therapies

Interventions	PFS rate	Median PFS (months)	OS rate	Median OS (months)	ORR	CR	DOR (months)
Tisagenlecleucel[13, 34]	6-months: 76% n=1	Not reached n=1	-	Not reached n=1	86% n=1	66% n=1	Not reached n=1
Idelalisib[9] [37, 38] [23, 39]	1 to 1.5 yrs.: 43% to 68% *n=2**	7.1 to 17.5 *n=3**	2 yrs.: 69.8% *n=1*	25.3 to 61.2 *n=2**	56% to 61% *n=3**	14% to 26% *n=3**	10.8 to 14.1 n=2
Copanlisib[36, 50]	-	11.2 *n=1*	2 yrs.: 67% n=1	38.4 n=1	59% n=1	20% n=1	12.2 n=1
Duvelisib[11, 40]	-	8.3 *n=1*	-	27.8 n=1	43% n=1	1% n=1	7.9 n=1
Salvage therapy post auto-SCT relapse** [49]	3 to 5 yrs.: 15% to 22% *n=1*	12 *n=1*	3 to 5 yrs.: 53.5% to 69% *n=1*	66 *n=1*	-	51% to 53% *n=1*	-
Axicabtagene ciloleucel[14]	1 yr: 77.5% n=1	Not reached n=1	1-yr: 93% n=1	Not reached n=1	94% n=1	80% n=1	Not reached n=1
Lenalidomide + rituximab (R^2) [17]	1 yr: 65% *n=1*	17.7	-	Not reached	45% *n=1*	21% *n=1*	Not reached n=1
Tazemetostat[18, 24]	1.8 to 3 yrs. FU: 57% to 59% n=1	11.1 to 13.8 *n=1*	-	-	77% *n=1*	7% *n=1*	8.3 to 13 n=1
Rituximab[53] [22] [41]	-	12 to 30 *n=3*	6 yrs.: 67% *n=1*	Not reached *n=1*	72% *n=1*	37% *n=1*	-
Chemotherapy/any 3L+ therapy[44] [45, 46]	2 to 5 yrs.: 19% to 39% *n=2*	5.4 to 24 *n=3*	2 to 5 yrs.: 20% to 65.9% *n=2*	12 to 105 *n=2*	11% to 54% *n=1*	0% to 42% *n=1*	-
Auto-SCT[26] [21]	10 yrs.: 33% *n=1*	57.6 *n=1*	3 to 10 yrs.: 60% to 70% *n=2*	-	40% *n=1*	-	-
Allo-SCT[7] [32] [26] [31]	2 to 5 yrs.: 48% to 81% *n=4*	-	2 to 5 yrs.: 44% to 82% *n=11*	-	94% *n=1*	90% *n=1*	-

Allo: Allogenic; Auto: Autologous; CR: Complete Response; DOR: Duration of Response; FU: Follow-up; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression Free Survival; Pi3K: Pi3 Kinase; SCT: stem-cell transplantation;*Median not reached for idelalisib; *Tarantini 2019/Andorsky 2019 assessing idelalisib in real-world setting will not contribute for historical control data, being non-availability of baseline details of 3L+ FL patients; ^As the studies assessing any intervention varied in time-point of assessment, the data values reported in the above table represents range over the different time-points; **Survival times were calculated using the Kaplan-Meier method after relapse. Patient outcome was calculated from first progression.

Studies with populations similar to E2202 (ELARA) trial

Overall, six studies were identified as historical controls to tisagenlecleucel. These included the following approved treatments: PI3K inhibitors (n = 4) (Salles et al 2017, Flinn et al 2019, Dreyling et al 2017, Eyre et al 2017), salvage therapies for relapse post ASCT (n = 1) (Sesques et al 2020), and axicabtagene ciloleucel (n=1) (Jacobson et al 2020).

In Sesques et al 2020, patients relapsing after ASCT received heterogenous treatments, including radiation therapy (n = 5, 6%), allogeneic HSCT (in consolidation after CR obtained by CT/ ICT) (n = 11, 12%), rituximab single agent therapy (n = 13, 14%), targeted agents (n = 16, 18%), and rituximab chemotherapy combinations or chemotherapy alone (n = 45, 50%).

Overall, response rates for PI3K inhibitors ranged from 43%-59% (Table 39) while an ORR >86% was observed with axicabtagene ciloleucel (Yescarta® USPI) and tisagenlecleucel. A complete response between 1% - 20% was observed with PI3K inhibitors, a range between 51% and 53% was observed with salvage therapies for relapse after ASCT, while >60% was observed with axicabtagene ciloceulel (Yescarta® USPI) and tisagenlecleucel.

Median DOR was 7.9 to 14.1 months for PI3K inhibitors. The median DOR was not reached for axicabtagene ciloleucel (Yescarta® USPI) and tisagenlecleucel, with the median follow-up for DOR of 14.5 (Yescarta® USPI) and 16.85 months, respectively.

The PFS rates at 1 year was 43% for idelalisib, approximately 50% for salvage therapies post ASCT relapse (Sesques et al 2020) and >65% for axicabtagene ciloleucel (Jacobson et al 2020) and tisagenlecleucel. Median OS ranged from 28 to 38 months with PI3K inhibitors, while it was 66 months with salvage therapy after ASCT. Median overall survival was not reached with axicabtagene ciloleucel (Jacobson et al 2020) and tisagenlecleucel at respective follow-up.

Table 38: Summary of efficacy outcomes across ELARA (E2202) trial and historical controls

Interventions	PFS rate	Median PFS (months)	OS rate	Median OS (months)	ORR	CR	DOR (months)
Tisagenlecleucel[13, 34]	6-months: 76% n=1	Not reached n=1	-	Not reached n=1	86% n=1	66% n=1	Not reached n=1
Idelalisib[9] [38, 39]	1 yr: 43% *n=1*	7.1 to 11.0 *n=2*	2 yrs.: 69.8% *n=1*	61.2/ Not reached *n=2*	56% to 57% *n=2*	14% to 15% *n=2*	10.8 to 14.1 n=2
Copanlisib[36, 50]	-	11.2 *n=1*	2 yrs.: 67% n=1	38.4 n=1	59% n=1	20% n=1	12.2 n=1
Duvelisib[11, 40]	-	8.3 *n=1*	-	27.8 n=1	43% n=1	1% n=1	7.9 n=1
Salvage therapy post auto-SCT relapse[49] *	3 yrs: 22% 5 yrs: 15% *n=1*	12 *n=1*	3 yrs: 69% 5 yrs: 53.5%	66 *n=1*	-	51% to 53% *n=1*	-

Axicabtagene ciloleucel[14]	1 yr: 77.5% n=1	Not reached n=1	1 yr: 93% n=1	Not reached n=1	94% n=1	80% n=1	Not reached n=1

Auto: Autologous; CR: Complete Response; DOR: Duration of Response; ORR: Overall Response Rate; OS:Overall Survival; PFS: Progression Free Survival; SCT: stem-cell transplantation; *Survival times were calculated using the Kaplan-Meier method after relapse. Patient outcome was calculated from first progression.

Summary of main study

The following table (Table 40) summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 39 – Summary of Efficacy for Trial CCTL019E2202

Title: A Phase II, single arm, multicenter open label trial to determine the efficacy and safety of tisagenlecleucel(CTL019) in adult patients with refractory or relapsed FL.			
Study identifier	CCTL019E2202		
Design	Phase 2, single-arm, open label efficacy and safety study in patients with r/r FL. Follow-up Phase included safety and efficacy follow-up for at least 24 months. Patients who received tisagenlecleucel infusion had additional survival follow-up to determine survival status every 3 months until end of study.		
	Duration of main phase		Treatment and follow-up phase for at least 24 months
	Duration of Run-in phase		Survival follow up until end of study
	Duration of Extension phase		*Not applicable*
Hypothesis	Superiority: The analysis of the primary efficacy endpoint was performed by testing the null hypothesis of Complete Response Rate (CRR) being less than or equal to 15% at a 1-sided cumulative 2.5% level of significance, i.e. H0: $p \leq 0.15$ vs. Ha: $p > 0.15$. This hypothesis is based on CRR obtained for Idelalisib in same population setting (Salles et al Haematologica 2017).		
Treatments groups	Tisagenlecleucel		Single infusion with a protocol-specified target dose of 0.6 to 6.0×10^8 CAR-positive viable T-cells.
Endpoints and definitions	Primary endpoint	Complete response rate (CRR)	CRR determined by IRC in the efficacy analysis set (EAS) based on Lugano 2014 classification response criteria (Cheson et al 2014). *EAS: All patients who received tisagenlecleucel, and had measurable disease at baseline per IRC.
	Secondary endpoint	Overall response rate (ORR)	ORR, including CR and PR, determined by IRC in the EAS based on Lugano 2014 classification.
	Secondary endpoint	Duration of response (DOR)	- DOR, defined as time from achievement of CR or PR to progression or death due to FL, based on IRC. - DOR for CR only, defined as time from achievement of CR to relapse or death due to FL, based on IRC.
	Secondary endpoint	Progression-free survival (PFS)	PFS, defined as time from tisagenlecleucel infusion to first documented disease progression or death due to any cause, based on IRC.
	Secondary endpoint	Overall survival (OS)	OS, defined as time from tisagenlecleucel infusion to death due to any cause.

	Secondary endpoint	Summary scores of PRO questionnaires	Summary scores from SF-36 version 2, EQ-5D-3L and FACT-Lym QoL questionnaires.
Database lock	7-May-2021		

Results and Analysis: The analysis presented in the original submission was the main follow up analysis when 97 patients were infused with tisagenlecleucel and 90 patients had either completed 12 months of follow-up from the time of infusion or had discontinued earlier (DCO: 29 March 2021, DBL 7 May 2021). Data was later submitted from a more recent DCO, 03-Aug-2021, and these results are presented in the current table.

Analysis description	**Primary efficacy endpoint**	
Analysis population and time point description	**Efficacy analysis set (EAS):** All the patients who received tisagenlecleucel, and had measurable disease at baseline per IRC. Non-measurable disease at baseline is defined as absence of index lesion at baseline disease evaluation (i.e. no disease at baseline). The EAS was used for all efficacy analyses as per protocol.	
Descriptive statistics and estimate variability	Treatment group	Tisagenlecleucel
	Number of subjects	Enrolled: 98; Infused: 97; EAS: 94
	CRR by IRC	69.1%
	95% CI	58.8%, 78.3%
Notes	Previous analyses: -The primary endpoint was met at the **interim analysis** (DCO 26-May-2020), when ≥50 patients had received tisagenlecleucel infusion and had either completed 6 months of follow-up or had discontinued earlier for any reason, with a CRR of 65.4% (34/52 patients) (99.5% CI: 45.1, 82.4). This result was statistically significant at a 1-sided critical alpha level of 0.0025 to reject the null hypothesis (H0) CRR ≤ 15%. -The **primary analysis** (DCO 28-Sep-2020), conducted when 94 patients had either completed 6 months of follow-up or had discontinued for any reason, had a CRR per IRC in the EAS of 66.0% (95% CI: 55.5, 75.4).	

Analysis description	**Secondary efficacy endpoints**		
		DCO 29-Mar-2021	DCO 03-Aug-2021
	ORR per IRC in EAS	- ORR per IRC was 86.2% (95% CI: 77.5, 92.4).	- ORR per IRC was 86.2% (95% CI: 77.5, 92.4).
	DOR per IRC in EAS	- Responses (CR or PR) per IRC were achieved in 81 patients where 22 (22.72%) experienced an event. - Median DOR for patients with CR or PR per IRC was not reached; the estimated probability of remaining in response for 9 months being 76.0% (95% CI: 64.6, 84.2) versus 86.5% (95% CI: 74.7, 93.1) for patients achieving CR.	- Responses (CR or PR) per IRC were achieved in 81 patients where 24 (29.6) experienced an event. - Median DOR for patients with CR or PR per IRC was not reached; the estimated probability of remaining in response for 9 months being 76.2% (95% CI: 64.9, 84.3) versus 87.0% (95% CI: 75.6, 93.3) for patients achieving CR.

	PFS per IRC in EAS	- 34 PFS events in total (36.2%) (disease progression or death). - Estimated PFS probability: 67.0% (95% CI: 56.0, 75.8) at Month 12. - Median PFS per IRC was 18.4 months; however, this should be interpreted with caution since there were limited numbers of patients remaining at risk after Month 18.	- 37 PFS events in total (39.4%) (disease progression or death). - Estimated PFS probability: 67.0% (95% CI: 56.1, 75.8) at Month 12. - Median PFS per IRC was 29.5 months; however, this should be interpreted with caution since there were limited numbers of patients remaining at risk after Month 25.
	OS in EAS	- Estimated probability of survival was 95.3% (95% CI: 88.0, 98.2) at Month 12 and 91.6% (95% CI: 81.7, 96.2) at Month 18. - Median OS was not reached; 7 out of 97 patients died during the study.	- Estimated probability of survival was 95.4% (95% CI: 88.2, 98.2) at Month 12 and 93.0% (95% CI: 85.0, 96.8) at Month 18. - Median OS was not reached; 10 out of 97 patients died during the study.
	Summary scores of FACT-Lym, SF-36, and EQ-5D-3L questionnaires in EAS (DCO: 29-Mar-2021)	-The FACT Lym and SF-36 scores showed improvement in QOL over time post-tisagenlecleucel infusion. -At Month 12, EQ-5D-3L scores remained similar to Baseline. -Mean EQ-VAS score was 69.4 at baseline, 72.9 at Month 6, and 75.3 at Month 12.	

[Salles G, Schuster SJ, de Vos S, et al (2017)] Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study. Haematologica.;102(4):e156-e159.

Supportive study

One completed pilot phase 2a study CTL019A2101J (hereafter referred to as study A2101J) is reported in two articles (Schuster et al 2017, Chong et al 2021). The MAH does not have access to individual patient data. This study included participants with DLBCL (n=23) and participants with FL (n=15). In the FL patient group, all except one patient received tisagenlecleucel (n=14). This summary of the A2101J study is restricted to the FL population.

Patients were eligible if they had CD19+ FL with measurable residual disease after primary and salvage therapies, had relapsed or residual disease after autologous HSCT, or were not eligible for autologous or allogeneic SCT. After steady state apheresis to collect peripheral blood leukocytes, the patients received LD chemotherapy based on each patient's treatment history, blood counts, and organ function (data not shown). Tisagenlecleucel were infused 1 to 4 days after the completion of LD chemotherapy. Enrolled patients received tisagenlecleucel infusions at a dose range of 1.0 to $5.0x10^8$ transduced anti-CD19 CAR T-cells between 11-Mar-2014 and 02-Aug-2016. The data on the clinical outcomes from the study were up to date as of 07-May-2017 (Schuster et al. 2017).

Analysis set

A total of 38 patients were enrolled in the study, and 28 patients received treatment as specified in the protocol. Among the patients who received tisagenlecleucel, 14 patients (50%) had FL. Ten patients did not receive treatment as specified in the protocol owing to rapid disease progression with clinical deterioration of which only 1 had FL. T-cell manufacturing was unsuccessful for 5 patients, all of whom

had absolute lymphocyte counts of 300/m^3 or fewer (3 had poor T-cell growth, and 2 did not undergo apheresis owing to the degree of lymphopenia). It is not clear whether these represented patients with DLBCL or FL.

Demographics and Baseline characteristics

Table 41 provides an overview of patient characteristics at baseline in the A2101J clinical study.

Table 40: Characteristics of Patients at Baseline (A2101J study)

Table 1. Characteristics of the Patients at Baseline.

Characteristic	Patients Enrolled (N=38)		Patients Treated (N=28)	
	Follicular Lymphoma (N=15)	Diffuse Large B-Cell Lymphoma (N=23)	Follicular Lymphoma (N=14)	Diffuse Large B-Cell Lymphoma (N=14)
Age — yr				
Median	62	56	59	58
Range	43–72	25–77	43–72	25–77
Female sex — no. (%)	8 (53)	7 (30)	7 (50)	3 (21)
Previous therapies				
Median	5	3	5	3
Range	2–10	1–8	2–10	1–8
Advanced stage disease — no. (%)*	13 (87)	17 (74)	12 (86)	9 (64)
Bone marrow involved — no./total no. (%)	4/15 (27)	4/21 (19)	4/14 (28)	3/14 (21)
Elevated lactate dehydrogenase — no. (%)	10 (67)	16 (70)	9 (64)	8 (57)
ECOG performance-status score†				
Median	0	1	0	1
Range	0–1	0–1	0–1	0–1
Refractory diffuse large B-cell lymphoma — no. (%)‡	—	21 (91)	—	12 (86)
Double refractory follicular lymphoma — no. (%)§	9 (60)	—	8 (57)	—
Previous stem-cell transplantation — no. (%)				
Autologous	3 (20)	9 (39)	3 (21)	7 (50)
Allogeneic	1 (7)	0	1 (7)	0

* Advanced stage disease is defined as stage III or IV according to the modified Ann Arbor staging system.[20]
† Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher numbers indicating increasing disability. A score of less than 3 indicates that the patient is at least ambulatory and capable of all self-care, although he or she may be unable to carry out any work activities, and that the patient is out of bed more than 50% of waking hours.
‡ Refractory diffuse large B-cell lymphoma is defined as disease in which progressive or stable disease is considered to be the best response to chemotherapy (with stable disease defined as disease that is less than 12 months in duration after the patient has undergone at least four cycles of first-line therapy or two cycles of second-line, third-line, or later therapy) or as relapse <12 months after autologous stem-cell transplantation. Patients must have received an anti-CD20 monoclonal antibody (unless they had negative test results for CD20) and an anthracycline as one of their previous treatment regimens.
§ Double-refractory follicular lymphoma is defined as progression of disease within 6 months after receiving the last dose of rituximab and within 6 months after receiving the last dose of an alkylating agent.

