16 October 2025
EMADOC-1700519818-2456442
Committee for Advanced Therapies (CAT)
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Breyanzi

International non-proprietary name: Lisocabtagene maraleucel / Lisocabtagene maraleucel

Procedure No. EMA/VR/0000265024

Note

Variation assessment report as adopted by the 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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
1L	having received no prior therapy for the disease under study (first-line treatment)
2L	having received one line of prior therapy for the disease under study (second-line treatment)
2L+	having received 1 or more lines of prior therapy for the disease under study (second-line or later treatment)
3L	having received two lines of prior therapy for the disease under study (third-line treatment)
3L+	having received two or more lines of prior therapy for the disease under study (third-line or later treatment)
4L	having received three lines of prior therapy for the disease under study (fourth-line treatment)
ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
ATA	anti-therapeutic antibody
AUC(0-28)	area under the blood concentration-time curve from time zero to 28 days after dosing
BMS	Bristol-Myers Squibb Company
BOR	best overall response
BTKi	Bruton's tyrosine kinase inhibitor
CAR	chimeric antigen receptor
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax	maximum (or peak) concentration
CNS	central nervous system
COVID-19	coronavirus disease of 2019
CR	complete response
CrCl	creatinine clearance
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CV%	geometric mean
Cy	cyclophosphamide
DBL	Data Base Lock
DL(1, 2, 3)	dose level (1, 2, 3)
DL1D	dose level 1 (50×10^6 CAR+ T cells) 2-dose regimen
DL1S	dose level 1 (50×10^6 CAR+ T cells) single-dose regimen
DL2S	dose level 2 (100×10^6 CAR+ T cells) single-dose regimen
DLBCL	diffuse large B cell lymphoma
DLT	dose limiting toxicity
DOR	duration of response
EAS	(Liso-cel-treated) efficacy analysis set
eCOA	electronic clinical outcomes assessment
ECOG PS	Eastern Cooperative Oncology Group Performance Status (score)

Abbreviation	Definition
eCRF	electronic Case Report Form
EGFRt	truncated epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOS	end of study
EQ-5D-5L	EuroQol 5-Dimension 5-Level (health-related quality of life questionnaire)
ESMO	European Society for Medical Oncology
EU	European Union
EuroQol	an instrument for measuring quality of life
FL	follicular lymphoma
FL3B	follicular lymphoma Grade 3B
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
GVHD	graft-versus-host disease
HEOR	Health Economics and Outcomes Research
HGBCL	high-grade B-cell lymphoma
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
ICANS	immune cell-associated neurotoxicity syndrome
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
IgG4	immunoglobulin G4
iiNT	investigator identified neurotoxicity
IL- (2, 4, 5, 6)	interleukin- (2, 4, 5, 6)
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
ITT	intention-to-treat (analysis population)
IV	intravenous
K-M	Kaplan-Meier (time-to-event estimation method)
LBCL	large B-cell lymphoma
LDC	lymphodepleting chemotherapy
LDH	lactate dehydrogenase
LLOD	lower limit of detection
LPLV	last patient last visit
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MAIC	matching-adjusted indirect comparison
MAS	macrophage activation syndrome

Abbreviation	Definition
MCL	mantle cell lymphoma
mCRM	modified continuous reassessment method
MDS	myelodysplastic syndrome
NA	not available
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
NR	not reached
NT	neurotoxicity
OR	odds ratio
ORR	overall response rate
OS	overall survival
PAS	primary analysis set (analysis population)
PD	progressive disease or disease progression
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMBCL	primary mediastinal B-cell lymphoma
PR	partial response
PRO	patient-reported outcome
PT	preferred term
QLQ-C30	(EORTC) Quality of Life Questionnaire - Core measure 30 Items
QoL	quality of life
qPCR	quantitative polymerase chain reaction
R/R	relapsed or refractory
R-BAC	rituximab, bendamustine, and cytarabine (combination regimen)
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (combination regimen)
SAA	serum amyloid A
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
scFv	single-chain variable fragment
SCP	Summary of Clinical Pharmacolgy
SCS	Summary of Clinical Safety
SD	standard deviation
SLR	systematic literature review
sMIPI	simplified MCL International Prognostic Index
smPC	Summary of Product Characteristics
SOC	system organ class
SPD	sum of the products of the perpendicular diameters
SPM	second primary malignancy
T2V	type 2 variation
TEAE(s)	treatment emergent adverse event(s)
tFL	DLBCL transformed from follicular lymphoma

Abbreviation	Definition
TLS	tumor lysis syndrome
Tmax	time at which maximum concentration (Cmax) occurs
TNE	transplant non-eligible
UK	United Kingdom
US	United States
VAS	visual analog scale
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 07 April 2025 an application for a group of variations.