The median number of days from apheresis to infusion was 39 (range: 27-145); 36% (10/28) of the patients received bridging therapy, which was administered after apheresis and before LD chemotherapy.

Efficacy

The primary objective of the study was to estimate the efficacy of tisagenlecleucel in NHL patients by measuring the ORR in evaluable patients at 3 months.

At a follow-up of 3 months, 79% (11/14; 95% CI: 49, 95) of the FL patients who had received ≥ 2 prior lines of chemotherapy or immunochemotherapy obtained an ORR to tisagenlecleucel infusion (Schuster et al 2017), where 50% (7/14) of the patients achieved a CRR and 29% (4/14) reported a

PR. Three of the patients who obtained a PR at 3 months had a CRR by 6 months, and the CRR was therefore 71% (10/14; 95% CI: 42, 92) for these patients after 6 months of follow-up. One patient continued to have a PR at 6 months and had progressed 1-year post-infusion. At a median follow-up of 28.6 months, 89% of patients with FL who had a response (95% CI: 43, 98) had maintained the response and 70% (95% CI: 38, 88) were reported to be progression-free.

Additionally, after a median follow-up of 60.7 months, the PFS rate at 5 years was 43% (95% CI: 18, 66), and 60% (95% CI: 25, 83) of the responders had a sustained response at 5 years. The median DOR and median OS were not reached (Chong et al 2021). Of note, the plateau of the PFS KM curve, not seen for currently available 3rd line and beyond treatments, could be suggestive of curative potential.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Data to support extending the current approved therapeutic indications of Kymriah to r/r FL is based on one single arm phase 2 clinical study E2202 that enrolled a total of 98 participants. From a regulatory point of view, a RCT would have been preferred based on the availability of alternative therapies for parts of the included population (i.e., the PI3K inhibitor idelalisib, which is approved for double refractory patients). Instead, the results from the study are contextualised through real world evidence based on ReCORD and Flatiron databases and a systematic literature review. This presents certain limitations, as discussed below.

The E2202 clinical study aimed to enroll three distinct patient groups based on the following inclusion critera. Patients could be either a) refractory to a second line or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent) or relapsed within 6 months after completion of a second line or later line of systemic therapy or b) relapsed during anti-CD20 antibody maintenance (following at least two lines of therapies as above) or within 6 months after maintenance completion or c) relapsed after autologous HSCT. Refractoriness was defined as failure to respond to previous treatment (SD/PD as best response) or PD within 6 months of prior therapy completion. In the first assessment round, a subgroup analysis was requested to ensure consistent efficacy across the populations defined by the inclusion criteria. This analysis confirmed similar CRR and ORR across groups. Overall, the inclusion and exclusion criteria were considered acceptable.

Study schedules and duration of follow up is considered appropriate.

It was also noted in the SA (EMA/SA/0000047236) that the primary efficacy analysis specified in the study protocol was to be conducted in the infused (mITT) population, but that the enrolled (ITT) population should be considered the primary efficacy population for regulatory purposes, as the overall treatment includes leukapheresis, LD chemotherapy and tisagenlecleucel administration, and that failures in between need to be considered as such. However, considering that the difference between the mITT and the ITT populations is only one patient, analysis in the mITT population can be considered acceptable.

Patients were allowed to receive antineoplastic bridging therapies based on the investigators choice to stabilize the disease while waiting for tisagenlecleucel infusion. Of the 97 patients infused, 44 patients (45.4%) received optional antineoplastic bridging therapy prior to tisagenlecleucel infusion. Theoretically, the type of bridging therapy each individual patient received prior to infusion may have had an impact on the efficacy outcome of this CAR-T cell therapy. A PET-CT scan was therefore routinely performed, with a few exceptions, after bridging therapy and prior to tisagenlecleucel

infusion, to ensure monitoring of the correlation between response to bridging therapy and clinical response to tisagenlecleucel. The observed response in terms of CRR in patients who received bridging therapy in the EAS was 65.9% (29/44; 95% CI: 50.1, 79.5), and was comparable to that in the overall study population. Similarly, CRR for those that did not receive bridging therapy in the EAS was 72% (36/50; 95% CI: 57.5, 83.8). These data which were obtained from the subgroup analysis did therefore not reveal any influence of bridging therapy on the efficacy outcomes in the studied patient population.

The primary objective of study E2202 was CRR. A single arm phase 2 study based on CRR can be accepted in the target population with r/r tumours where limited therapies exist. While ORR is a more commonly used endpoint, CRR has been observed to correlate better than PR rate with prolonged response in the case of CAR-T cell therapies. The use of CRR as a primary endpoint in this trial is therefore considered acceptable. However, as also noted in the Scientific Advice (EMA/SA/0000047236), the CRR would need to be assessed in conjunction with DOR, and these data would need to be sufficiently mature to establish a benefit also in terms of response durability. For comparison, idelalisib demonstrated a median DOR of 11.8 months in an older and more refractory patient population (Zydelig EPAR). The secondary and exploratory objectives proposed are considered appropriate considering the objectives and overall aim of the study.

In the Enrolled set (n=98), protocol deviations were reported in 58 patients (59.2%). These findings were similar in the EAS which incorporated 55 (58.5%) patients with protocol deviations of which 10 (10.6%) were inclusion deviations and 1 (1.1%) exclusion deviations. These patients nevertheless were part of the EAS and contributed to the endpoint data whilst, in principle, these patients should have been excluded from the study. In addition, these deviations add to the heterogeneity of the patient population. The MAH states that the deviations were not considered to affect the overall conclusions of the study and subsequently provided data on the EAS where these 11 patients were excluded from the analysis. In this modified EAS (n=83), CRR is 71.1% and ORR 86.7%, confirming a comparable efficacy with the EAS (n=94: CRR 69.1%, ORR 86.2%) and the enrolled set (n=98) with CRR 68.4% and ORR 85.7%

Publications from one supportive study were provided. This pilot phase 2a study A2101J included participants with DLBCL (n=23) and participants with FL (n=15). In the FL group, all except one patient received tisagenlecleucel (n=14). The study populations were similar in that the A2101J study enrolled adults with CD19+ FL having experienced at least 2 prior chemotherapy or immune-chemotherapy regimens (not including single agent monoclonal antibody therapy), who had a limited prognosis (several months to $\leq$2 year expected survival) with currently available therapies. The therapies were current as of 2014 in agreement with RWE used to contextualise the results. It is not possible to compare the study populations further, but both appear to have had advanced disease. The dose of tisagenlecleucel was slightly different in the A2101J study than in the E2202 study (1 – 5 x10^8 CART-19 cells vs 0.6 – 6 x10^8 CART-19 cells).

Efficacy data and additional analyses

Study population

As noted above, the study population, as defined by the inclusion criteria, could potentially be quite heterogeneous. The MAH was therefore requested to further assess the efficacy in the subgroups defined by the originally proposed indication wording. This analysis confirmed similar CRR and ORR across these subgroups of patients. The enrolled patient population in study E2202 represented FL patients with advanced disease with a median of four lines of prior therapy (range: 2 to 13) and 28.6% of patients received ≥ 5 lines of prior antineoplastic therapies. Of the enrolled patients, 77.6% of

patients were refractory to their last line of therapy. Of these, 54 patients (55.1%) showed SD/PD as their best response to their most recent regimen and 22 patients (22.4%) had disease relapse within 6 months from completion of this last regimen. Thirty-six patients received prior HSCT, of whom 15 patients relapsed within 12 months from transplant. Moreover, a high percentage of patients had bulky disease, high to intermediate FLIPI, POD24, or were double refractory.

The timing of HSCT in disease and treatment course is not specified in either the inclusion criteria or the indication. The number of enrolled participants that had experienced HSCT was small (n=36) of which 15 relapsed within 12 months and the remainder thereafter. It is not known when in disease course the HSCT had taken place. The majority of patients were refractory to the last line of therapy (n=74/94, 78.7%) compared to relapsed (n=17/94, 18.0%). All patients had received prior anti-CD20 therapy. Among patients in the EAS relapsing >6 months after the last line of treatment, 5 patients relapsed during (n=4) or within (n=1) 6 months from the end of anti CD20 maintenance, while 15 patients relapsed after HSCT.

Indication wording:

The originally proposed wording of the sought indication was: "*Adult patients with follicular lymphoma (FL) after two or more lines of therapy who are refractory or relapsed during or within 6 months after completion of anti-CD20 antibody maintenance or relapsed after autologous haematopoietic stem cell transplantation (HSCT)".* A revised and simplified wording of the indication, reflective of the enrolled patients in study E2202 with r/r FL who had received at least two lines of prior systemic therapy, and giving consideration to patients with earlier relapse, or with relapse after HSCT, reflective of a more aggressive form of FL, for which the benefit/risk of tisagenlecleucel could be assessed, was requested in the first assessment round. The MAH was further asked to discuss whether the B/R observed in the studied patient population might be extrapolated to other subgroups of FL, in particular patients with low-risk disease, that have not been included or are not well represented in the pivotal study.

The agreed indication is "Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic treatment". It is acknowledged that a simplified wording of the indication would also encompass patients with FL Grade 3b for which no data is available since they were excluded from the clinical study. In clinical practice, these patients are often treated as DLBCL, for which tisagenlecleucel is also indicated. The extrapolation of the positive B/R balance of Kymriah observed in the studied FL and DLBCL populations to patients with FL grade 3b, as well as grade 3a, can therefore be considered acceptable.

Primary endpoint

As noted in scientific advice (EMA/SA/0000047236), the CR rate would need to be assessed in conjunction with DOR, and these data should be sufficiently mature to establish a benefit also in terms of response durability. Whilst the primary outcome, CRR, was met, the secondary outcome of DOR per IRC was not reached at the time of the data cut-off (29-Mar-2021). The MAH had been advised to potentially revise the timing of the analysis to demonstrate, with high precision, a potential difference in median DOR compared to the external data sets (RWD) included to contextualise the results. The MAH subsequently provided data from a planned DCO of 03-Aug-2021, corresponding to additional 4 months of median follow-up (median follow up: 21 months in the EAS, range: 14-30). No new responders and no new conversions from PR to CR were observed with longer followup. Median DOR was not reached at this DCO either, with 9-month DOR unchanged, and 12-month DOR similar to the main analysis (DCO: 29-Mar-2021), supporting a sustained response.

Statistical analysis

The statistical hypothesis compares the CRR rate in E2202 against that in the idelalisib pivotal study.

It was noted in the scientific advice (EMA/SA/0000047236), that the pivotal study for idelalisib included older (median age 64 vs 56.5 years) and more refractory patients (89.6% vs 78.4% refractory to last treatment line) than study E2202. Thus, the validity of the applied reference CR rate is uncertain. Nonetheless, as was noted in the SA, this issue is likely overcome by compelling actual study results, with a CRR per IRC assessment in the EAS of 69.1% (95% CI: 58.8, 78.3) at the current data cut-off date (29-Mar-2021).

Secondary endpoints

At the time of the main analysis (DCO 29-Mar-2021), the median DOR per IRC was not reached. Responses (CR or PR) per IRC review were achieved in 81 patients, with the estimated probability of remaining in response for 9 months being 76.0% (95% CI: 64.6, 84.2) and for 12 months being 71.6% (95% CI: 58.9, 80.9) Out of the 81 responders, 59 patients were censored. An updated analysis (DCO: 03-Aug-2021), corresponding to additional 4 months of median follow-up (median follow up: 21 months in the EAS, range: 14-30) also did not reach median DOR. 9-month remained DOR unchanged, and 12-month DOR was similar to the main analysis (DCO: 29-Mar-2021).

At the time of the DCO of 29-March 2021, the median PFS per IRC was 18.4 months (95% CI: 12.3, NE); however, this should be interpreted with caution since there were limited numbers of patients remaining at risk after Month 18. At a later DCO (03-Aug-2021), with median follow up of 21 months (range: 14-30) in the EAS, 12-month PFS remained unchanged, while median PFS increased from 18.4 months to 29.5 months, with the caveat of a low number of patients at risk after month 25.

The median OS was not reached at the time of the data DCO. Seven deaths had occurred in the study (Table 4). (See section on Safety). In the EAS, the estimated probability of survival was 95.3% (95% CI: 88.0, 98.2) at Month 12 and 91.6% (95% CI: 81.7, 96.2) at Month 18. At the DCO of 03-Aug-2021, 12-month OS remained essentially unchanged.

Patient reported outcomes

Patient reported outcomes (PRO) were also assessed as part of the study using three validated questionnaires. All patients in the tisagenlecleucel-infused population should have completed the questionnaires, however, the number of respondents was low at baseline, ranging from 65 to 76 patients, and declined over time providing a strong potential for selection bias. Patients continued to respond to the questionnaire for two visits after disease progression which explains some of the fall in respondents, but other reasons for failing to respond to the questionnaire are not provided. There is also no control group in the study for comparison. It was noted that anxiety/depression and effects on usual activities are noted to be greater than baseline at 6 months post-tisagenlecleucel infusion. This is a similar time point where greater deterioration was noted for the mental health component of the SF36 questionnaire. A total of 17 participants (17.1%) received further treatments and 2 (2.1%) participants received allogenic stem cell therapy post-tisagenlecleucel infusion. It is difficult to assess the effect on QoL in the latter group since no data was collected for the two patients that received HSCT. Furthermore, data is completely lacking for one of the 17 that received further treatment and has insufficient follow-up data for 6-7 of the remaining patients (depending on questionnaire). In general, the number of respondents declined over time. Reasons provided by the MAH include device issues, patient willingness or covid-19 pandemic related issues. The QoL data corresponding to the first three months following infusion was collected pre-pandemic. The non-technical reasons provided could nevertheless contribute to selection bias.

Real World Data (ReCORD and Flatiron)

The real-world analyses were based on two non-interventional studies. Clinically meaningful differences in CRR and ORR after weighting were observed for Study E2202 vs ReCORD with 31.8% (95% CI: 18.1, 45.3) and 22% (95% CI:9.4, 34.5), respectively, and for Study E2202 vs Flatiron 51.4% (95% CI: 21.2, 68.8) and 27.4% (95% CI: 3.0, 65.0), respectively. The median OS was not reached for Study E2202, ReCORD or Flatiron. The Kaplan-Meier estimate of the OS rate at 12 months was 96.6% [95% CI: 92.9%, 100%] in Study E2202, 71.7% [95% CI: 61.2%, 82.2%] in ReCORD (HR=0.2 [95% CI:0.02, 0.38]), and 84.5% [95% CI: 64.9%, 95.9%] in Flatiron (HR=0.41 [95% CI: 0.11, 1.47]). The median PFS considering start of a new therapy as an event was not reached for Study E2202 and was reached at 13.1 months for ReCORD. The estimated probability of being progression-free at 12 months was 70.5% [95% CI: 61.4%, 79.7%] in Study E2202 and 51.9% [95% CI: 40.6%, 63.3%] in ReCORD (HR=0.60 [95% CI: 0.34, 0.86]). The median PFS was not reached for Study E2202 and was reached at 9.9 months for Flatiron after weighting. The estimated probability of being progression-free at 12 months was 73.2% [95% CI: 64.1%, 82.1%] in Study E2202 and 41.8% [95% CI: 20.0%, 67.2%] in Flatiron (HR=0.45 [95% CI: 0.26, 0.88]).

The above adjusted analyses were supported by unadjusted analyses showing similar results. Analyses restricted to the time point from 2014 and 2020 have also been provided, based on scientific advice, such that the treatment options would be similar to those for the E2202 study, and show similar results. Nevertheless, interpretation of the RWD is complicated by the fact that it was not possible to fully emulate the inclusion criteria in the E2202 study. As such the patient populations were similar but not identical. Important prognostic values were lacking and could not be adjusted for in the analyses. Also, response assessments were lacking in the RWD, necessitating changes to the endpoint definition (ReCORD), or further exclusion of patient that otherwise would qualify (Flatiron). This provides some uncertainty when used to contextualise the pivotal phase 2 clinical study E2202. These studies are despite the remaining uncertainty of the effect estimates nevertheless providing valuable context, and are in general deemed supportive of the pivotal study, due to the clear differences in outcomes they show.

Supportive studies

One pilot phase 2a study, A2101J, enrolling 15 patients with FL, of which 14 received tisagenlecleucel, was provided in support of the E2202 study. The data is based on articles in the literature. Although the sample size was small, the patient population was similar, where all had received at least 2 systemic lines of prior therapy, and the patients had advanced disease. A total of 11/14 patients responded to tisagenlecleucel infusion at Month 3 follow-up (Schuster et al 2017). The CRR was 71%, with an ORR of 79%, which can support the findings in the E2202 study. At a median follow-up of 28.6 months, 89% of patients with FL who had a response (95% CI, 43 to 98) had maintained the response.

Additionally, after a median follow-up of 60.7 months, the PFS rate at 5 years was 43% (95% CI: 18 to 66), and 60% (95% CI: 25, 83) of the responders had a sustained response at 5 years. The median DOR and median OS were not reached (Chong et al 2021) suggesting that the response was durable. This supportive study can only provide an indication on CRR and DOR in the longer term, due to the small sample size, but supports the potential for a durable response to tisagenlecleucel treatment in patients with advanced FL after two or more lines of systemic therapy.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

No relevant – all participants were >18 years of age in the E2202 pivotal clinical study.

2.4.4. Conclusions on the clinical efficacy

In conclusion, the efficacy data presented by the MAH suggests that clinically relevant responses can be obtained with Kymriah treatment in relapsed or refractory FL patients after two or more lines of systemic therapy.

2.5. Clinical safety

Introduction

The RMP, summary of important safety concerns for Kymriah (tisagenlecleucel):

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	• Cytokine release syndrome • Serious neurological adverse reactions • Infections • Tumor lysis syndrome • Prolonged depletion of normal B-cells/Agammaglobulinemia • Hematological disorders including cytopenias
Important potential risks	• Cerebral edema • Generation of replication competent lentivirus • Secondary malignancies (including vector insertion site oligo/monoclonality) • New occurrence or exacerbation of an autoimmune disorder • Aggravation of graft-versus-host disease • Transmission of infectious agents • Decrease in cell viability due to inappropriate handling of the product
Missing information	• Use in pregnancy and lactation • Use in patients with HBV/HCV/HIV • Use in patients with active CNS involvement by malignancy • Long-term safety • Immunogenicity

In B-cell ALL indication, the most common non-haematological adverse reactions are cytokine release syndrome (77%), infections (73%), hypogammaglobulinaemia (53%), pyrexia (42%) and decreased appetite (38%). The most common haematological laboratory abnormalities were decreased white blood cells (100%), decreased haemoglobin (100%), decreased neutrophils (100%), decreased lymphocytes (100%) and decreased platelets (97%).

In DLBCL indication, the most common non-haematological adverse reactions were cytokine release syndrome (57%), infections (58%), pyrexia (35%), diarrhoea (31%), nausea (29%), fatigue (27%) and hypotension (25%). The most common haematological laboratory abnormalities were decreased lymphocytes (100%), decreased white blood cells (99%), decreased haemoglobin (99%), decreased neutrophils (97%), and decreased platelets (95%).

The RMP, summary of important safety concerns for Kymriah (tisagenlecleucel):

Table 9-1	Table Part II SVIII.1: Summary of safety concerns
Important identified risks	• Cytokine release syndrome • Serious neurological adverse reactions • Infections • Tumor lysis syndrome • Prolonged depletion of normal B-cells/Agammaglobulinemia • Hematological disorders including cytopenias
Important potential risks	• Cerebral edema • Generation of replication competent lentivirus • Secondary malignancies (including vector insertion site oligo/monoclonality) • New occurrence or exacerbation of an autoimmune disorder • Aggravation of graft-versus-host disease • Transmission of infectious agents • Decrease in cell viability due to inappropriate handling of the product
Missing information	• Use in pregnancy and lactation • Use in patients with HBV/HCV/HIV • Use in patients with active CNS involvement by malignancy • Long-term safety • Immunogenicity

New safety data are provided for the indication r/r FL (relapsed or refractory follicular lymphoma) based on data from the pivotal phase 2 Study E2202, including 97 patients treated with tisagenlecleucel infusion with a median duration of follow-up post-infusion of 16.59 months (range: 10.3 to 25.7 months). The enrollment of this study is complete, although the study is ongoing. In the pivotal study E2202 patients are followed on-study for at least 2 years post-infusion for safety. After the end of the study, patients will continue to be followed for long-term safety, under the long-term follow-up protocol (Study CCTL019A2205B). This study aims for 15 years safety follow-up.

Supportive data is provided from a pilot study (study A2101J) providing safety data on 38 patients diagnosed with DLBCL (n = 24) or FL (n = 14) treated with tisagenlecleucel infusion, and which followed patients for a median of 60.7 months (5.1 years). The results from the study are published by Schuster et al 2017 Chimeric antigen receptor T-cells in refractory B-cell lymphomas. N Engl J Med; 377(26):2545-5) for the 2 year follow-up and by Chong et al 2021 Lymphoma Program Investigators at the University of Pennsylvania. Five-year outcomes for refractory B-cell lymphomas with CART-cell therapy. N Engl J Med; 384(7):673-4 for the 5 year follow-up.

Patient exposure

The targeted dose range was 0.6 to 6 × 10^8 CAR-positive viable T-cells in a single administration.

All 97 patients received a single dose of tisagenlecleucel. The median number of CAR-positive viable T-cells administered was 2.06 × 10^8 cells (range: 0.1 to 6.0 × 10^8). The median total viable cell count was 12 × 10^8 cells (range: 0.4 to 34.0 × 10^8). All patients, except 4, received tisagenlecleucel within the targeted dose range.

Median age 57.0 years (range:29-73), 66% male, 75.3% were White, 13.4% were Asian.

Concomitant therapy

At the time of the current data cut-off, all patients in the Infused set (97 patients) with one exception received non-study concomitant medications. The most commonly used concomitant medications (in >30% of patients) by ATC class are listed below, presented in decreasing order of frequency:

- Anti-infectives for systemic use in 93.8% of patients [primarily sulfamethoxazole/trimethoprim (42.3%)]
- Alimentary tract and metabolism medications in 79.4% of patients [primarily ondansetron (32.0%)]
- Nervous system medications in 71.1% [primarily paracetamol (53.6%)
- Blood and blood-forming organs medications in 58.8% [primarily enoxaparin (22.7%)
- Dermatologicals in 50.5% [primarily acyclovir (27.8%)
- Musculoskeletal system medications in 50.5% [primarily allopurinol (40.2%)
- Antineoplastic and immuno-modulating agents in 47.4% [primarily filgrastim (25.8%)
- Cardiovascular system medications in 37.1% of patients

Seventeen patients (17.5%) in the Infused Set received at least one anti-cytokine medication for CRS. All 17 patients received tocilizumab and 4 of them also received corticosteroids.

Bridging therapy

Of the 97 patients infused, 44 patients (45.4%) received optional antineoplastic bridging therapy prior to tisagenlecleucel infusion. The most commonly used agents (in ≥ 5% of patients) were rituximab (21.6%), dexamethasone (11.3%), gemcitabine (10.3%), oxaliplatin (7.2%), prednisolone (7.2%), etoposide (6.2%), cyclophosphamide (5.2%) and vincristine (5.2%). Furthermore, 2 patients received radiotherapy alone.

Lymphodepleting (LD) chemotherapy

All infused patients received lymphodepleting chemotherapy prior to tisagenlecleucel infusion. Ninety-two of them received fludarabine + cyclophosphamide and 5 received bendamustine

Adverse events

Collection of AEs followed the following scheme:

Table 41 Collection on AEs, haematology and chemistry

Phase			Screening			Pre-Treatment			Treatment and Follow-up														
Visit	Category	Protocol Section	Screening	Leukapheresis	Enrollment	Pre-lymphodepletion evaluation	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Post-infusion												End of Study
Visit Number			1	2	3	110	120	130	210	220	230	240	250	260	270	280	290	300,320, 330	310, 340,350, 360	370	380	390..	1999
Study day			W -10 to W -6	W -10 to W -4	W -6 to W -4	W -4 to D -8	D -6 to D -2	D -1	D 1	D 2	D 4 ±1 d	D 7 ±1 d	D 11 ±1 d	D 14 ±1 d	D 17 ±1 d	D 21 ±3 d	D 28 ±7 d	M 2, 4, 5, ±14d	M 3, 6, 9, 12 ±14d	M 18 ±1 4d	M 24 ±1 4d	Q6M ... (M30 ...) ±14d	EOS +1 4d
CSF cytology by lumbar puncture	D	7.2.1	As clinically indicated																			
Adverse events	D	8.1 8.2	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	D	7.2.2.5	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.5	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

According to the inclusion criteria, patients must meet the following laboratory values without transfusion at screening:

- Absolute neutrophil count (ANC) ≥ 1,000/mm^3 (≥ 1×10^9/L)
- Absolute lymphocyte count (ALC) > 300/mm^3 (> 0.3×10^9/L)
- Absolute number of CD3+ T cells > 150/mm^3 (> 0.15×10^9/L)
- Platelets ≥ 50 000/mm^3 (≥ 50×10^9/L)
- Hemoglobin ≥ 8.0 g/dl (≥ 4.9 mmol/L)
- A serum creatinine of ≤1.5 times ULN or eGFR ≥ 60 mL/min/1.73 m^2
- ALT/AST ≤ 5 times the ULN
- Total bilirubin ≤ 1.5 times ULN (with the exception of patients with Gilbert's syndrome. Patients with Gilbert's syndrome may be included if their total bilirubin is ≤ 3.0 times ULN and direct bilirubin ≤ 1.5 times ULN

In addition to the cumulative safety data from Study E2202, safety data were derived from 3 epochs post-tisagenlecleucel infusion: the initial 8-week period, the periods between 8 weeks and 1 year, and subsequently after 1 year.

The impact of changes implemented due to COVID-19 pandemic on the safety results was considered low because mitigation measures like performing safety assessments remotely (by phone, telemedicine) were taken. In one patient, tisagenlecleucel infusion was delayed (>8 weeks from enrollment) due to site issues.

Adverse events prior to lymphodepletion phase

Seventy-five patients (76.5%) experienced a broad range of AEs of all grades prior to treatment with LD chemotherapy or tisagenlecleucel infusion. AEs were consistent with those expected in patients receiving chemotherapy for r/r FL. The most common AEs (occurring in >10% of patients) were

anemia, nausea, constipation, headache and low platelet count. These events were manageable per the relevant product information. Of note, 44/97 (45%) patients received bridging therapy prior to infusion.

AEs during LD chemotherapy

A total of 92 patients received fludarabine+cyclophosphamide and the 5 other patients received bendamustine as lymphodepleting regimen. Of the 97 patients who received LD chemotherapy, 5 patients (77.3%) had at least 1 AE during the LD period (i.e. following LD chemotherapy and before administration of tisagenlecleucel). Thirty-six patients (37.1%) had AEs of grade 3/4 severity [Study E2202-Table 14.3.1-1.10]. All grade 4 AEs were cytopenia. There was no difference in the safety profile between the two LD regimens. The most commonly reported AEs (≥ 10%) irrespective of relationship to LD chemotherapy were nausea (35.1%), anemia (12.4%) and headache (10.3%). The AEs reported during the LD chemotherapy were consistent with those anticipated due to current and prior antineoplastic treatments and due to the underlying r/r FL.

Adverse events post-tisagenlecleucel infusion

Of the 97 patients infused with tisagenlecleucel, 96 patients (99.0%) experienced at least 1 post-infusion AE, irrespective of relationship to treatment.

The SOC with most commonly reported grade ≥3 AEs in ≥15% of the patients was blood and lymphatic system disorders (59.8%) investigations (29.9%) and infections and infestations (15.5%). AEs within the 'immune system disorders' SOC were also very commonly reported (55.7%) as this SOC includes CRS, which is an expected AE with tisagenlecleucel.

Table 42 AEs any time post-tisagenlecleucel infusion, irrespective of tisagenlecleucel relationship, by PT and maximum grade, and occurring in more than 10% of patients in all grades (Safety set)

	All patients N=97	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one AE	**96 (99.0)**	**76 (78.4)**
Cytokine release syndrome	48 (49.5)	1 (1.0)
Neutropenia	41 (42.3)	41 (42.3)
Anemia	25 (25.8)	16 (16.5)
Headache	24 (24.7)	1(1.0)
Diarrhea	21 (21.6)	1(1.0)
White blood cell count decreased	21 (21.6)	17 (17.5)
Pyrexia	19 (19.6)	1 (1.0)
Thrombocytopenia	19 (19.6)	11 (11.3)
Neutrophil count decreased	17 (17.5)	17 (17.5)
Fatigue	16 (16.5)	3 (3.1)
Nausea	15 (15.5)	2 (2.1)
Constipation	14 (14.4)	0
Hypogammaglobulinemia	14 (14.4)	1 (1.0)
Cough	12 (12.4)	0
Febrile neutropenia	12 (12.4)	12 (12.4)
Arthralgia	10 (10.3)	0
Platelet count decreased	10 (10.3)	6 (6.2)

A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.
PTs are presented in descending frequency of the all grades column.
MedDRA version 24.0 and CTCAE version 4.03 have been used for the reporting of adverse events.

Irrespective of study drug relationship, the most frequently reported AEs (all grades) by PT in > 20% of the patients were CRS, neutropenia, anemia, headache, diarrhea and white blood cell count decreased The most common grade ≥ 3 AEs reported in ≥ 10% of patients any time post-infusion were neutropenia (42.3%), neutrophil count decreased (17.5%), WBC count decreased (17.5%), anemia (16.5%), febrile neutropenia (12.4%) and thrombocytopenia (11.3%). Of note, all CRS events were grade 1-2, apart from one fatality more than one year after infusion, attributed to a late onset of CRS by the Investigator and described in below.

Table 43 AEs post-tisagenlecleucel infusion, irrespective of tisagenlecleucel relationship, by PT, time period, and maximum grade, and occurring in more than 10% of patients in within 8 weeks column (Safety set)

	Within 8 weeks N=97		>8 weeks to 1 year N=96		>1 year N=71	
Preferred terms	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one AE	94 (96.9)	69 (71.1)	80 (83.3)	41 (42.7)	19 (26.8)	7 (9.9)
Cytokine release syndrome	47 (48.5)	0	1 (1.0)	0	1 (1.4)	1 (1.4)
Neutropenia	32 (33.0)	31 (32.0)	19 (19.8)	17 (17.7)	3 (4.2)	3 (4.2)
Anemia	24 (24.7)	13 (13.4)	8 (8.3)	5 (5.2)	0	0
Headache	23 (23.7)	1 (1.0)	2 (2.1)	0	0	0
Diarrhea	17 (17.5)	1 (1.0)	10 (10.4)	0	0	0
White blood cell count decreased	17 (17.5)	12 (12.4)	12 (12.5)	7 (7.3)	2 (2.8)	0
Thrombocytopenia	16 (16.5)	9 (9.3)	8 (8.3)	5 (5.2)	2 (2.8)	1 (1.4)
Fatigue	15 (15.5)	3 (3.1)	4 (4.2)	0	0	0
Neutrophil count decreased	15 (15.5)	15 (15.5)	6 (6.3)	6 (6.3)	0	0
Constipation	13 (13.4)	0	2 (2.1)	0	0	0
Nausea	12 (12.4)	2 (2.1)	3 (3.1)	0	0	0
Pyrexia	11 (11.3)	1 (1.0)	8 (8.3)	0	0	0
Febrile neutropenia	10 (10.3)	10 (10.3)	2 (2.1)	2 (2.1)	0	0

- A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.
Preferred terms are presented in descending frequency of the all grades column, as reported in the within 8 weeks column.
MedDRA version 24.0 and CTCAE version 4.03 have been used for the reporting of adverse events.

As observed in other NHL indications, the majority of the AEs occurred within the initial 8- week period post -tisagenlecleucel infusion (96.9%). The incidence of AEs decreased after this time period: 83.3% at > 8 weeks to 1 year post-infusion and 26.8% (19/71 patients) > 1 year post-infusion.

The most common AEs reported in ≥ 10% of patients between >8 weeks to 1 year post-infusion were neutropenia (19.8%), WBC count decreased (12.5%), and diarrhea (10.4%).

The most common AEs reported in ≥ 2% of patients >1 year post-tisagenlecleucel infusion were neutropenia (4.2%), pneumonia (4.2%), arthralgia (2.8%), COVID-19 (2.8%), thrombocytopenia (2.8%) and WBC count decreased (2.8%).

Grade ≥ 3 AEs were reported in a total of 76 patients (78.4%).

- Within 8 weeks of tisagenlecleucel infusion, grade ≥ 3 AEs were reported in 71.1% of patients.
- From 8 weeks to 1 year post-tisagenlecleucel infusion, grade ≥ 3 AEs were reported in 42.7% of patients.

- More than 1 year post-tisagenlecleucel infusion, grade ≥ 3 AEs were reported in 9.9% of patients (n = 7).

CRS grade 1 or 2 was reported in 48 patients (49.5%). In 47 patients, CRS was reported within 8 weeks post-infusion and was suspected to be related to tisagenlecleucel. In 1 patient, CRS occurred more than 200 days after infusion and was not suspected to be related to tisagenlecleucel, but to other antineoplastic treatment given for disease progression after infusion. Moreover, there was 1 fatal event attributed to a late onset of CRS more than twelve months after infusion that was suspected by the investigator to be related to tisagenlecleucel, see below.

Tisagenlecleucel-related AEs

The majority of the patients (78.4%) had AEs suspected to be related to tisagenlecleucel that occurred anytime post-tisagenlecleucel infusion. The majority of these AEs were reported within the initial 8 weeks post-infusion. The most commonly reported AEs of any grade with a potential causal relationship to tisagenlecleucel are shown in **Table 45**.