The following changes were proposed:

Variation(s) requested		**Type**
B.II.d.1.e	B.II.d.1.e Change outside the approved specifications limits range	Variation type II
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

A grouped application comprised of two Type II variations, as follows:

- Type II (C.I.6): Extension of indication to include the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor for BREYANZI, based on results from the pivotal Study 017001 MCL Cohort (TRANSCEND-NHL-001); this is a Phase 1, Multicenter, Open-Label Study of JCAR017, CD19-targeted Chimeric Antigen Receptor (CAR) T Cells, for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL). As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package leaflet is updated in accordance. Version 7.0 of the RMP was also submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the list of local representatives in the Package Leaflet.
- Type II (B.II.d.1.e): To modify a specification limit for the CD8+ drug product component, Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0448/2023 on the granting of a (product-specific) waiver.

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.

Scientific advice

The MAH did not seek Scientific Advice from the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Concetta Quintarelli Co-Rapporteur: Claire Beuneu

Timetable	Actual dates
Submission date	7 April 2025
Start of procedure:	26 April 2025
CAT Rapporteur's preliminary assessment report circulated on	20 June 2025
PRAC Co-Rapporteur's preliminary assessment report circulated on	26 June 2025
CAT Co-Rapporteur's preliminary assessment circulated on	2 July 2025
Joint Rapporteurs' updated assessment report circulated on	15 July 2025
Request for supplementary information and extension of timetable adopted by the CAT on	18 July 2025
MAH's responses submitted to the CAT/CHMP on	11 August 2025
CAT Rapporteurs' preliminary assessment report on the MAH's responses circulated on	17 September 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on	6 October 2025
CAT opinion	9 October 2025
CHMP opinion	16 October 2025
The CAT/CHMP adopted a report on similarity of Breyanzi with Tecartus on	9/16 October 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Mantle cell lymphoma (MCL) is an aggressive and relatively uncommon form of non-Hodgkin lymphoma (NHL). MCL is considered incurable with standard chemotherapy and is characterised by relapsing/remitting disease course, with progressive chemoresistance and poor long-term survival (see e.g. Armitage JO et al, NEJM 2022). Results from clinical trials showed that the median duration of remission from initial diagnosis is approximately 5 years, with median OS ranging from 3 to 10 years (see e.g. Vico C et al, Br J Haematol 2019).

Claimed therapeutic indication

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

Epidemiology

MCL accounts for 3% to 7% of malignant non-Hodgkin lymphomas in Western Europe. The annual incidence of MCL has increased in recent decades to 1–2 cases per 100,000 individuals, occurring more commonly among older adults (median age at diagnosis is 67-68 years). MCL is characterised by a

striking sex imbalance, with approximately 70% of all cases reported in men, and is more common in ethnic white individuals compared to individuals of African ancestry (see Teras LR et al, CA Caner j Clin 2016; Sant M et al, Blood 2010; Smith A et al, Br J Cancer 2011).

Biologic features

MCL is characterized by a specific chromosomal translocation, t(11;14), that results in Cyclin D1 overexpression in pre-B cells, and the transcription factor SOX11 is expressed in more than 90% of all cases. MCL cells exhibit increased replication rates and resistance to apoptosis, driven, respectively, by Cyclin D1 and Bcl-2 overexpression. Cytologic subtypes of nodular MCL include classic, pleomorphic and the blastoid MCL. The pleomorphic and blastoid morphologies are characterised by an aggressive clinical behaviour. Other high-risk biological features associated with a negative impact on prognosis are the presence of TP53 mutations/del17p, high tumor proliferation index (measured by Ki-67), high sMIPI scores, refractoriness to upfront therapy, and secondary CNS involvement.

Clinical presentation, diagnosis prognosis

The clinical presentation of MCL is heterogeneous and can include the presence of enlarged and painless superficial lymph nodes and lymphocytosis at routine analysis; sometimes, large (mostly asymptomatic) abdominal masses may occur, while the presence of constitutional symptoms is less frequent compared to other aggressive forms of NHL. MCL is usually widely disseminated at the time of diagnosis and could involve the spleen or the bone marrow. Involvement of other "extra-lymphatic" organs is not uncommon, with the gastrointestinal tract and the kidney being preferential sites. Involvement of the central nervous system may also occur, especially in aggressive forms.

A leukemic, non-nodal form of MCL with little or no expression of SOX11 has also been described. Non-nodal MCL is generally asymptomatic and is mainly characterised by the involvement of peripheral blood, bone marrow and spleen. Compared to nodal MCL, non-nodal MCL has an indolent clinical behaviour and favourable prognosis.