Table 44 AEs anytime post-tisagenlecleucel infusion, suspected to be treatment related, by PT and maximum grade and occurring in more than 5% of patients (Safety set)

	All patients N=97	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one event	**76 (78.4)**	**45 (46.4)**
Cytokine release syndrome	47 (48.5)	1 (1.0)
Neutropenia	20 (20.6)	20 (20.6)
Anemia	13 (13.4)	7 (7.2)
Hypogammaglobulinemia	10 (10.3)	1 (1.0)
Neutrophil count decreased	10 (10.3)	9 (9.3)
White blood cell count decreased	8 (8.2)	6 (6.2)
Fatigue	7 (7.2)	3 (3.1)
Headache	7 (7.2)	0
Thrombocytopenia	7 (7.2)	5 (5.2)
Febrile neutropenia	6 (6.2)	6 (6.2)
Lymphocyte count decreased	6 (6.2)	5 (5.2)
Nausea	6 (6.2)	2 (2.1)
Platelet count decreased	6 (6.2)	4 (4.1)
Pyrexia	6 (6.2)	1 (1.0)

PTs are presented in descending frequency of the all grades column.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03.

Tisagenlecleucel related reactions

Most common ADRs were the following:

- The most common non-hematological ADRs (>25%) were CRS (50%), infections (50%), and headache (26%).
- Most common Blood and lymphatic system disorders were neutropenia (42%), anaemia (26%), thrombocytopenia (20%) and febrile neutropenia (12%).

- The most common hematological laboratory abnormalities were decreased lymphocytes (92%), decreased hemoglobin (94%), decreased white blood cells (91%), decreased neutrophils (89%), and decreased platelets (89%).
- Grade 3 and 4 ADRs were reported in 76% of patients. The most common Grade 3 and 4 non-hematological ADRs were infections (16%).
- The most common (≥25%) Grade 3 and 4 hematological laboratory abnormalities were lymphocyte count decreased (87%), white blood cell count decreased (74%), neutrophil count decreased (71%), platelet count decreased (26%) and hemoglobin decreased (25%).

Serious adverse event/deaths/other significant events

Deaths

Seven patients died during the course of the study, with all deaths occurring >30 days post tisagenlecleucel infusion. Of these 7 deaths, 5 occurred due to progression of the underlying disease.

Table 45 Deaths, other serious or clinically significant adverse events post-tisagenlecleucel infusion (Safety set)

	All subjects N=97
Number of subjects with at least one AE	**96 (99.0)**
Suspected to be study drug related	76 (78.4)
Death within 30 days post CTL019 infusion	0
Death >30 days post CTL019 infusion	7 (7.2)
Subjects with serious or other significant events	
Any time post CTL019 infusion	
SAE	42 (43.3)
Suspected to be study drug related	29 (29.9)
Grade >=3 AE	76 (78.4)
Suspected to be study drug related	45 (46.4)
Within 8 weeks post CTL019 infusion	
SAE	27 (27.8)
Suspected to be study drug related	23 (23.7)
Grade >=3 AE	69 (71.1)
Suspected to be study drug related	39 (40.2)
AE of special interest (AESI)	88 (90.7)
Grade >=3 AESI	68 (70.1)
Suspected to be study drug related	65 (67.0)
>8 weeks post CTL019 infusion	N=96
SAE	21 (21.9)
Suspected to be study drug related	9 (9.4)
Grade >=3 AE	41 (42.7)
Suspected to be study drug related	23 (24.0)

- All deaths during both study follow-up and survival follow-up are summarized.
- A subject with multiple severity grades for an AE is only counted under the maximum grade.
- MedDRA version 24.0, CTCAE version 4.03.
- For the summary of >8 weeks post-tisagenlecleucel infusion, the percentage is based on the number of subjects who are still in study follow-up at 8 weeks post-tisagenlecleucel infusion.

One patient died 1 year after tisagenlecleucel infusion due to a second episode of CRS as per Investigator assessment, and one patient died following euthanasia chosen for worsening progressive neurological symptoms due to possible PML.

A 72-year-old male patient had one episode of CRS on Day 7, which resolved on Day 30. The patient received tisagenlecleucel at a dose of 1.1×10^8 CAR positive viable T-cells. On Day 345 in the setting of ongoing pancytopenia and pneumonia, the patient had hypotension (60 mm Hg) that was attributed to sepsis or hypercytokinemia, with concurrent grade 3 encephalopathy. By means of exclusion, the Investigator diagnosed CRS. The treatment included vasopressin initially for progressive hypotension, tocilizumab (8 mg/kg, 2 doses) and high-dose corticosteroids (methylprednisolone 1 g). On Day 375, adalimumab (1 dose) and antithymocyte immunoglobulin (1 dose) were administered. The patient died on the same day due to multiorgan failure despite four lines of treatment for CRS. In the absence of a definitive diagnosis of sepsis or autoimmune disorder, the Investigator attributed the death to CRS. The Investigator suspected a causal relationship between tisagenlecleucel and the death. Novartis comment: Transgene levels at Month 3 were 96 copies/µg, and at Month 6 and Month 9 (6 and 3 months before the death, respectively) were below the limit of sensitivity, which makes a new onset of CRS at Month 12 due to tisagenlecleucel unlikely. Since a blood sample for transgene and cytokine analysis were not collected at Month 12 and in the absence of supporting investigations at the time of the event, the causality of fatal CRS was conservatively considered not assessable with tisagenlecleucel. In addition, pancytopenia and pneumonia further confounded the assessment. Autopsy results were not available at the time of the study report.

A 57-year-old female patient received tisagenlecleucel at a dose of 1.8×10^8 CAR-positive viable T-cells. The patient achieved CR at Month 3 assessment. The patient experienced grade 1 CRS on Day 4 that resolved. On Day 11, the patient developed encephalopathy. On Day 12, the patient was diagnosed with encephalitis due to HHV6 (Human Herpes Virus 6) and was treated with ganciclovir for 3 weeks and also corticosteroids, after which the event resolved. Because the HHV6 DNA levels in CSF were at the limit of sensitivity, it was not fully diagnostic for HHV6 encephalitis, and the Principal Investigator considered that the neurological symptoms could have also been related to tisagenlecleucel and recorded 2 distinct events (encephalopathy grade 4 (immune effector cell-associated neurotoxicity syndrome) related to tisagenlecleucel, and HHV6 related encephalitis). Approximately 8 months after the infusion, the patient developed non-fluent aphasia and mild left paresis. The MRI showed multifocal white matter abnormalities and the CSF was negative for JC virus, although JC virus was isolated in the blood. Based on these findings, the Investigator provided a diagnosis of "possible" progressive multifocal leukoencephalopathy (PML) (radiological and clinical findings in keeping with PML, but viral screening on CSF negative, so a definitive diagnosis of PML was not possible). One month later, the patient presented with worsening of neurologic symptoms (grade 3), as well as new symptoms including ptosis and right hemiparesis. The patient chose euthanasia due to progressive neurological symptoms and died on Day 302. Last transgene levels performed on Day 250 (11-Jan-2021) were 139.6 copies/µg [Study E2202- CSR Section 12.2.1]. The patient was in ongoing CR at Month 6. The last planned efficacy assessment (Month 9) was not performed due to deterioration of the neurological symptoms. The patient did not receive any further anticancer treatment post-tisagenlecleucel infusion. Novartis comment: The causality between PML and tisagenlecleucel was considered not assessable. Prolonged immunosuppression due to multiple treatments for FL might have contributed to PML. Lack of autopsy results preclude a meaningful case assessment.

Other serious adverse events

Post-tisagenlecleucel infusion, forty-two patients (43.3%) experienced at least 1 SAE, 29 of whom (29.9%) had at least 1 SAE suspected to be related to tisagenlecleucel. Serious AEs were reported more frequently within the initial 8 weeks post-tisagenlecleucel infusion than in the period from >8 weeks to 1 year and >1 year post-infusion (27.8% vs. 19.8% and 7.0%). From >8 weeks to 1 year post-infusion, 8 patients had SAEs which were considered to be related to tisagenlecleucel and from >1year post-infusion, 2 patients had SAEs that were considered to be related to tisagenlecleucel. Serious AEs such as CRS (19.6%) and febrile neutropenia (6.2%) were expected tisagenlecleucel-related events and were managed by standard supportive care and concomitant medications. Two individual SAEs were noteworthy. They include a case of encephalopathy followed by possible PML and a fatal case of CRS (see above).

Table 46 SAEs anytime post-tisagenlecleucel infusion, irrespective of study drug relationship, by PT and maximum grade and reported in at least 2 patients (Safety set)

	All patients N=97	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of subjects with at least one event	**42 (43.3)**	**25 (25.8)**
Cytokine release syndrome	19 (19.6)	1 (1.0)
Pneumonia	8 (8.2)	5 (5.2)
Febrile neutropenia	6 (6.2)	6 (6.2)
Pyrexia	3 (3.1)	0
Encephalopathy	2 (2.1)	1 (1.0)
Infusion related reaction	2 (2.1)	2 (2.1)
Neutropenia	2 (2.1)	2 (2.1)
Pleural effusion	2 (2.1)	0
Squamous cell carcinoma	2 (2.1)	0

PTs are presented in descending frequency of the all grades column.
A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.

Adverse Events of Special Interest (AESIs)

Important identified safety concerns for Kymriah:

- Cytokine release syndrome
- Serious neurological adverse reactions
- Infections
- Tumor lysis syndrome
- Prolonged depletion of normal B-cells/Agammaglobulinemia
- Hematological disorders including cytopenias

Important potential safety concerns for Kymriah:

- Cerebral edema
- Generation of replication competent lentivirus

- Secondary malignancies (including vector insertion site oligo/monoclonality)
- New occurrence or exacerbation of an autoimmune disorder
- Aggravation of graft-versus-host disease
- Transmission of infectious agents
- Decrease in cell viability due to inappropriate handling of the product

Cytokine Release Syndrome (CRS)

Forty-seven patients (48.5%) had CRS. With the exception of one fatal grade 5 CRS case, all of these patients had either grade 1 (n = 26) or grade 2 (n = 20) CRS. There were no patients with grade 3/4 CRS. The CRS events had resolved at the time of the data cut-off.

The median time to onset of CRS was 4.0 days (range: 1 to 14 days) and the median duration of CRS events was 4 days (range: 1 to 24 days), excluding the two late events that occurred on Day 207 and Day 368, respectively post-infusion:

One of these cases did not have CRS within 8 weeks after infusion. Following documented disease progression (Day 85) the patient received a new antineoplastic investigational treatment (T-cell engaging bispecific antibody) since Day 120. Subsequently, the patient developed 3 consecutive episodes of grade 1 CRS from Day 207 to Day 222 while he was on the investigational treatment. The Investigator suspected a causality for CRS related to the investigational antineoplastic drug but not to tisagenlecleucel. The patient subsequently received radiotherapy, rituximab, and lenalidomide. Last detectable transgene levels were recorded at Month 6 (25.69 µg/copies of DNA). Transgene levels were subsequently not quantifiable at Month 9 and Month 12. The patient was continuing in the study for survival follow up at the time of this report.

The other patient had a first episode of CRS grade 1 after infusion that did not require anti-cytokine treatment. Almost 1 year after infusion, the patient developed encephalopathy, fever, persistent hypotension and hypoxia in the context of pancytopenia and pneumonia. Despite 4 lines of treatment for CRS, this event led to death. (for more information see above)

Table 47 Cytokine release syndrome (Safety set)

	All subjects N=97
Cytokine release syndrome (CRS) - n (%)	
No	50 (51.5)
Yes*	47 (48.5)
Maximum CRS grade (Lee grading system) - n (%)	
Grade 1	26 (26.8)
Grade 2	20 (20.6)
Grade 3	0
Grade 4	0
Grade 5	1 (1.0)

-Only CRS events considered related to tisagenlecleucel are presented in this table.
-[Patient E2202 3000-004] was not captured in this table, for whom Grade 1 CRS was reported on Day 207 post-infusion and the CRS was related to another investigational drug (T-cell engaging bi-specific antibody).

Concurrent infections were observed in 7 patients (14.9%). These infections were esophageal candidiasis, urinary tract infection, HHV6 infection, Pseudomonas sepsis, bacteremia (Staphylococcus aureus), Escherichia sepsis and rhinovirus infection. Fever was reported in 43 patients and in the remaining 5 patients without concurrent fever, 2 patients had febrile neutropenia/neutropenic fever. Organs that were affected with CRS toxicity included the heart (grade 2 cardiac toxicity), the kidney (grade 1 blood creatinine increased) and the skin (grade 2 maculopapular rash). Each toxicity was reported in 1 patient each. All these toxicities had resolved at the time of the data cut-off date

Table 48 Description of CRS first episodes (Safety set, in patients with CRS)

Other CRS-related organ toxicities - n (%)	**3 (6.4)**
Cardiac - n (%)	1 (2.1)
Respiratory - n (%)	0
Hepatic - n (%)	0
Renal - n (%)	1 (2.1)
Neurologic - n (%)	0
Skin - n (%)	1 (2.1)
Other - n (%)	0
Systemic anti-cytokine therapy given - n (%)	**16 (34.0)**
Tocilizumab	16 (34.0)
1 dose	8 (17.0)
2 doses	5 (10.6)
3 doses	3 (6.4)
Siltuximab	0
Corticosteroids	3 (6.4)
Other	0

-All percentages presented are based on the number of subjects with CRS. Only the first CRS episode is summarized for each subject.

Systemic anti-cytokine treatment with tocilizumab or corticosteroids was required in 17 patients (17.5%) in the Infused set, which included 16 of the 47 patients (34.0%) who had CRS in the first 8 weeks from infusion. Thirteen of those patients required only 1 (n=8) or 2 (n=5) doses of tocilizumab, and 4 patients required both tocilizumab and corticosteroids [i.e. dexamethasone (n=1) and methylprednisolone sodium succinate (n=3)]. None of the patients received high dose steroids apart from the fatal case (described in subsection "Deaths" in section 4.6.4. As per the protocol CRS management algorithm, tocilizumab 8 mg/kg could be administered every 8 hours starting from grade 2 CRS (for a maximum of 3 doses within 24 h).

According to the Clinical Study Report v1.0, all CRS events, with the exception of one fatal CRS AE, were of grade 1/2 severity, indicating adequate management of these events through the CRS management algorithm. The absence of grade 3/4 CRS within initial 8 weeks in this trial differs from previous experience in DLBCL in the JULIET study and could be explained partially by the less aggressive nature of FL, but also by the use of a modified treatment algorithm which includes earlier use of anti-cytokine therapy like tocilizumab in the presence of symptoms requiring mild intervention. Data suggest this may decrease the incidence of high grade CRS and potential complications from CRS, resulting in improved outcomes for the patients.

Table 49 CRS management according to study protocol.

CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
Grade 1 Mild general symptoms requiring symptomatic treatment only e.g. fever, nausea, fatigue, headache, myalgia, etc.	After excluding other causes (e.g. infection), treat specific symptoms with e.g. antipyretics, anti-emetics, anti-analgesics, etc.	Not applicable	Not applicable
Grade 2 Symptoms requiring moderate intervention: Hypoxia requiring low-flow oxygen supplementation (<40%) or Hypotension requiring intravenous fluids and low dose of one vasopressor or Grade 2 organ toxicities	Oxygen supplementation Start intravenous fluids and, if no improvement, follow with a low-dose vasopressor Treat organ toxicities as per local guidelines	8 mg/kg intravenously (maximum 800 mg) over 1 hour. Repeat every 8 hours, if not responsive to intravenous fluids and increasing oxygen supplementation. Limit to 3 doses within 24 hours: maximum total of 4 doses.	If no improvement after 24 hours of treatment with tocilizumab, administer 1 mg/kg methylprednisolone intravenously twice daily (2 mg/kg as initial bolus can be given) or equivalent steroid dose. Continue until Grade 1 or less, then taper over 3 days.
Grade 3 Symptoms requiring aggressive intervention: Hypoxia requiring high-flow oxygen supplementation (≥40%) or Hypotension requiring high-dose* or multiple vasopressors or Grade 3 organ toxicities or Grade 4 transaminitis	Oxygen supplementation Intravenous fluids and high-dose* vasopressor/s Treat organ toxicities as per local guidelines	See Grade 2	See Grade 2
Grade 4 Life-threatening symptoms requiring ventilator support, etc. or Grade 4 organ toxicity (excluding transaminitis)	Oxygen supplementation incl. ventilator support Intravenous fluids and high-dose* vasopressor/s Treat organ toxicities as per local guidelines	See Grade 2	Administer methylprednisolone 1000 mg intravenously daily (or equivalent steroid dose) for 3 days. If improves, then manage as per Grade 2.

*See Table 6-2

Table 50 High-dose vasopressors

Vasopressor	Dose to be given for ≥ 3 hours
Norepinephrine monotherapy	≥ 20 mcg/min
Dopamine monotherapy	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200 mcg/min
Epinephrine monotherapy	≥ 10 mcg/min
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 10 mcg/min*
If on combination vasopressors (not vasopressin)	NE of ≥ 20 mcg/min*

*Vasopressin and Septic Shock Trial (VASST) Norepinephrine Equivalent Equation:
NE dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷10] (Russell et al 2008)

Table 51 Cytokine release syndrome management algorithm as presented in updated SmPC Table 1

<table>
<tr><th>Cytokine release syndrome severity</th><th>Symptomatic treatment</th><th>Tocilizumab</th><th>Corticosteroids</th></tr>
<tr><td>Mild symptoms requiring symptomatic treatment only, e.g.
- low fever
- fatigue
- anorexia</td><td>Exclude other causes (e.g. infection) and treat specific symptoms with, for example, antipyretics, anti-emetics, anti-analgesics, etc.
If neutropenic, administer antibiotics per local guidelines</td><td>Not applicable</td><td>Not applicable</td></tr>
<tr><td>Symptoms requiring moderate intervention:
- high fever
- hypoxia
- mild hypotension</td><td>Antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed</td><td rowspan="3">If no improvement after symptomatic treatment administer tocilizumab intravenously over 1 hour:
- 8 mg/kg (max. 800 mg) if body weight ≥30 kg
- 12 mg/kg if body weight <30 kg
If no improvement, repeat every 8 hours (max total of 4 doses)*</td><td rowspan="3">If no improvement within 12-18 hours of tocilizumab, administer a daily dose of 2 mg/kg intravenously methylprednisolone (or equivalent) until vasopressor and oxygen no longer needed, then taper*</td></tr>
<tr><td>Symptom requiring aggressive intervention:
- hypoxia requiring high-flow oxygen supplementation or
- hypotension requiring high-dose or multiple vasopressors</td><td>High-flow oxygen
Intravenous fluids and high-dose vasopressor(s)
Treat other organ toxicities as per local guidelines</td></tr>
<tr><td>Life-threatening symptoms:
- haemodynamic instability despite intravenous fluids and vasopressors
- worsening respiratory distress
- rapid clinical deterioration</td><td>Mechanical ventilation
Intravenous fluids and high-dose vasopressor(s)
Treat other organ toxicities as per local guidelines</td></tr>
<tr><td colspan="4">* If no improvement after tocilizumab and steroids, consider other anti-cytokine and anti-T cell therapies following institutional policy and published guidelines.</td></tr>
</table>

Alternative cytokine release syndrome management strategies may be implemented based on appropriate institutional or academic guidelines.

Table 52 Cytokine release syndrome management algorithm in current SmPC

Cytokine release syndrome severity	Management
Prodromal syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
Cytokine release syndrome requiring mild intervention - one or more of the following: – High fever – Hypoxia – Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
Cytokine release syndrome requiring moderate to aggressive intervention - one or more of the following: – Haemodynamic instability despite intravenous fluids and vasopressor support – Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation – Rapid clinical deterioration	• Administer high-dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. • Administer tocilizumab. - Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour - Patient weight ≥30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement. If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of cytokine release syndrome. Limit to a maximum total of 4 tocilizumab doses. • If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2 mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high-flow oxygen are no longer needed, then taper.

Serious neurological adverse reactions (SNARs)

Thirteen episodes of SNAR (including both non-serious AEs and SAEs) were reported in 11 patients (11.3%) post-tisagenlecleucel infusion. Nine patients experienced SNARs within 8 weeks post-tisagenlecleucel infusion. Preferred terms reported were Effector cell-associated neurotoxicity syndrome (4 cases), Encephalopathy (3 cases), Tremor (2 cases), Delirium, Dyskinesia, Dysphagia and Muscular weakness (one case each).

Grade 3/4 AEs (delirium and serious immune effector cell-associated neurotoxicity (ICANS) were reported in 3 patients:

- In a 56 year old female patient, the SAE of immune effector cell-associated neurotoxicity syndrome (ICANS) grade 4 (encephalopathy) was reported on Day 11 and was suspected to be related to tisagenlecleucel. The ICANS was improved to grade 1 on Day 14 and the event resolved on Day 16. Concomitant HHV6 encephalitis was reported as a concomitant SAE for this patient. The patient received high-dose steroids (for ICANS treatment) and ganciclovir (for

HHV6 encephalitis) with complete resolution of the events. The patient subsequently developed an SAE of possible PML and died for euthanasia related to worsening neurological symptoms. For a more detailed information, see description on fatal cases under "Deaths" in section 4.6.4

- In a 42 year old male, grade 3 delirium was reported on Day 190. At the time of the event, the patient's disease had progressed and treatment had started with a new systemic antineoplastic therapy. This event was not suspected to be related to tisagenlecleucel. It resolved on the same day without treatment.
- Another patient developed grade 3 encephalopathy (SAE) on Day 345, followed by CRS (SAE), approximately 1 year after tisagenlecleucel infusion. The patient died on Day 375 due to CRS per Investigator assessment with concomitant organ toxicities of acute kidney injury and capillary leak syndrome. For more detailed information, see description on fatal cases under "Deaths" in section 4.6.4

The MAH states in the Clinical overview addendum that Immune effector cell-associated neurotoxicity syndrome (ICANS) is introduced as a newly selected stand-alone ADR (by PT) in SmPC section 4.8 based on safety experience in Study CCTL019E2202. The PT ICANS was first introduced as a medical term in literature end of 2019 (Lee et al 2019) and subsequently included as PT with the release of MedDRA version 23.1 on 19-Apr-2020. Since the currently effective ADR Table 2 is based on statistical outputs generated in 2018, ICANS is not presented as ADR by nature. Since ICANS is based on a complex definition, appropriate re-mapping of previously reported ADRs reflective of CAR T-cell therapy associated neurotoxicity to ICANS is considered not feasible.

SNARs suspected to be related to tisagenlecleucel were reported in 8 patients (8.2%). The median time to onset of the first SNARs was 9.0 days (range: 4 to 345 days). At the time of the data cut-off date, 12 of the 13 SNARs had resolved. At Day 28 (from the day of event onset), the probability of all the cases of SNARs having completely resolved was 91.2% (95% CI: 67.7, 99.5), and at Day 91 it was 100%. There were no fatalities attributable to SNARs. The majority of the tisagenlecleucel-related SNARs required no specific protocol-defined intervention other than supportive care, unless an additional identified cause was defined (e.g. infection).

Hematological disorders including cytopenias

Post-tisagenlecleucel infusion, 76 patients (78.4%) experienced AEs of the SOC hematological disorders including cytopenias, mostly of grade ≥ 3 (74.2%) severity. Forty-two patients (43.3%) had AEs suspected to be related to tisagenlecleucel. These AEs were reported more frequently within the initial 8 weeks post-tisagenlecleucel infusion than in the periods from >8 weeks to 1 year after infusion and >1 year after infusion (75.3% vs. 42.7% and 11.3%).

Post-tisagenlecleucel hematological disorders including cytopenias most commonly reported (in ≥ 10% of the patients) were neutropenia (42.3%), anemia (25.8%), WBC count decreased (21.6%), thrombocytopenia (19.6%), neutrophil count decreased (17.5%), febrile neutropenia (12.4%) and platelet count decreased (10.3%).

Based on KM analysis of hematological laboratory parameters, by Month 6 the probability of resolution of all the cytopenias (leukopenia, anemia, thrombocytopenia, neutropenia and lymphopenia) ranged from 70% to 100% (see Table below).

These AEs were generally managed with standard measures of observation, blood product support, growth factors and/or antibiotics, as indicated in the protocol.

Table 53 Resolution of hematopoietic cytopenias post-tisagenlecleucel infusion (Safety set)

		All patients N=97							
	Week 4 event[1]	By Month 3[2]		By Month 6[2]		By Month 9[2]		By Month 12[2]	
Parameter	n (%)	Patients at risk	% Resolved probability	Patients at risk	% Resolved probability	Patients at risk	% Resolved probability	Patients at risk	% Resolved probability
WBC	13 (13.4)	5	61.5	2	84.6	1	92.3	1	92.3
Hemoglobin	3 (3.1)	0	100.0	0	100.0	0	100.0	0	100.0
Platelets	16 (16.5)	7	56.3	3	81.3	2	81.3	0	NE
Neutrophils	15 (15.5)	4	73.3	1	93.3	0	100.0	0	100.0
Lymphocytes	22 (22.7)	9	55.0	6	70.0	5	75.0	4	80.0

- Based on laboratory results regardless of blood transfusion.
- NE=Not estimable.
Week 4: defined as day 35 (i.e. Day 28 +7 day time-window for Day 28 visit).
[1] Number of patients with last value on or prior to Week 4 indicating grade 3 or 4 cytopenia
[2] Resolution of cytopenia is defined as achieving lab results of grade 2 or below.
% resolved probability is among patients with cytopenia at Week 4, obtained from the KM survival estimates

Prolonged depletion of normal B-cells/agammaglobulinemia

At the time of study entry, 25 patients (25.8%) had hypogammaglobulinemia, 2 patients (2.1%) had blood immunoglobulin G decreased. Sixteen patients (16.5%) had AEs of prolonged depletion of normal B-cells/agammaglobulinemia post-tisagenlecleucel infusion. These AEs were ongoing in 10 patients at the time of the data cut-off date. Of the 16 patients, 10 patients (10.3%) had AEs suspected to be related to tisagenlecleucel. One patient had a grade 3 AE. No grade 4 AEs were reported. Prophylactic iv immunoglobulins were administered to 33 patients. None of the AEs were serious or led to fatal infections.

Infections

Infections occurring at any time post-infusion were reported in 48 patients (49.5%), 13 (13.4%) of whom had infections suspected to be related to tisagenlecleucel. Most of the patients had either grade 1 or 2 infections. Grade ≥ 3 infections were reported in 15 patients (15.5%), 8 of whom (8.2%) had AEs suspected to be related to tisagenlecleucel. There were no patients with grade 4 or fatal infections.

The majority of the patients had infections either within the initial 8 weeks (n=18, 18.6%) or in the period from >8 weeks to 1 year post-tisagenlecleucel infusion (n=37, 38.5%). Only 5 patients had infections >1 year after the infusion. Infections were managed with standard supportive measures and antibiotics.

Tumor lysis syndrome

TLS was reported in 2 patients (2.1%):

- In a 46-year-old male patient, the TLS (grade 3), which was suspected to be related to tisagenlecleucel by the Investigator, started on Day 10 and resolved on Day 16 with rasburicase treatment.
- In a 42-year-old male patient, disease progression was diagnosed on Day 93. The patient developed TLS (grade 3) on Day 125 that was not suspected by the Investigator to be related to tisagenlecleucel but to progressive disease. Of note, the patients received treatment with etoposide, carboplatin, ifosfamide and rituximab from Day 128 to Day 131. The TLS resolved on Day 132 with treatment (allopurinol).

There were no AEs reported concerning Cerebral edema, Generation of replication competent lentivirus, Transmission of infectious agents and Decrease in cell viability due to inappropriate handling of the product.

Aggravation of GVHD

GVHD was observed in one patient. This patient experienced disease progression on Day 91 post-infusion and subsequently received allogeneic SCT on Day 246. On Day 278, a diagnosis of grade 2 skin GVHD was made; it resolved with sequelae on Day 288 with treatment (tacrolimus and mycophenolate). On Day 292, the patient had grade 3 intestinal GVHD that was considered an SAE. The patient was given the same treatment as the first GVHD episode and the event resolved on Day 345. The events were not suspected to be related to tisagenlecleucel but to allogeneic transplant by the Investigator.

Secondary malignancies (including vector insertion site oligo/monoclonality)

Secondary malignancies were reported in 4 patients (4.1%) of which only one suspected to be related to both LD chemotherapy and tisagenlecleucel by the Investigator. The rest of the cases were not suspected to be related to tisagenlecleucel.

Laboratory findings

Local clinical laboratory parameters collected in Study E2202 included hematology, blood chemistry, urinalysis, coagulation, pregnancy screening, influenza, viral serology and serum immunoglobulin levels. Laboratory data were classified into CTCAE grades using version 4.03. For laboratory tests where grades were not defined by CTCAE 4.03, results were graded by the low/normal/high classifications based on laboratory normal ranges.

Hematologic laboratory abnormalities

Hematologic laboratory abnormalities were frequent. Post-tisagenlecleucel cytopenias were seen in 78.4% of patients. The hematological laboratory parameters that worsened to grade 3/4 post-baseline most commonly (in >50% of patients) are shown in **Table 54**.

Table 54 Hematology laboratory abnormalities post-tisagenlecleucel infusion based on CTCAE grade (Safety set)

Laboratory parameters	All patients N=97	
	Post-BL All grades n (%)	Worsened from BL G0 to G2 to Post-BL G3/4 s/m (%)
Neutrophils (hypo)	86 (88.7)	45/67 (67.2)
Lymphocytes (hypo)	89 (91.8)	10/16 (62.5)
Leukocytes (hypo)	88 (90.7)	26/49 (53.1)
Hemoglobin (hypo)	91 (93.8)	19/91 (20.9)
Platelets (hypo)	86 (88.7)	15/87 (17.2)
Activated partial thromboplastin time (hyper)	24 (24.7)	6/89 (6.7)
Lymphocytes (hyper)	11 (11.3)	2/91 (2.2)
Fibrinogen (hypo)	14 (14.4)	0/92
Prothrombin Intl. normalized ratio (hyper)	3 (3.1)	0/49
Leukocytes (hyper)	0	0/97

- BL=Baseline, Gx=Grade x
- n = Number of patients with worst post-baseline grade 1 to 4.
- m= number of patients with baseline grade 0 to 2 laboratory values.
- s = Number of patients with grade 0 to 2 laboratory values at baseline and shifted to grade 3 to 4 post-baseline.
- Patients are counted only for the worst grade observed post-baseline.
- Events in this table are arranged in descending number of patients in "Worsened from BL G0 to G2 to Post-BL G3/4" column.

The most common (>25%) Grade 3 and 4 haematological laboratory abnormalities were lymphocyte count decreased (87%), white blood cell count decreased (74%), neutrophil count decreased (71%), platelet count decreased (26%) and haemoglobin decreased (25%) (data not shown).

Clinical chemistry

Post-baseline clinical chemistry abnormalities were mostly grade 1 or 2. The most common clinical chemistry abnormalities that worsened to grade 3/4 post-baseline were decreased phosphate (10.9%), increased glucose (5.4%) and decreased potassium (5.2%).

Liver enzymes

Minor elevations of liver enzymes were observed in a limited numbers of patients - ALT or AST >3× ULN was noted in 6 patients, ALT or AST >5× ULN was noted in 2 patients, and total bilirubin >3× ULN was noted in 1 patient. One patient had ALT or AST >20x ULN. Four patients had total bilirubin (TBL) >2x ULN. There were no serious adverse hepatic events reported.

Table 55 Biochemistry laboratory abnormalities post-tisagenlecleucel infusion based on CTCAE grade (Safety set)

	All patients N=97	
Laboratory parameters	**Post-BL All grades**	**Worsened from BL G0 to G2 to Post-BL G3/4**
	n (%)	**s/m (%)**
Phosphate (hypo)	38 (39.2)	10/92 (10.9)
Glucose (hyper)	65 (67.0)	5/92 (5.4)
Potassium (hypo)	25 (25.8)	5/97 (5.2)
Corrected calcium (hypo)	46 (47.4)	2/93 (2.2)
Albumin (hypo)	45 (46.4)	2/95 (2.1)
Alanine aminotransferase (hyper)	45 (46.4)	2/97 (2.1)
Urate (hyper)	26 (26.8)	2/95 (2.1)
Aspartate aminotransferase (hyper)	30 (30.9)	1/97 (1.0)
Sodium (hypo)	26 (26.8)	1/96 (1.0)
Potassium (hyper)	24 (24.7)	1/97 (1.0)
Sodium (hyper)	18 (18.6)	1/97 (1.0)
Bilirubin (hyper)	15 (15.5)	1/97 (1.0)
Corrected calcium (hyper)	10 (10.3)	1/96 (1.0)
Alkaline phosphatase (hyper)	44 (45.4)	0/97
Creatinine (hyper)	36 (37.1)	0/97
Magnesium (hypo)	26 (26.8)	0/96
Glucose (hypo)	13 (13.4)	0/92
Magnesium (hyper)	6 (6.2)	0/96
Gamma glutamyl transferase (hyper)	2 (2.1)	0/4

- n = Number of patients with worst post-baseline grade 1 to 4.
- m= number of patients with baseline grade 0 to 2 lab values.
- s = Number of patients with grade 0 to 2 lab values at baseline and shifted to grade 3 to 4 post-baseline.
- Patients are counted only for the worst grade observed post-baseline.
- Events in this table arranged in descending number of patients in "Worsened from BL G0 to G2 to Post-BL G3/4" column.

Urinalysis

Findings below or above normal ranges for urinary parameters were infrequent.

Vital signs, physical findings, and other observations related to safety

Abnormal vital signs values, high fever in particular, were mainly associated with events of CRS. The abnormal values eventually returned to normal levels with supportive care and were reported as AEs when considered clinically relevant by the Investigator.

Safety in special populations

In Study E2202, the incidence of AEs was analysed in different subgroups by gender, race, ethnicity, and bulkiness of the disease and it was noted that there were no major differences observed in AE incidences across these subgroups.

Pregnancy

There were no patients with positive pregnancy results at baseline or during the study. However, there was one case of pregnancy of a female partner of a male patient (Patient 2008-004). No further information was available at the time of this report.

Safety related to drug-drug interactions and other interactions

No information provided.

Discontinuation due to adverse events

No patients discontinued the study due to adverse events at time of DCO (29 March 2021).

Immunological events

Humoral immunogenicity

A patient was only defined as positive for tisagenlecleucel treatment-induced or -boosted anti-mCAR19 antibodies when the anti-mCAR19 antibody median fluorescence intensity (MFI) at any time post-infusion was at least 2.28-fold higher than pre-infusion levels for patients whose baseline status was positive (boosted) or if the baseline status was negative but any post-baseline interpretation was positive (induced). Treatment-induced or boosted anti-mCAR19 antibodies were observed in 27 patients in the CKAS (cellular kinetics analysis set), while 56 patients did not show induced or boosted response.

Table 56: Humoral immunity – Safety set.