Management

No curative options exist for patients with R/R MCL, with the exception of allogeneic haematopoietic stem cell transplant, which is limited to a subset of younger and fitter patients with a suitable donor. Most patients require multiple lines of salvage therapy in their lifetime. Outcomes progressively worsen after each line of therapy, with a median PFS and OS of 4.0 years and 9.7 years, respectively, in the 1 line of therapy, and 5.0 months and 14.4 months, respectively, in the 4th line of therapy.

As per ESMO guidelines, the Bruton tyrosine kinase inhibitors (BTKis) are the preferred option after failure of upfront treatment in MCL. Ibrutinib, treatment with the covalent BTKi ibrutinib, initially approved in the EU on the basis of results from a single-arm Phase 2 study, showed PFS superiority vs. temsirolimus (HR 0.43 [95% CI: 0.32, 0.58]; P < 0·0001), with a median PFS of 14.6 months (95% CI 10.4,NE) vs 6.2 months (95% CI: 4.2, 7.9) with temsirolimus. The ORR assessed by IRC was also significantly higher for ibrutinib (72%) than for temsirolimus (40%, P <0.0001). Ibrutinib and additional covalent BTKi have shown to improve outcomes in R/R MCL; however, development of resistance or intolerance to covalent BTKi therapies is common, typically occurring within 18 to 24 months.

There is no single standard-of-care in the post-BTKi setting, the optimal approach/sequence to treat R/R MCL is yet to be defined and there is lack of data comparing the available treatment options in a randomized controlled fashion. The treatment choice for R/R MCL patients is guided by age, performance status, comorbidities, and prior therapy. Treatment options in the EU include

temsirolimus, lenalidomide and bortezomib. Both temsirolimus and lenalidomide are approved for the treatment of R/R MCL but showed limited efficacy (ORR in the range 22.2% to 40.0%, CRR in the range 3% to 4.7%). Bortezomib is indicated in combination with rituximab, cyclophosphamide, doxorubicin and prednisone in patients with untreated MCL and those who are unsuitable for haematopoietic stem cell transplant (HSCT), based on its superiority vs R-CHOP, but has limited efficacy as monotherapy in the R/R setting (ORR 33%, CR rate 8%). Temsirolimus, lenalidomide and bortezomib were all licensed before covalent BTKi entered clinical practice, and therefore limited data are available on their efficacy in the post-BTKi setting. Chemoimmunotherapy regimens (e.g. rituximab bendamustine ± cytarabine) are also options that have been associated with high response rates (up to 83%) but toxicity remains critical and survival improvements are limited.

Recently, 2 additional agents have been granted conditional marketing authorizations (CMA) in EU for the treatment of R/R MCL in the post-BTKi setting:

- Brexucabtagene autoleucel (KTE-X19; Tecartus; brexu-cel), an autologous CD19-directed CAR T-cell therapy that received a conditional marketing authorization in EU on 14-Dec-2020 for the treatment of R/R MCL after ≥ 2 lines of systemic therapy, including a BTKi, based on the single-arm ZUMA-2 study. Treatment with brexu-cel resulted in high rates of deep and durable responses (ORR 91%, CRR 68%, median DOR 28.2 months), yet non-negligible toxicity was also observed (Grade ≥3 AEs 98.5%; Grade ≥3 CRS 13%, Grade ≥3 CART-related encephalopathy syndrome 32%, Grade ≥3 infections 30%).
- Pirtobrutinib (Jaypirca), a non-covalent BTKi, was granted a conditional marketing authorization in EU on 31-Oct-2023 for the treatment of adults with R/R MCL who have been previously treated with a BTKi, based on the single-arm BRUIN study. Results from the registrational trial showed an ORR of 56.7% (CRR 18.9%) and a median DoR of 17.61 months.

2.1.2. About the product

Lisocabtagene maraleucel (Breyanzi; JCAR017; liso-cel) is an advanced therapy medicinal product consisting of autologous CD4+ and CD8+ T cells that have been transduced using a replication-incompetent, self-inactivating lentiviral vector encoding a CD19-specific chimeric antigen receptor (CAR). The CD19-specific CAR contains a murine single chain variable fragment binding domain (FMC63) and the 4-1BB and CD3ζ chain signalling domains. Breyanzi is administered as separate infusions consisting of a 1:1 ratio of CD4+ and CD8+ cell components.

Breyanzi is already approved in the EU for the treatment of adult patients with:

- DLBCL, HGBCL, PMBCL and FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy
- relapsed or refractory DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy
- relapsed or refractory R/R FL after 2 or more lines of systematic therapy.

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

Liso-cel is being developed for the treatment of patients with B-cell malignancies as monotherapy and in combination with other anticancer agents. In particular, the primary efficacy and safety data to support the proposed indication in R/R MCL are from the pivotal Study 017001 MCL Cohort.