		CR/PR N=84		SD/PD N=12		Unknown N=1		All Patients N=97	
		n	(%)	n	(%)	n	(%)	n	(%)
Baseline	Positive	52	(61.9)	11	(91.7)	1	(100.0)	64	(66.0)
	Negative	21	(25.0)	1	(8.3)			22	(22.7)
	Unknown	11	(13.1)					11	(11.3)
Day 14	Positive	54	(64.3)	10	(83.3)	1	(100.0)	65	(67.0)
	Negative	22	(26.2)	1	(8.3)			23	(23.7)
	Unknown	8	(9.5)	1	(8.3)			9	(9.3)
Day 28	Positive	54	(64.3)	11	(91.7)	1	(100.0)	66	(68.0)
	Negative	17	(20.2)	1	(8.3)			18	(18.6)
	Unknown	13	(15.5)					13	(13.4)
Month 3	Positive	50	(59.5)	9	(75.0)	1	(100.0)	60	(61.9)
	Negative	18	(21.4)	1	(8.3)			19	(19.6)
	Unknown	16	(19.0)	3	(25.0)			19	(19.6)
Month 6	Positive	48	(57.1)	3	(25.0)			51	(52.6)
	Negative	19	(22.6)	3	(25.0)			22	(22.7)
	Unknown	20	(23.8)	6	(50.0)	1	(100.0)	27	(27.8)
Month 12	Positive	32	(38.1)	4	(33.3)			36	(37.1)
	Negative	12	(14.3)					12	(12.4)
	Unknown	41	(48.8)	8	(66.7)	1	(100.0)	50	(51.5)
Month 18	Positive	15	(17.9)	2	(16.7)	1	(100.0)	18	(18.6)
	Negative	4	(4.8)					4	(4.1)
	Unknown	66	(78.6)	10	(83.3)			76	(78.4)
Month 24	Positive	2	(2.4)					2	(2.1)
	Unknown	82	(97.6)	12	(100.0)	1	(100.0)	95	(97.9)
At any time post-baseline *	Positive	74	(88.1)	12	(100.0)	1	(100.0)	87	(89.7)
	Negative	9	(10.7)					9	(9.3)
	Unknown	1	(1.2)					1	(1.0)

* Summary of at any time post-baseline also includes unscheduled assessments. 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.

The geometric mean AUC0-28d was similar in both the groups, whereas the geometric mean AUC0-84d and Cmax were observed to be 46% higher in patients with treatment-induced or boosted anti-mCAR19 antibodies post-tisagenlecleucel infusion. CTL019 Transgene levels were found to be highest amongst patients with unknown anti-mCAR19 antibody (Figure 32).

The pre-existing antibodies, i.e. at enrollment, or maximum fold change from baseline to post-infusion were not associated with any impact on clinical response (Figure 30 and Figure 31) There was no apparent relationship between CRS grade and maximum fold change from baseline for anti-mCAR19 antibody levels. There were no grade 3 / 4 CRS events within 8 weeks of infusion.

Treatment-boosted or treatment induced anti-mCAR19 antibodies did not appear to have an impact on the in vivo expansion of CAR-positive T-cells and persistence or clinical response.

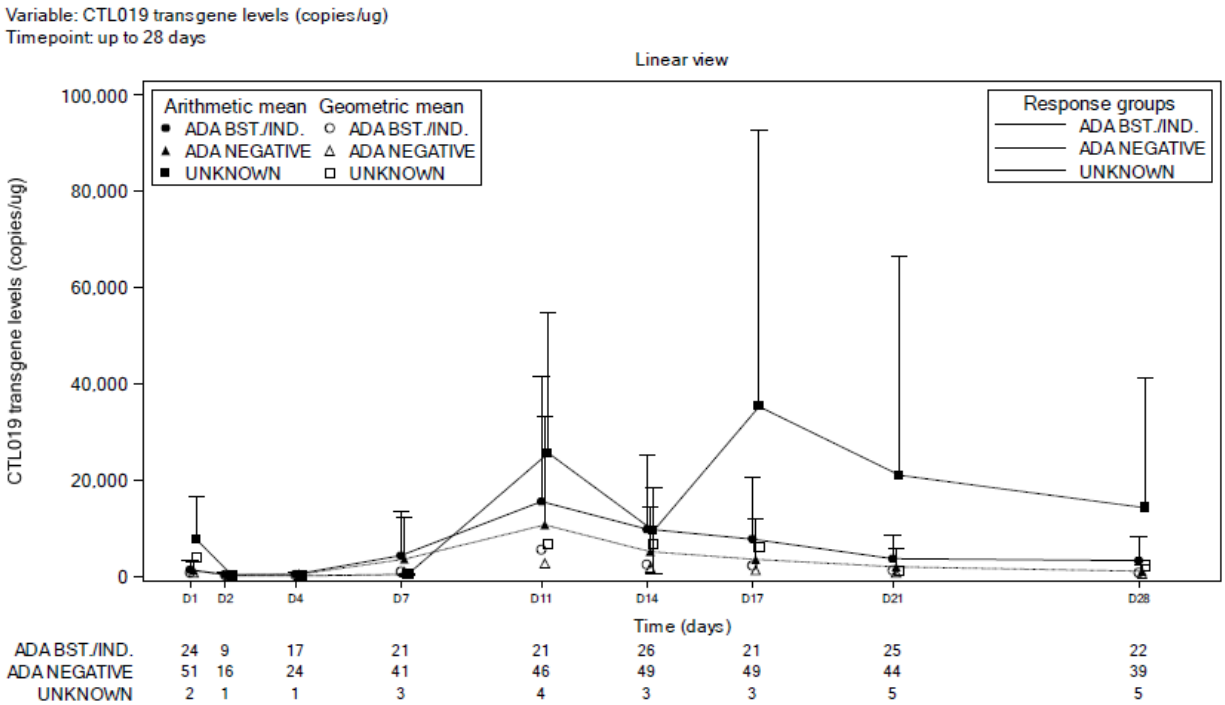


Figure 29. Geometric mean and arithmetic mean (SD) concentration-time profiles for Tisagenlecleucel in peripheral blood, by anti-drug antibody status - Tisagenlecleucel infused set

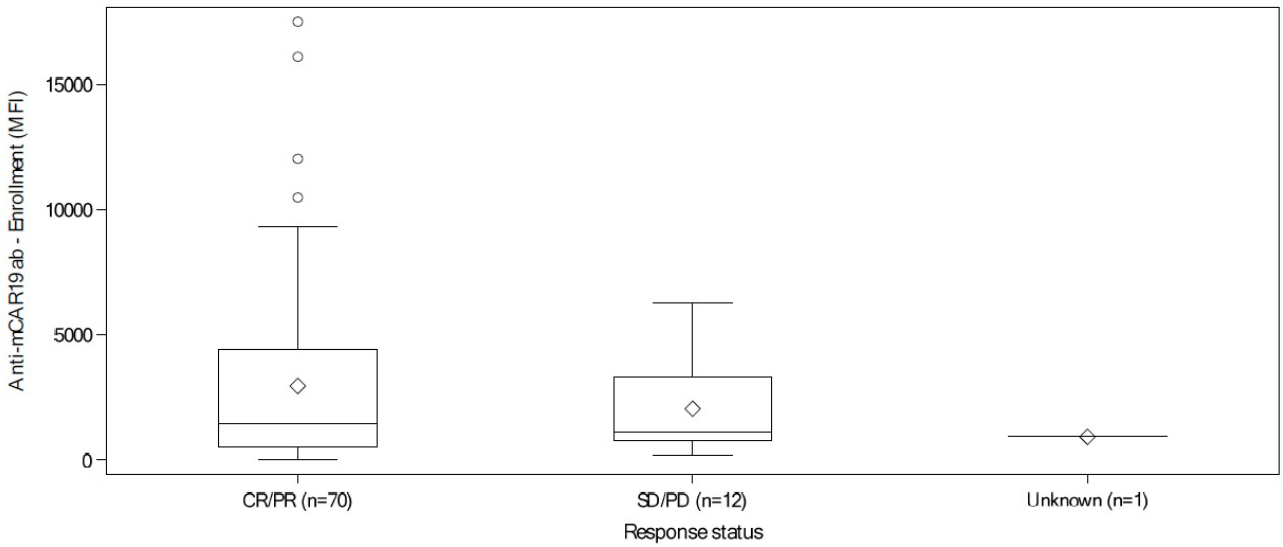


Figure 30: Boxplot of anti-mCAR antibodies at baseline and maximum fold change post-infusion by BOR – EAS

Diamond represents the mean and circle represents values outside of 1.5*IQR.
Lower and the upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3 respectively.
For baseline anti-mCAR19 ab (MFI) is plotted
For post-infusion ant-mCAR19 ab maximum fold change relative to baseline is plotted

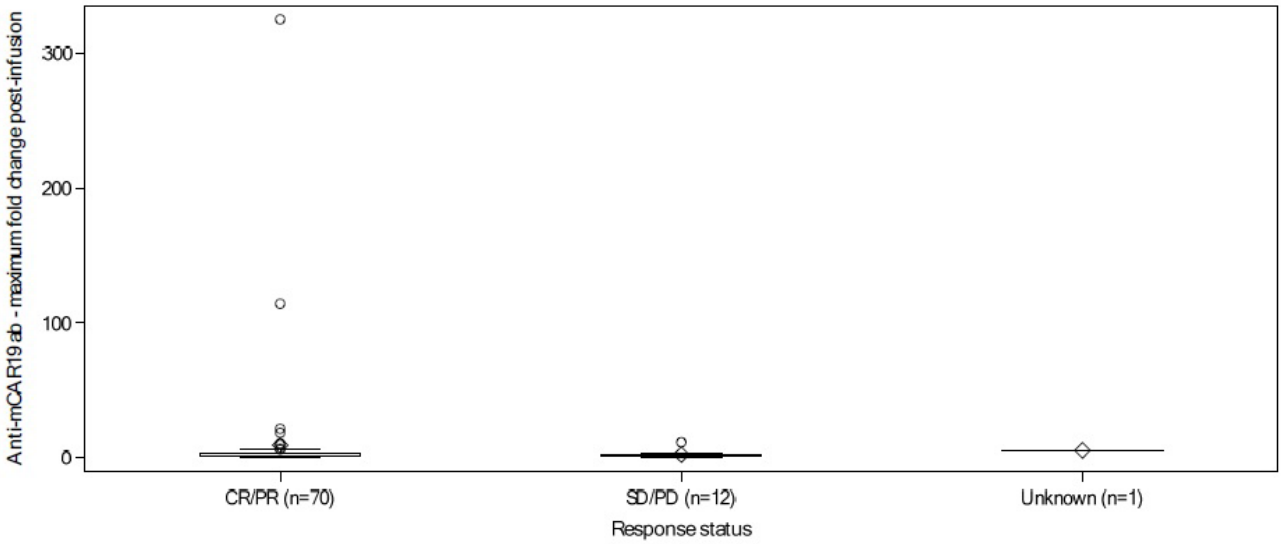


Figure 31: **Boxplot of anti-mCAR antibodies at baseline (a; over) and maximum fold change post-infusion by BOR (b) - Efficacy analysis set**

Diamond represents the mean and circle represents values outside of 1.5*IQR.
Lower and the upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3 respectively.
For baseline anti-mCAR19 ab (MFI) is plotted
For post-infusion ant-mCAR19 ab maximum fold change relative to baseline is plotted

Cellular immunogenicity

Activation of T-cells in peripheral blood mononuclear cells collected from patients 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 (IFNg+) cells by flow cytometry. The response measured by the assay is referred to as net response (%) and calculated for two mCAR19 peptide pools (Pool 1 and Pool 2). The two nonidentical peptide pools are comprised of approximately 60 overlapping 15-mer peptides, each, which are derived from the mCAR19 protein sequence.

The analysis 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.

Cellular responses to mCART peptides were measured pre-infusion (enrollment) and post-tisagenlecleucel infusion. In general, cellular immunogenicity responses were consistent and remained low (<1%) for most patients throughout the study, demonstrating that cellular immunogenicity does not fluctuate over time.

The analysis for the maximum net response post-baseline, for CD4+ and CD8+ T-cell responses for both Pool 1 and Pool 2 peptides, by BOR response, suggested cellular immunogenicity did not impact clinical outcome.

Post marketing experience

In the post marketing setting between 13-Aug-2020 and 12-Feb-2021, cumulatively an estimated 3223 patients (1116 patients with B-ALL and 2107 with DLBCL) have been treated worldwide [PSUR 5-Section 5.2.1]. There were no new or changing safety signals based on the evaluation of safety data obtained during the PSUR 5 reporting interval or cumulatively. A critical analysis of the efficacy and safety data revealed that the overall benefit-risk profile of tisagenlecleucel remains favourable.

Supportive data

Supportive data from the pivotal study A2101J

The study included 38 patients diagnosed with DLBCL (n = 24) or FL (n = 14). Among the 14 patients with FL in Study A2101J, the median age was 59 years (range: 43-72 years). Half of the patients were female (7/14).

Lymphodepleting chemotherapy in Study A2101J included bendamustine; cyclophosphamide alone or in combination with fludarabine or radiation therapy; carboplatin+gemcitabine and modified EPOCH (doxorubicin, etoposide, cyclophosphamide).

The most comprehensive description of the AE profile in Study A2101J is available from the 2-year follow-up. At this follow-up, most AEs were of grade 1 or 2 in severity with only a few grade 3 or 4 AEs, and only one grade 5 AE (Schuster et al 2017).

The publication by Schuster et al 2017 describes efficacy and safety in 28 patients enrolled in the study. Severe cytokine-release syndrome occurred in 5 patients (18%). Serious encephalopathy occurred in 3 patients (11%); 2 cases were self-limiting and 1 case was fatal. All patients in complete remission by 6 months remained in remission at 7.7 to 37.9 months (median, 29.3 months) after induction, with a sustained reappearance of B cells in 8 of 16 patients and with improvement in levels of IgG in 4 of 10 patients and of IgM in 6 of 10 patients at 6 months or later and in levels of IgA in 3 of 10 patients at 18 months or later.

Table 2. Adverse Events of Special Interest That May Have Been Related to CTL019 Therapy.*

Adverse Event	Grade					Total Events	Grade 3 or Higher
	1	2	3	4	5		
						number (percent)	
Cytokine release syndrome	0	11	4	1	0	16 (57)	5 (18)
Neurotoxicity	4	4	1	1	1	11 (39)	3 (11)
Encephalopathy	0	0	1	1	1	3 (27)	
Delirium	0	2	0	0	0	2 (18)	
Tremor	2	0	0	0	0	2 (18)	
Cognitive disturbance	1	0	0	0	0	1 (5)	
Confusion	0	1	0	0	0	1 (5)	
Involuntary movements	1	0	0	0	0	1 (5)	
Memory impairment	0	1	0	0	0	1 (5)	

* A list of all adverse events is provided in the Supplementary Appendix.

Sixteen of 28 patients experienced a CRS. Five patients had CRS events that were grade ≥3 in severity. One patient was treated with tocilizumab, experienced a rapid reversal of symptoms and had a complete response to treatment. No patients received glucocorticoids. No patient died due to CRS (Schuster et al 2017).

Eleven patients had neurotoxic events such as encephalopathy, delirium, tremor, cognitive disturbance, confusion, involuntary movements, memory impairment suspected to be related to tisagenlecleucel therapy. All the events were less than grade 3, except 3 events of grade ≥ 3 encephalopathy occurring in 3 individual patients. One 43-year-old male patient with prior history of optic atrophy developed CRS grade 2 and encephalopathy on Day 8 post tisagenlecleucel. He experienced protracted worsening of neurological disease and died from encephalopathy on Day 232. Post-mortem of this patient revealed diffuse gliosis with severe, widespread neuronal loss and degeneration of white matter but did not reveal a viral cause for the PML. There was no evidence of herpes simplex virus 1 or 2, cytomegalovirus, varicella–zoster virus, JC virus, adenovirus, or Epstein–Barr virus. The investigator stated that antecedent history of optic atrophy suggests that the patient might have had autoimmune CNS disease prior to receiving tisagenlecleucel (see Section 1.1.3.1.7). With the exception of this fatal event, the neurologic symptoms were selflimiting and resolved fully within 1 week (Schuster et al 2017, Chong et al 2021).

At the 5-year follow-up, limited safety data is available from 38 patients infused with tisagenlecleucel. Of note, 6 of 38 (16%) patients had secondary malignancies. No cases of RCL were detected (Chong et al 2021). No further data on adverse events was described in the publication.

Death

One patient with a history of optic atrophy died due to encephalopathy that led to progressive neurologic deterioration in Study A2101J. This death was reported at the time of the 2-year follow-up. (Schuster et al 2017). No additional deaths were reported in the 5-year follow-up (Chong et al 2021).

2.5.1. Discussion on clinical safety

Safety data are provided for the indication r/r FL (relapsed or refractory follicular lymphoma) based on data from the pivotal phase 2 Study E2202, including 97 patients treated with tisagenlecleucel infusion with a median duration of follow-up post-infusion of 16.59 months (range: 10.3 to 25.7 months). The enrolment of this study is complete, although the study is ongoing. Seventy-one patients had been followed-up >1 year at the data cut-off for the study.
The pivotal study has few patients included, indicating only common AEs are captured, but the data presented seems reassuring as AEs events reported in the study is similar to what has been seen in adult patients with other NHL indications (B-cell ALL and DLBCL); almost all (99.0%) having at least one AE following tisagenlecleucel infusion.