Study 017001 is complete. The Final Analysis of the MCL Cohort is based on the LPLV on 16-May-2024 data cutoff, which provides 24-months of follow-up with all subjects who completed the study or discontinued earlier.

No scientific advice was requested to the CHMP for the development of liso-cel in the MCL indication.

2.1.4. General comments on compliance with GCP

The MAH stated that clinical trials included in this submission were performed in accordance with the principles of Good Clinical Practice, as defined by the International Conference on Harmonization (ICH). The clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.

2.2. Quality aspects

Introduction

The purpose of this grouping of two Type II variations is to support a label expansion to mantle cell lymphoma (MCL) therapy and additionally, to modify a specification limit for the CD8+ drug product component. The proposed update to the acceptance criteria is based on the data analysis of the approved and proposed indication. No changes are proposed for the specification of CD4+ drug product component.

All clinical trial materials supporting the label expansion were manufactured per the approved manufacturing process (v4) and at commercially approved manufacturing sites. No changes are being proposed to the manufacturing process.

The vector RNA sequence encoding the amino acid sequence of the CD19-targeted CAR for the mantle cell lymphoma (MCL) cohort in Study 017001 (referred to hereafter as "MCL Cohort 017001") is identical to that of the 3L+ LBCL cohort in Study 017001 (referred to hereafter as "DLBCL Cohort 017001"). Thus, CAR structure and function and the DP mechanism of action remain unchanged.

While DLBCL Cohort 017001 pertained to patients with relapsed or refractory LBCL after two or more lines of systemic therapy (3L+), MCL Cohort 017001 pertains to patients with relapsed or refractory MCL after at least two prior lines of systemic therapy. Therefore, since these patient populations may differ in the characteristics of their starting materials (*e.g.,* memory T cell phenotypes) and their clinical response to the DP, the following studies are included in this section in support of MCL Cohort 017001:

- Phenotypic and functional characterization of DP components manufactured in support of MCL Cohort 017001
- Exploratory correlative analysis of quality attributes associations with clinical efficacy, safety, and pharmacokinetics in MCL Cohort 017001

Manufacturing Process Development

The Leukapheresis Product was reassessed for R/R MCL to confirm that process characterization results using healthy donor leukapheresis product are still relevant to R/R MCL. This assessment was presented.

The DP v4 manufacturing process produces similar DP when using leukapheresis from patients or healthy donors as all attributes passed the analyses. The methodology described in the original Application is unchanged, and is applied to the MCL clinical study (MCL Cohort 017001) herein.

The residual patient risk assessment based on each unique product quality attribute considered the

integrated control strategy (ICS). Based on this comprehensive assessment, the overall risk of the DP to patient safety and product efficacy is considered low.

Assessor's comments:

The Healthy Donor (HD) Leukapheresis product was reassessed for R/R MCL to confirm that process characterization results using HD leukapheresis product are still relevant to R/R MCL. Overall, as all attributes passed the analyses, it can be therefore concluded that the use of HD leukapheresis product for process characterization purposes is still relevant to the R/R MCL patients' setting.

Indeed, the currently EU-approved specifications, including the specification limit (CD8+ cell component) that is updated and accepted (see sections below) within this procedure, are still valid (see sections below). Overall, the MAH's approach is considered informative and therefore endorsed.

Specifications

The specification for lisocabtagene maraleucel DP components (liso-cel) cover relevant CQAs. The quality parameters taken into account for each cell component include appearance, identity, purity, strength, potency and safety.

The evolution of the specification was presented.

Assessor's comments:

To support the proposed indication, Relapsed/Refractory mantle cell lymphoma (R/R MCL) label expansion, the Applicant is proposing to update the acceptance criteria for one attribute for the $CD8^+$ component. The proposed update to the acceptance criteria is based on the data analysis of the approved (3L+ Large LBCL, 2L LBCL and FOL) and proposed indication (MCL). No changes are proposed for the specification of $CD4^+$ DP component. A detailed assessment of the specification acceptance criteria was provided.

Justification of Specifications

The acceptance criteria in the specification have been established to confirm the appearance, identity, purity, strength, potency, and safety and to ensure that the quality of released DP component lots remain within experience demonstrated to be safe and effective in Study 017001, JCAR017-BCM-001 (BCM-001), JCAR017-BCM-003 (BCM-003), JCAR017-FOL-001 (FOL-001), Relapsed/Refractory mantle cell lymphoma Cohort 017001 (MCL Cohort 017001). The analytical procedures and acceptance criteria in the specification are applicable to release and stability of drug product components in accordance with ICH Q6B. Conformance to the specification is required prior to release of liso-cel. The justification for the analytical procedures and acceptance criteria in the specification for release and stability testing of drug product components is described.