The current follow-up time is short for capturing long-term AEs. The study is ongoing and all patients will be followed for 12 months from infusion. After the end of this study, patients will continue to be followed for long-term safety under the long-term follow-up protocol CCTL019A2205B, a category 3 PASS. The purpose of this PASS is to monitor all patients treated with lentiviral vector based CD19 CAR -T- cell therapy in clinical trials for 15 years from the last CD19 CAR -T-cell infusion, to assess the risk of delayed AEs suspected to be related to CD19 CAR -T-cell therapy. Based on these aspects the number of patients and follow-up time is considered acceptable.
Most common AEs irrespective of tisagenlecleucel relationship are cytokine release syndrome (CRS, 49.5%) and cytopenias like neutropenia (42.3%), anaemia (25.8%), white blood cell count decreased (21.6%) and thrombocytopenia (19.6%) and febrile neutropenia (12.4%). Hypogammaglobulinemia

were seen in 14.4%. Febrile neutropenia was reported in 12.4% of the patients. Other very common AEs were headache (24.7%), diarrhoea (21.6%) and pyrexia (19.6%).
Cytopenias Grade ⩾3 was very common: Neutropenia (42.3%), anaemia (16.5%), white blood cell count decreased (17.5%) and thrombocytopenia (11.3%). All cases with febrile neutropenia were of Grade ⩾3.
A high degree of the AEs (78.4%) is suspected to be related to tisagenlecleucel. Most common treatment related AEs was CRS (48.5%), headache (7.2%) and blood and lymphatic system disorders like neutropenia (20.6%), anaemia (13.4%), thrombocytopenia (7.2%) and febrile neutropenia (6.2%). Most common grade ⩾3 study drug-related AE was neutropenia (20.6%).

As observed in other NHL indications, the majority of the AEs occurred within the initial 8-week period post-tisagenlecleucel infusion (96.9%). Still a high frequency of patients experienced AEs after this time period: 83.3% between 8 weeks and 1 year post-infusion. The frequency is however significantly lower > 1 year post-infusion (26.8%).

Cytokine release syndrome was an expected AE with tisagenlecleucel treatment. The frequency of CRS (48.5%) seems to be similar to what have been seen in patients with DLBCL (57%) in study CCTL019C2201. However, in contrast to patients with DLBCL (Grade 3/4 CRS: 23%), no patients with r/r FL had grade 3 or 4 CRS. This difference might be partly explained by the less aggressive nature of the FL disease, partly by the revised CRS management algorithm, which is now reflected in the proposed SmPC. The use of a modified treatment algorithm includes earlier use of tocilizumab in the presence of mild symptoms requiring intervention. The revised algorithm is considered acceptable.
All CRS cases occurred within 8 weeks with median TTO 4.0 days (range:1-14 days) and median duration was 4 days (range:1 to 24 days). Systemic anti-cytokine treatment with tocilizumab or corticosteroids was required in 17.5% of patients experiencing CRS. One grade 5 CRS syndrome occurring >1 year post-infusion were considered unlikely related to tisegenlecleucel infusion (see below).

Serious neurological adverse reactions (SNARs) were reported in 11.3%. Grade3 and 4 AEs (ICANS/encephaloapthy and/or delirium) were reported in 3 patients (3%). The median TTO was 9.0 days (range:4 to 345 days). It is estimated that by D91 post-infusion all SNARs have completely resolved without specific protocol-defined interventions other than supportive care. The MAH includes both serious and non-serious neurological reactions under the umbrella called SNARs.
ICANS (immune effector cell-associated neurotoxicity syndrome) is a new PT added as an ADR in SmPC section 4.8, table 2, which is considered acceptable. The proposed frequency is "common", which seems reasonable based on the number of cases described in the E2202 study. A footnote listing symptoms associated with ICANS is added.

Monitoring and management of ICANS is discussed in literature recently. It is agreed that the combined information on monitoring of neurological adverse reactions reflective of ICANS in (several sections of) the SmPC is adequate and that no further guidance is warranted.
A paragraph on ICANs as selected adverse events in the paragraph concerning Neurological adverse reactions in section 4.8. is adequately implemented**.**

Cytopenias were reported in 78.4% of patients, of which 74.2% had grade ⩾3. These AEs were reported more frequently within the initial 8 weeks post-tisagenlecleucel infusion than in the periods from >8 weeks to 1 year after infusion and >1 year after infusion (75.3% vs. 42.7% and 11.3%). Based on Kaplan-Meier analysis of hematological laboratory parameters, by month 6 the probability of resolution of all cytopenias range from 70% to 100%. The most common (>25%) Grade 3 and 4

haematological laboratory abnormalities were lymphocyte count decreased (87%), white blood cell count decreased (74%), neutrophil count decreased (71%), platelet count decreased (26%) and haemoglobin decreased (25%).

Infections are among the most common safety concerns following CAR-T treatment and is included as an important safety concern in the RMP. In FL patients infections were reported in 49.5% of patients, a somewhat lower frequency than seen in the DLBCL patients in study CCTL019C2201 (58%). Grade ⩾3 infections were reported in 15.5% of patients. There were no grade 4 infection, but one grade 5 case, a suspected case of PML about 8 months post-infusion. Causality was not assessable according to the MAH. PML is associated with a life-threatening opportunistic viral infection (JC virus). Cumulatively three cases of PML are listed in PSUR 5 for tisagenlecleucel. Two cases of PML have been reported in the literature suspected to be related to CAR-T cell treatment (axicabtagene ciloleucel) occurring 14 months and 7 months post-infusion.
In the SmPC section 4.4 it is informed that "Serious infections, including life-threatening or fatal infections, occurred frequently in patients after Kymriah infusion (see section 4.8). Patients should be monitored for signs and symptoms of infection and treated appropriately" and "Infections - pathogen unspecified, viral infections, bacterial infections" is listed as very common ADR in SmPC section 4.8. PML is not listed specifically as side effect of Kymriah. It is not considered that patients with FL are at higher risk of opportunistic infections or PML than other lymphoma patients treated with tisagenlecleucel or other CAR-T cell products. The MAH has, as requested, presented narratives of all suspected cases with late occurrence of opportunistic infections, agreed to include a text regarding monitoring for late occurrence of opportunistic CNS infections in the SmPC section 4.4, and agreed to update the RMP and educational materials accordingly. This is acceptable.

Prolonged depletion of normal B-cells/agammaglobulinemia were seen in 25.8% of patients. Hypogammaglobulinemia were reported in 14.4%, similar to what was seen in the DLBCL population (17%). One patient had a grade 3 AE. No grade 4 AEs were reported. 10 patients (10.3%) had hypogammaglobulinaemia suspected to be related to tisagenlecleucel. There were two cases of Tumor lysis syndrome, of which one was considered related to tisagenlecleucel. There was observed one case of GVHD, however this case was not suspected to be related to tisagenlecleucel infusion.
Secondary malignancies were reported in 4 patients. Two events in one patient – a grade 2 squamous cell carcinoma on Day 283 and a grade 2 malignant melanoma on Day 324 - were suspected to be related to both LD chemotherapy and tisagenlecleucel. The events in the three other patients were not suspected to be related to tisagenlecleucel

No AEs concerning Cerebral edema, Generation of replication competent lentivirus, Transmission of infectious agents and Decrease in cell viability due to inappropriate handling of the product were reported in study E2202 in r/r FL patients.

Seven patients died during the course of the study, with all deaths occurring >30 days post tisagenlecleucel infusion. Of these 7 deaths, 5 occurred due to progression of the underlying disease. The one death related to CRS syndrome occurring >1 year post-infusion, seems less likely to be related to tisagenlecleuecel infusion since transgene levels had been decreasing and were below the limit of sensitivity at Month 6 and Month 9 (6 and 3 months before the death, respectively). The other deaths was a possible case of PML (see above).

Supportive data from the pilot study A2101J are provided, based on two publications, one presenting data from a 2-year follow-up, the other from 5-year follow-up. The study includes 14 patients with FL. The most frequent AEs events were CRS and neurotoxicity. The safety data from the 5-year follow-up

is not described in detail, but overall, safety data presented from the pilot study A2101J seems in line with what has been seen in the pivotal study E2202.

Additional expert consultations

Not applicable

Assessment of paediatric data on clinical safety

Not applicable

2.5.2. Conclusions on clinical safety

The AEs events reported in the pivotal study including r/r FL patients are similar to what has been seen in adult patients with other NHL indications (B-cell ALL and DLBCL). CRS, cytopenias, infections and neurotoxicity are the most common AEs and most frequently reported first 8 weeks following tisagenlecleucel infusion.

The revised CRS management algorithm used in the study of FL patients recommends earlier use of systemic anti-cytokine treatment with tocilizumab or corticosteroids. It is considered acceptable that the revised algorithm is now proposed included in the SmPC section 4.4.

Serious neurological adverse reactions (SNARs) including cases classified as ICANS were reported in 11.3% and it is considered acceptable that ICANS is included as a specific term in SmPC section 4.8..

It can be concluded that the unfavourable effects and risks can be addressed by adequate risk mitigation measures in the SmPC and RMP, which is considered acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CAT received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.2 is acceptable.

The CAT endorsed this advice without changes.

Safety concerns

Important identified risks	• Cytokine release syndrome • Serious neurological adverse reactions • Infections • Tumor lysis syndrome • Prolonged depletion of normal B-cells/Agammaglobulinemia • Hematological disorders including cytopenias
Important potential risks	• Cerebral edema • Generation of replication competent lentivirus • Secondary malignancies (including vector insertion site oligo/monoclonality) • New occurrence or exacerbation of an autoimmune disorder • Aggravation of graft-versus-host disease • Transmission of infectious agents • Decrease in cell viability due to inappropriate handling of the product
Missing information	• Use in pregnancy and lactation • Use in patients with HBV/HCV/HIV • Use in patients with active CNS involvement by malignancy • Long-term safety • Immunogenicity

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
CCTL019B2401 (PASS) Non-interventional study with secondary use of data from the registries conducted by CIBMTR and EBMT, respectively, to evaluate the long-term safety of patients with malignancies treated with CAR T-cell therapies (ongoing)	The primary objective is to evaluate the safety of patients with B-lymphocyte malignancies treated with tisagenlecleucel in a real-world setting. The main secondary objective is to evaluate the long-term effectiveness of tisagenlecleucel.	• Cytokine release syndrome • Serious neurological adverse reactions • Infections • Tumor lysis syndrome • Prolonged depletion of normal B-cells/ Agammaglobulinemia • Hematological disorders including cytopenias • Cerebral edema • Secondary malignancies (including vector insertion site oligo/monoclonality) (as feasible) • New occurrence or exacerbation of an autoimmune disorder • Aggravation of graft-versus-host disease • Transmission of infectious agents • Use in pregnancy and lactation • Use in patients with HBV/HCV/HIV • Use in patients with active CNS involvement by malignancy Long-term safety	FPFV	Dec-2018
			Study completion date	Dec-2037
			Update reports	Annual reports (based on CIBMTR and EBMT registry data)
				Semi-annual reports (based on EBMT data only)
				5-yearly interim reports (first report in 2020)
			Final report of study results	Dec-2038

Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CCTL019A2205B (PASS) Long-term follow-up study in patients exposed to lentiviral-based CD19 directed CAR T-cell therapy in preceding clinical trials (ongoing)	The primary objective of the study is to describe selected, delayed AEs suspected to be related to previous CD19 CAR T-cell therapy as outlined in current Health Authority guidelines. The secondary objectives are to monitor the persistence of CD19 CAR transgene in peripheral blood, monitor the expression of RCL, assess the long-term efficacy of CD19 CAR-T, monitor lymphocyte levels and describe the growth, development, and female reproductive status for patients who were aged < 18 years at the time of the initial CD19 CAR T-cell infusion	• Cytokine release syndrome • Serious neurological adverse reactions • Infections • Tumor lysis syndrome • Prolonged depletion of normal B-cells/ Agammaglobulinemia] • Hematological disorders including cytopenias • Cerebral edema • Generation of replication competent lentivirus • Secondary malignancies (including vector insertion site oligo/monoclonality) • New occurrence or exacerbation of an autoimmune disorder • Aggravation of graft-versus-host disease • Transmission of infectious agents • Long-term safety • Immunogenicity	FPFV	Nov-2015
			Study completion date	Dec-2036
			Update reports	Annual reports
				5-yearly interim reports (first report in 2020)
			Final report of study results	Dec-2037

Risk minimisation measures

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
Important identified risks		
Cytokine release syndrome	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • Controlled distribution program • Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Serious neurological adverse reactions	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.7 Effects on ability to drive and use machines • SmPC Section 4.8 Undesirable effects	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
	• SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • Controlled distribution program • Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet	
Infections	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Tumor lysis syndrome	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Prolonged depletion of normal B-cells/Agammaglobulinemia	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.6 Fertility, pregnancy and lactation • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Hematological disorders including cytopenias	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Important potential risks		

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
Cerebral edema	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.7 Effects on ability to drive and use machines • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Generation of replication competent lentivirus	**Routine risk minimization measures** • None **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019A2205B
Secondary malignancies (vector insertion site oligo/ monoclonality)	**Routine risk minimization measures** • SmPC Section 5.3 Preclinical safety data • SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 (as feasible) • CCTL019A2205B
New occurrence or exacerbation of an autoimmune disorder	**Routine risk minimization measures** • None **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Aggravation of graft-versus-host disease	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Transmission of infectious agents	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 6.3 Shelf life • SmPC Section 6.4 Special precautions for storage • SmPC Section 6.5 Nature and contents of container and special equipment for use, administration or implantation • SmPC Section 6.6 Special precautions for disposal and other handling • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 5 How to store Kymriah • SmPC Section Other sources of information **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B

Safety concern	Risk minimization measures (routine and additional)	Pharmacovigilance activities
Decrease in cell viability due to inappropriate handling of the product	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 6.3 Shelf life • SmPC Section 6.4 Special precautions for storage • SmPC Section 6.5 Nature and contents of container and special equipment for use, administration or implantation • SmPC Section 6.6 Special precautions for disposal and other handling • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 5 How to store Kymriah • SmPC Section Other sources of information **Additional risk minimization measures** • Controlled distribution program • Educational program including the Pharmacy/Cell Lab/Infusion Center Training Material	**Additional pharmacovigilance activities** • None
Missing information		
Use in pregnancy and lactation	**Routine risk minimization measures** • SmPC Section 4.6 Fertility, pregnancy and lactation • SmPC Section 5.3 Preclinical safety data • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401
Use in patients with HBV/HCV/HIV	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 6.6 Special precautions for disposal and other handling • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Section Other sources of information **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401
Use in patients with active CNS involvement by malignancy	**Routine risk minimization measures** • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 5.1 Pharmacodynamic properties – Patients with active CNS leukemia **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401
Long-term safety	**Routine risk minimization measures** • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B
Immunogenicity	**Routine risk communication** • SmPC Section 5.2 Pharmacokinetic properties **Additional risk minimization measures** ● None	**Additional pharmacovigilance activities** • CCTL019A2205B

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and corresponding sections in the Package Leaflet are updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: No major changes to the PL have been introduced only minor text additions where done. The layout and design of the artwork has not been changed.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

3.1.2. Available therapies and unmet medical need

The management of symptomatic relapsed or refractory FL in the EU includes non-cross resistant chemo-immunotherapy agents, radio-immunotherapy, rituximab monotherapy, the PI3K inhibitor idelalisib and duvelisib, the combination of rituximab and lenalidomide, obinutuzumb in combination with bendamustine, and in selected cases autologous/allogeneic HSCT. The PI3K inhibitor idelalisib has been approved in the EU since 2014, for the treatment of relapsed FL after at least two prior lines of systemic therapy, with a CRR of 14%, ORR of 56% and DOR of 11.8 months (Salles et al 2017). Duvelisib is another PI3K inhibitor approved by EMA in May 2021 for the treatment of adult patients with refractory FL who have received at least 2 prior systemic therapies, with a 0% CRR and 40% PRR (Copiktra SmPC). The lenalidomide and rituximab combination (so-called R2) was approved by EMA in 2019 for the treatment of FL patients after at least 1 prior line of therapy, with a CRR of 34% and ORR of 81% (Rummel et al 2020). High-dose therapy (HDT) followed by ASCT can be a therapeutic option for certain patients with relapsed FL. The median PFS and OS in patients who relapsed after ASCT (n=95) was approximately 1 year after relapse (Sesques et al 2020). Allogeneic HSCT is a potentially curative therapy, and can be considered at relapse after autologous HSCT, but only a small fraction of patients with an available donor are candidates for it. Transplant-related mortality is 8-17% at 1 year (Epperla et al 2017), with a 3-year OS of 66%, and treatment-related mortality of 25% at 3 years (Sureda et al 2018).

The ESMO clinical guidelines specify which treatments are considered appropriate for which groups in the r/r FL population (Dreyling, 2021). In general, FL grade 1, 2 and 3a should be treated as indolent disease, whereas grade 3b should be treated as an aggressive lymphoma (Dreyling, 2021). In the case of relapsed disease, localised symptomatic disease may be managed with low-dose ISRT, while in early systemic relapses (<12-24 months), a non-cross resistant chemoimmunotherapy regimen is used. Rituximab is added if the previous antibody-containing scheme achieved >6-12-month DOR. Rituximab maintenance therapy every 3 months for up to 2 years is recommended for most r/r FL patients, except for those who have relapsed during their first rituximab maintenance period (Dreyling et al. 2021; Vidal et al. 2011). In rituximab-refractory cases or remissions lasting <6 months, obinutuzumab-bendamustine (or other chemotherapy regimen) plus obinutuzumab maintenance is recommended. High-dose chemotherapy with ASCT may be considered in patients with short-term first remissions after rituximab-containing regimens. In relapsed FL, lenalidomide plus rituximab may be

considered for patients with short remissions after chemotherapy. In symptomatic cases with low tumour burden, rituximab monotherapy may be applied. Radioimmunotherapy with yttrium-90 [^{90}Y]-radiolabelled ibritumomab tiuxetan may be considered in elderly patients with comorbidities. In later relapses, a non-chemotherapy approach is recommended, including treatment with lenalidomide plus rituximab, and idelalisib and duvelisib in double-refractory cases. In selected younger patients with later relapses with a high-risk profile or relapse after ASCT, allogeneic HSCT may be considered.