Analytical Procedures

The appearance, identity, purity, strength, potency, and safety attributes that are included in the DP specification were selected based on risk assessments that considered product understanding and process capability. The analytical procedures in the commercial specification were selected based on their performance characteristics and suitability for routine and reliable evaluation of these attributes in a quality control environment.

Acceptance Criteria in the Specification for Drug Product

In accordance with ICH Q6B, Q8, Q9, and Q10, the following assessment of liso-cel DP lots acceptance criteria were established based on:

1. Clinical manufacturing batches used for evaluating clinical safety and efficacy

2. T cell biology and the quality attribute-clinical outcome relationship established by correlative analyses

3. Data obtained from manufacturing process development and characterization studies

4. Capabilities of the analytical procedures

5. Pharmacopeia specifications

Assessor's comment:

To support the proposed indication, Relapsed/Refractory mantle cell lymphoma (R/R MCL) label expansion, the Applicant has assessed the approved commercial acceptance criteria using the same methodology as previously presented in the initial filing (initial marketing application).

The MAH proposes to use the same release specification limits for all quality attributes except for one attribute of the CD8+ component that is proposed to be updated. No changes are proposed for the specification of CD4+ DP component and the approved acceptance criteria is maintained.

The specification-setting approach is intended to be holistic, with proposed specification limits based on the totality of clinical, manufacturing, and analytical experience. This is considered well justified and therefore acceptable.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CAT/CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

The MAH provided a justification for not submitting a new Environmental Risk Assessment (ERA), which extends the treatment of liso-cel to include adult patients with relapsed or refractory MCL after at least two lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibition.

No release of Liso-cel into the environment is foreseen. No relevant changes in the manufacturing process of liso-cel were implemented. Testing for absence of replication-competent lentivirus (RCL) in vector lot is in place. Generation of RCL in patients treated with liso-cel is still unlikely. As the enlargement of the treated population, now including adult patients with relapsed or refractory MCL as per the approved indication does not affect the environmental risk of liso-cel, no monitoring in the environment is considered necessary to protect human health and the environment.

2.4. Clinical aspects

2.4.1. 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

Table 1. Description of Study 017001 - MCL Cohort

Study	Design	Study Population	Number of Liso-cel Treated Subjects	Dosing	PK Sampling Timepoints by qPCR
Study 017001 Completed LPLV: 16-May-2024	Phase 1, multicenter, open-label study of JCAR017, CD19-targeted chimeric antigen receptor (CAR) T cells, for relapsed and refractory (R/R) B-cell non-Hodgkin lymphoma (NHL)	Subjects with R/R disease having received ≥ 2 prior lines of systemic MCL therapy and having been treated with an alkylating agent, a Bruton's tyrosine kinase inhibitor, and rituximab (or other CD20-targeted agent)[a]	Dose Level 1: 6 Dose Level 2: 82	**Dose Level 1:** 50×10^6 CAR+ T cells [b] **Dose Level 2:** 100×10^6 CAR+ T cells [c]	Pre-treatment Evaluation, Days 1, 4, 8, 11, 15, 22, 29; 60, 90, 180, 270, 365, 545, 730

[a] Data from the DLBCL Cohort are not included in this SCP.
[b] Single and 2-dose regimens (DL1S and DL1D). No MCL Cohort subjects were treated with DL1D.
[c] Single-dose regimen only (DL2S).

2.4.2. Pharmacokinetics

The clinical pharmacology information for lisocabtagene maraleucel is based on data from MCL Cohort of Phase 1 Study 017001 (Table 1)

The cut-off date and Data base Lock (DBL) date are 19-Jan-2023 and 31-Mar-2023, respectively. Transgene persistence, B-cell aplasia, and immunogenicity results were updated with longer follow-up (16-May-2024 data cut).

Study 017001 includes the characterization of PK profile of liso-cel as secondary objective. Among the exploratory objectives there are: evaluation of the pharmacodynamic effects of liso-cel, including presence of B-cells and serum immunoglobulins, the immune response to liso-cel, the relationship of PK parameters with BOR, DOR, and PFS and the relationship between PK and pharmacodynamic parameters with CRS and iiNT.

Bioanalytical methods

Evaluation of PK, pharmacodynamic, and immunogenicity profile of the drug product for the MCL was performed using previously validated methods.

A partial validation due to minor modifications was conducted for anti-therapeutic antibody (ATA) detection method already submitted within the initial marketing authorization application.

Pharmacokinetic results

The PK analyses were based on qPCR. Noncompartmental PK parameters such as Cmax, Tmax, and AUC(0-28) were calculated for subjects who had PK measurement 28 days after infusion or later.

For flow cytometry, persistence was defined as CD3+ EGFR+ count greater than or equal to LLOD of 0.1 cells/µL, with at least 25 events captured in the CAR T flow cytometry detection gate. All PK data, including persistence, were summarized descriptively.

Pharmacokinetic assessments by flow cytometry (CD3+ EGFRt+, CD4+ EGFRt+, and CD8+ EGFRt+) were considered supportive data that allow for the evaluation of PK parameters per drug product component.

PK Sampling Timepoints by qPCR were collected as follow: Pre-treatment Evaluation, Days 1, 4, 8, 11, 15, 22, 29; 60, 90, 180, 270, 365, 545, 730.

PK sampling for flow cytometry were collected as follow. Pre-treatment Evaluation, Days 1, 4, 8, 11, 15, 22, 29; 60, 90, 180, 270, 365.

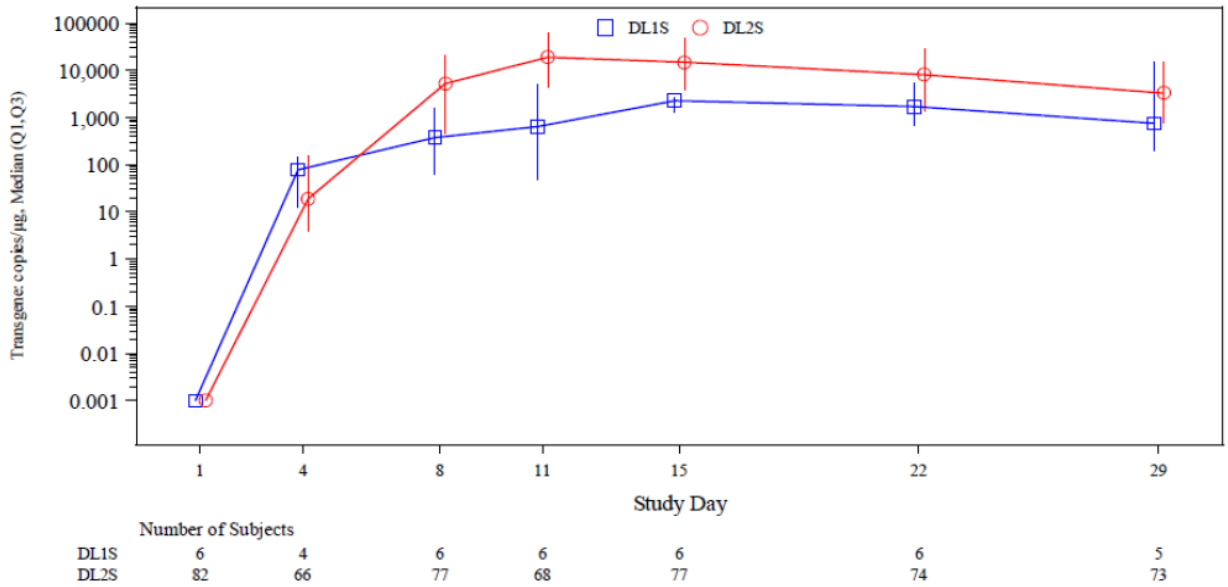
The dataset considered is as follow:

Table 2. Analysis dataset and population

Dataset	Definition	DL2S	DL1S	Total
Liso-cel-treated Analysis Set (Safety Analysis Set)	All subjects who have received at least one dose of liso-cel	82	6	88
Liso-cel-treated Efficacy Analysis Set	All subjects in the Liso-cel-treated Analysis Set who have PET-positive disease present before liso-cel administration based on IRC assessment	77	6	83
qPCR PK Analysis Set	All subjects in the Liso-cel-treated Analysis Set who have both baseline and on study PK measurements in blood assessed by qPCR	82	6	88

Following infusion, the liso-cel concentration in the peripheral blood detected by qPCR exhibited a rapid expansion followed by a monophasic decline up to 28 days after infusion in both DL1S and DL2S (Figure 1).

Figure 1. Median Transgene Concentration by qPCR Over Time by Dose Level - qPCR PK Analysis Set MCL



Upper error bar represents the third quartile, lower error bar represents the first quartile
liso-cel was given on Study Day 1

For all dose levels (N=79), median Cmax, AUC(0-28) and Tmax by qPCR were 29335.0 copies/µg, 288556.8 day*copies/µg and 10.0 days, respectively (Table 3).