There is an unmet medical need in r/r FL in that treatment efficacy and duration of remission decline with every successive line of therapy. In the third or later lines of therapy, the overall proportion of patients with DOR >6 months among all treated patients remains low at only 18-30%. Death occurrs due to histological transformation to DLBCL or because FL becomes refractory to chemotherapy. Thus, there can be considered to be an unmet medical need in FL patients with frequent relapses, where therapies generally result in modest CRR and responses are not durable, thus necessitating further treatments with associated toxicities and the risk of histological transformation.

3.1.3. Main clinical studies

The MAH has submitted data from one ongoing pivotal phase 2 study E2202 (ELARA) in adult patients with r/r FL. In addition, they have submitted the results from a completed supportive pilot phase IIa study, A2101J, which is reported in two articles and where the MAH does not have access to individual patient data. To contextualise the findings presented in the pivotal single-arm study E2202, the MAH carried out two analyses of real-world data, ReCORD and Flatiron, in addition to a systematic literature review.

The pivotal study E2202 is an ongoing open-label, multicenter, single arm, phase 2 study, designed to determine the efficacy and safety of tisagenlecleucel in adult patients with r/r FL. Eligible patients were either i) refractory to a second line or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent) or relapsed within 6 months after completion of a second line or later line of systemic therapy or ii) relapsed during anti-CD20 antibody maintenance (following at least two lines of therapies as above) or within 6 months after maintenance completion or iii) relapsed after autologous HSCT. The primary endpoint was CRR as assessed by IRC, according to the Lugano response criteria (Cheson et al., 2014). CRR was defined as the proportion of patients with a BOR of CR recorded from tisagenlecleucel infusion until PD or start of new anticancer therapy, whichever came first. The null hypothesis in study E2202 was CRR being less than or equal to 15% at a 1-sided cumulative 2.5% level of significance, i.e. H0: $p \leq 0.15$ vs. Ha: $p > 0.15$. This hypothesis was based on the CRR reported for idelalisib in a similar patient population (Salles et al., 2017).

Autologous T-cells were harvested from eligible patients who then underwent optional bridging therapy and lymphodepleting chemotherapies while the harvested cells were processed into the study product Tisagenlecleucel was then re-administered via a single intravenous infusion at a target dose of 0.6 to 6.0×10^8 CAR-positive, viable T cells.

The data provided is based on an extended follow up analysis when 97 patients were infused with tisagenlecleucel and 90 patients had either completed 12 months of follow-up from the time of infusion or had discontinued earlier. 119 patients were screened, 21 of which did not meet the exclusion criteria. 98 patients were enrolled in the study. All patients who received a tisagenlecleucel infusion (n=97) were included in the Tisagenlecleucel infused set and the Safety set. Of these, 94 patients who had measurable disease at baseline per IRC were included in the EAS. Nine patients were excluded from the EAS to form the PPS (n=85). The first visit for the first patient was on 12-Nov-2018. The DCO for the interim analysis was 26-May-2020. The DCO for the extended follow-up analysis was 29-Mar-

2021. Database lock was on 07-May-2021. The DCO date for subsequent extended follow-up analysis was 03-Aug-2021. The study was ongoing at the time of CAT/CAHMP opinion.

3.2. Favourable effects

The primary endpoint was CRR determined by IRC in the EAS was met at the interim analysis (DCO: 26-May-2020), with a CRR of 65.4% (34/52; 99.5% CI: 45.1, 82.4). The result was statistically significant at a 1-sided critical alpha level of 0.0025 to reject the H0 of CRR $\leq$ 15%. No further significance testing was done at the primary and extended follow-up analyses. At the DCO of 29-Mar-2021, after a median of 16.9 months (range: 10.3-25.7) of follow-up, the CRR was 69.1% (65/94; 95% CI: 58.8, 78.3).

Subgroup analyses showed that the CRRs in various demographic and prognostic subgroups, including high-risk patients such as those with high FLIPI score (36/57; 63.2%; 95% CI: 49.3, 75.6), those with POD24 (36/61; 59%; 95%CI:45.7, 71.4), those who were double refractory (43/65; 66.2%; 95%CI: 53.4, 77.4), and those who were refractory to last line of prior therapy (51/74; 68.9%; 95%CI: 57.1, 79.2) were consistent with that observed in the overall study population. The CRR values by IRC assessment ranged from 40.0% to 87.9% in all subgroups analysed. The secondary endpoints were supportive of the observed benefit in terms of CRR. The ORR was 86.2% (81/94; 95% CI: 77.5, 92.4) per IRC assessment at the 29-Mar-2021 DCO. CRR and ORR remained unchanged at a later DCO (03-Aug-2021).

The median DOR per IRC assessment at the DCO of 29-Mar-2021 was not reached, but the estimated probability of remaining in response at 9 months was 76.0% (95% CI: 64.6, 84.2). The median OS was not reached. The estimated probability of survival was 91.6% (95% CI: 81.7, 96.2) at Month 18. At a later DCO (03-Aug-2021), with median follow up of 21 months (range: 14-30) in the EAS, 9-month DOR, 12-month PFS and OS remained unchanged from the previous DCO. Median PFS increased from 18.4 months to 29.5 months, with the caveat of a low number of patients at risk after month 25.

Supportive evidence for CRR and durable responses comes from the A2101J study 5 year follow up analysis. At a median follow-up of 28.6 months, DOR and OS were not reached. CRR was 71% (10/14) at 6 months. The probability of remaining in response was 60% (95% CI: 25, 83) at 5 years.

Contextualisation of the results was provided by two RWD studies, ReCORD and Flatiron. These showed a clinically meaningful difference in CRR to study E2202 of 31.8% (95% CI: 18.1, 45.3) and 51.4% (95% CI: 21.2, 68.8), for ReCORD and Flatiron studies, respectively The Kaplan-Meier estimate of the OS rate at 12 months was 96.6% [95% CI: 92.9%, 100%] in Study E2202, 71.7% [95% CI: 61.2%, 82.2%] in ReCORD (HR=0.2 [95% CI:0.02, 0.38]), and 84.5% [95% CI: 64.9%, 95.9%] in Flatiron (HR=0.41 [95% CI: 0.11, 1.47]).

In a systemic literature review, based on a historical cohort, a similar effect size was only observed for axicabtagene ciloleucel which uses the same overall technology as tisagenlecleucel.

3.3. Uncertainties and limitations about favourable effects

The E2202 pivotal single arm phase 2 trial was not a randomised controlled study. This can be understood in light of the rarity of the condition, poor prognosis and low response rates to currently available therapies, but nevertheless poses uncertainty. The sample size was also limited, with 94 patients included in the EAS. Patients with FL grade 3b were excluded from the pivotal study, but are nonetheless included in the sought indication. Further, few patients with grade 3a FL were included. The primary endpoint, CRR, is not an established surrogate endpoint in r/r FL and thus needs to be

supported by sufficiently mature DOR data. At the most recent DCO of 03-Aug-2021, median DOR was not reached, thus hampering precise comparisons with external data sets, but nonetheless suggesting a durable response. Some support for a sustained DOR is provided in the supportive study A2101J, which had longer follow-up, but very few FL patients (n=14) included. The reference CR rate of 15% used for hypothesis testing was based on the CRR from the approved PI3K inhibitor idelalisib. However, the idelalisib pivotal study includer older and more refractory patients than study E2202, thus the validity of the applied reference CR is uncertain. In addition, the interpretation of the efficacy results of tisagenlecleucel in terms of relevant time-to-event endpoints such as PFS and OS is difficult based on data from only one single-arm study.

To attempt to contextualize the single arm data, RWE derived from two RW databases, ReCORD and Flatiron was used. However, the RWE was not able to incorporate all inclusion criteria from the E2202 study, and information relating to some important baseline characteristics, such as FLIPI score, was unavailable or had missing values in the RW data such that the patient populations were not identical, which could not be adjusted for in the analysis, limiting comparability. Also, response assessments were lacking in the RW databases, leading to changes in definition of the PFS endpoint for the analysis, or further exclusion of otherwise eligible patients, potentially introducing bias and increasing uncertainty.

While the QoL data suggested that patient quality of life improved over time, and the questionnaires used were validated for the patient populations, not all patients responded to these questionnaires from baseline, and the number of respondents declined by month 18, providing a strong potential for selection bias. The reasons for the missing QoL data points included both technical issues, patient willingness to respond and complications arising from the covid-19 pandemic. Also, in the absence of a control arm, the PRO data are difficult to interpret. Not all RWD for contextualisation included quality of life data. In the infused set, 17.5% (17/97) received at least one new antineoplastic medication post tisagenlecleucel infusion, mostly due to SD or PD. Two patients received allogeneic HSCT. The timing and impact of these events on QoL data is unclear mainly due to missing data (no data for the two patients that received HSCT, and incomplete or missing data for the 17 patients that started new anti-neoplastic treatment.

3.4. Unfavourable effects

The AEs events reported are similar to what has been seen in adult patients with other NHL indications (B-cell ALL and DLBCL). Almost all (99.0%) having at least one AE following tisagenlecleucel infusion. A high degree of the AEs (78.4%) are suspected to be related to tisagenlecleucel.

Most common AEs irrespective of tisagenlecleucel relationship are cytokine release syndrome (CRS, 49.5%) and cytopenias like neutropenia (42.3%), anaemia (25.8%), white blood cell count decreased (21.6%) and thrombocytopenia (19.6%) and febrile neutropenia (12.4%). Hypogammaglobulinemia were seen in 14.4%. Other common AEs were headache (24.7%), diarrhoea (21.6%) and pyrexia (19.6%).

Few patients had Grade ≥3 CRS (1.0%). Cytopenias Grade ≥3 was very common: Neutropenia (42.3%), anaemia (16.5%), white blood cell count decreased (17.5%) and thrombocytopenia (11.3%). All cases with febrile neutropenia were of Grade ≥3.

Most common treatment related AEs was CRS (48.5%), headache (7.2%) and blood and lymphatic system disorders like neutropenia (20.6%), anaemia (13.4%), thrombocytopenia (7.2%) and febrile neutropenia (6.2%). Most common grade ≥3 study drug-related AE was neutropenia (20.6%).

As observed in other NHL indications, the majority of the AEs occurred within the initial 8-week period post-tisagenlecleucel infusion (96.9%). Still a high frequency of patients experienced AEs after this time period: 83.3% at > 8 weeks to 1 year post-infusion. The frequency is however significantly lower > 1 year post-infusion (26.8%).

Infections were reported in 49.5% of patients. Grade ≥3 infections were reported in 15.5%. There were no grade 4 infection, but one grade 5 case with a possible PML. Late occurring life-threatening opportunistic viral infection that can introduce serious complications like PML, may occur following CAR-T treatment. The MAH has included a text regarding monitoring for late occurrence of opportunistic infections in the SmPC section 4.4 and in educational materials to make both HCP and patients aware of the risk.

Neurological adverse reactions (SNARS) were reported in 11.3%. Grade≥ 3 AEs of ICANS (Immune effector cell-associated neurotoxicity syndrome) /encephaloapthy and/or delirium) were reported in 3 patients (3%). ICANS is added to the list of ADRs in the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

The pivotal study has few patients included (97 patients), indicating only common AEs are captured

The current median follow-up time is short for capturing long-term AEs. However, the study is ongoing and all patients will be followed until the end of the study when all patients have completed month 24 evaluation or discontinued prematurely. After the end of the pivotal study, patients will continue to be followed for long-term safety under the long-term follow-up protocol for study A2205B, which is defined as a category 3 PASS. The purpose of this PASS is to monitor all patients treated with lentiviral vector based CD19 CAR-T cell therapy in clinical trials for up to 15 years from the last CD19 CAR-T cell infusion, to assess the risk of delayed AEs suspected to be related to CD19 CAR-T cell therapy. Semiannual and annual evaluations will be performed during this study from the date of infusion on all patients. Based on these aspects the number of patients and follow-up time is considered acceptable.

3.6. Effects Table

Table 57. Effects Table for Kymriah for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects (DCO 03-Aug-2021)						
CRR	Per central IRC assessment in accordance with Lugano Classification (Cheson 2014)	n/N %	EAS population (65/94) 69.1% (95% CI: 58.8%, 78.3%).	N/A	Uncertainties: -Single arm trial -	
DOR	Per central IRC assessment	Median Months	EAS population N=81 NE (95% CI: 15.6%, NE)	N/A	Not reached	
DOR	Per central IRC	% event-	EAS population N=81	N/A		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	assessment	free probability at 9 months	76.2% (95% CI: 64.9%, 84.3%)			
		% event-free probability at 12 months	EAS population n=81 73.1% (95% CI: 61.3%, 81.8%)	N/A		
ORR	Per central assessment	n/N %	EAS population (81/94) 86.2% (95% CI: 77.5%, 92.4%)	N/A		
Unfavourable Effects, Safety set: 97 patients, DCO 29-mar-2021						
AEs irrespective of relatedness/ Study drug related AEs		%	99.0/78.4	N/A		
Cytopenias		%	78.4/43.3	N/A		
CRS		%	49.5/48.5	N/A		
Infections		%	49.5/13.4	N/A		
Hypogamma-globulinemia		%	14.4/10.3	N/A		
SNARs ICANS		% %	11.3/8.2 3.1/1.0	N/A		

Abbreviations: SNARs = serious neurological adverse reactions (including both SAEs and non-serious AEs), ICANS= immune effector cell-associated neurotoxicity syndrome, which is Grade 3 and 4 SNARs.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Relapsed and refractory (r/r) FL represents an unmet medical need in that treatment efficacy and duration of remission declines with every successive line of therapy, with death occurring due to histological transformation to DLBCL or because FL becomes refractory to chemotherapy.

The results from study E2202 indicate a robust CRR in the r/r FL population (69.1%, 95% CI:58.8%-78.3%) in response to a single infusion of tisagenlecleucel at a target dose of 0.6 to 6.0×10^8 CAR-positive, viable T cells, with the lower bound of the 95% confidence interval above the pre-specified threshold of 15%. The observed CR rate was consistent across high-risk subgroups. Achieving CR, i.e. the disappearance of all measurable evidence of disease, is considered relevant for the patient and therefore indicative of a relevant favourable effect.

While the median DOR has not been reached in the pivotal study as the follow-up duration is currently too short, achieving a sustained DOR provides some indication that patients may achieve long-term remission. Supportive data from study A2101J also suggest potential for a sustained duration of response.

Results from secondary endpoints support the primary endpoint. In particular, ORR was 86.2% (95%CI: 77.5%-92.4%). Median DOR and OS were not reached, which compares favourably with the literature and indicates that the high response rates may translate into a clinical and/or survival benefit.

The main uncertainties regarding the B/R assessment relate to the limited sample size and short duration of follow up. Some uncertainties regarding the formal extrapolation to patients with FL grade 3b remain, as these were not included in the pivotal trial. It is, however, thought that such an extrapolation is permissible, as in clinical practice, FL grade 3b is often treated as DLBCL, for which tisagenlecleucel is also indicated. Few patients with grade 3a were also included in the pivotal trial. Further, there are challenges related to RWE, including capturing an appropriate patient population in RW data. However, the uncertainties of the RWE do not detract from the clinical data which showed a substantial effect size.

Based on the number of patients included in the pivotal study, only common AEs have been reported. The safety profile in FL patients seems to be similar to what has been seen in other NHL indications approved for tisagenlecleucel. Most important safety concerns are cytopenias, CRS, infections and neurological reactions. Long-term safety could not be assessed based on the data provided, but will be further studied under the long-term follow-up protocol CCTL019A2205B (PASS).

3.7.2. Balance of benefits and risks

The overall B/R balance of tisagenlecleucel for the heavily pre-treated patients with r/r FL included in study E2202 is considered favourable. Some uncertainties remain concerning the clinical data, such as short follow-up duration and limited sample size and single arm study design. However, the benefits for the treated population are considered to outweigh the unfavourable effects and risks which can be addressed by adequate risk mitigation measures in the SmPC and RMP.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Kymriah is positive.

The MAH should submit the inspection report, including a summary of the findings, for site 1700 (study E2202), when available (LEG).

4. Recommendations

Outcome

Based on the review of the submitted data, the CAT considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an	Type II	I, II and IIIB

	approved one		

Extension of indication to include treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic treatment for Kymriah. As a consequence, Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and corresponding sections in the Package Leaflet are updated accordingly. The RMP has been updated to version 4.2 to align with the indication extension. The updates to Module 3 include mainly the incoming FL material characterization, final product characterization and FL batch analyses data.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CAT by consensus is of the opinion that Kymriah is not similar to Gazyvaro within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Additional market protection

Furthermore, the CAT reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Kymriah-H-C-4090-II-0044’