Table 3. PK Parameters by qPCR vs Dose Level - qPCR PK Analysis Set MCL

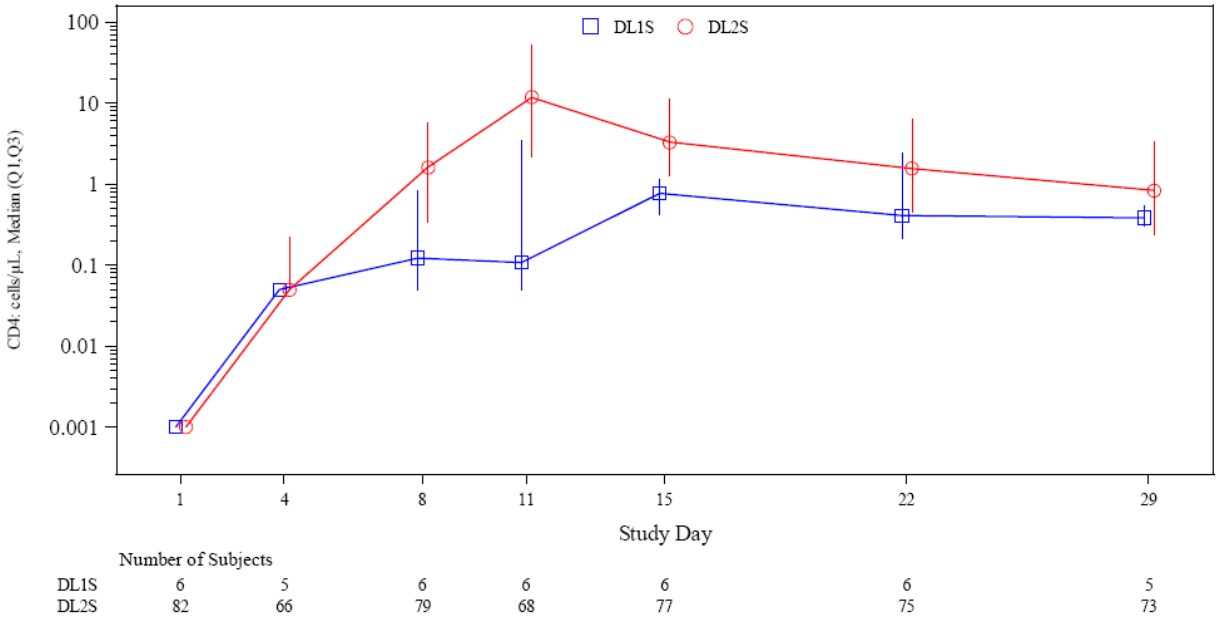
	DL2S	DL1S	Total
Transgene	**N=82**	**N=6**	**N=88**
Cmax, qPCR (copies/ug)			
N	73	6	79
Median	31631.0	9793.0	29335.0
Q1, Q3	15740.0, 139924.0	2287.0, 17315.0	9255.0, 136684.0
Min, Max	206, 5236190	1297, 57257	206, 5236190
Geometric Mean (CV%)	34433.1 (667.8)	7740.5 (250.3)	30743.0 (664.9)
Tmax, qPCR (day)			
N	73	6	79
Median	10.0	17.5	10.0
Q1, Q3	9.0, 14.0	10.0, 27.0	9.0, 14.0
Min, Max	3, 28	10, 29	3, 29
AUC Day 0-28, qPCR (day*copies/ug)			
N	73	6	79

Transgene	DL2S N=82	DL1S N=6	Total N=88
Median	329992.3	73158.1	288556.8
Q1, Q3	117687.8, 914881.0	36820.4, 167235.2	91758.9, 900207.6
Min, Max	2200, 17047357	13954, 281007	2200, 17047357
Geometric Mean (CV%)	299285.2 (540.5)	68928.4 (154.3)	267703.1 (532.0)

1. The PK Analysis Set includes subjects in the Liso-cel-treated Analysis Set who have baseline and post-baseline PK measurements.
2. Noncompartmental PK parameters such as Cmax, Tmax and AUC(0-28) were calculated for subjects who had PK measurement 28 days after infusion or later.
3. Geometric mean is obtained by computing the arithmetic mean of the logarithm-transformed values of PK parameters and then using the exponentiation to return the computation to the original scale. Geometric CV(%) is calculated as follows: CV (%)=100×sqrt(exp(S^2) – 1), where S^2 denotes the variance of the log-transformed values.

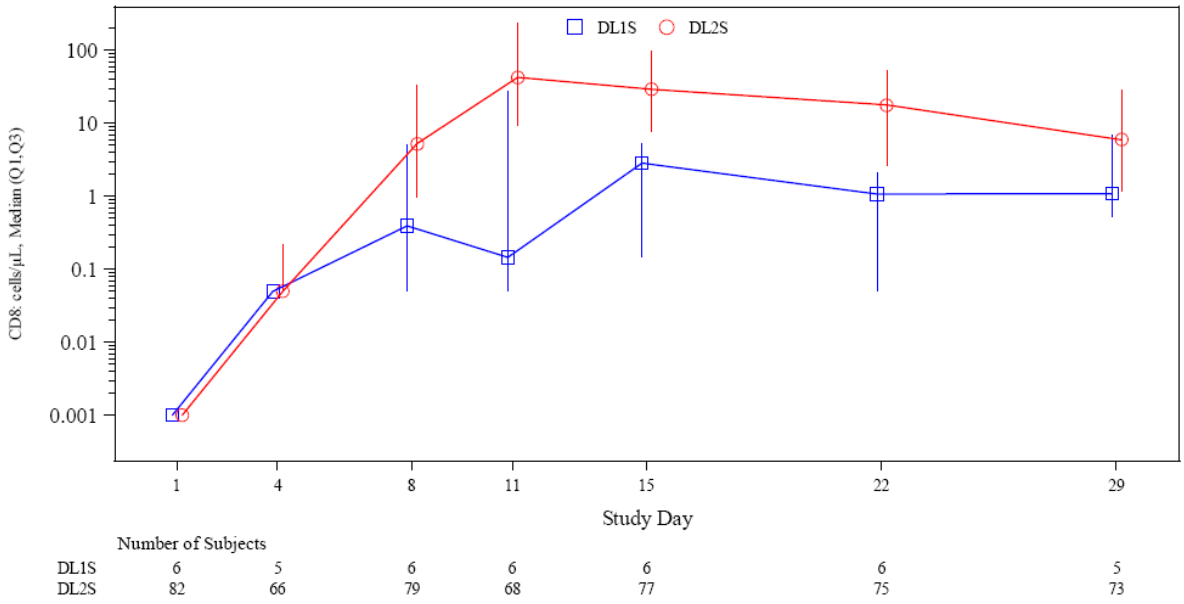
Flow cytometry-based PK assessment demonstrated the ability of CD4+ and CD8+ drug product components to expand following liso-cel infusion. A higher expansion of CD8+ EGFRt+ cells was observed compared with CD4+ EGFRt+ cells in both the DL1S and DL2S (Figure 2 and Figure 3).

Figure 2. Flow cytometry PK analysis set (CD4+)



Curves relative to each administration are shown for patients on the two dose schedule.
Upper error bar represents the third quartile, lower error bar represents the first quartile
JCAR017 was given on study day 1

Figure 3. Flow cytometry PK analysis set (CD8+)



Curves relative to each administration are shown for patients on the two dose schedule.
Upper error bar represents the third quartile, lower error bar represents the first quartile
JCAR017 was given on study day 1

Pharmacokinetic parameters of CD3+ EGFR+, CD4+ EGFR+, and CD8+ EGFR+ T-cells in the Flow Cytometry PK Analysis Set are summarized by dose level in Table 4.

Table 4. PK parameters by Flow Cytometry vs dose levels

PK Parameters by Flow cytometry vs Dose Level - PK Analysis Set MCL			
	DL2S	**DL1S**	**Total**
	N=82	**N=6**	**N=88**
CD3+			
Cmax, flow (cells/uL)			
N	74	6	80
Median	103.933	31.146	87.339
Q1, Q3	20.337, 410.987	1.826, 65.190	20.296, 395.974
Min, Max	0.352, 4536.539	0.713, 146.275	0.352, 4536.539
Geometric Mean (CV%)	85.826 (846.478)	15.140 (908.503)	75.354 (920.745)
Tmax, flow (day)			
N	74	6	80
Median	10.0	17.0	10.0
AUC Day 0-28, flow (day*cells/uL)			
N	74	6	80

PK Parameters by Flow cytometry vs Dose Level - PK Analysis Set MCL			
	DL2S	**DL1S**	**Total**
	N=82	**N=6**	**N=88**
Median	679.942	215.792	645.573
Q1, Q3	186.918, 2786.831	20.479, 295.484	167.894, 2767.425
Min, Max	5.985, 31736.356	8.261, 661.834	5.985, 31736.356
Geometric Mean (CV%)	669.758 (564.304)	106.812 (421.200)	583.607 (611.799)
CD4+			
Cmax, flow (cells/uL)			
N	73	6	79
Median	14.321	2.959	13.787
Q1, Q3	2.953, 50.332	0.597, 30.276	2.643, 49.711
Min, Max	0.182, 986.895	0.423, 49.711	0.182, 986.895
Geometric Mean (CV%)	11.914 (658.882)	3.842 (686.844)	10.933 (675.115)
Tmax, flow (day)			
N	73	6	79
Median	10	17	10
AUC Day 0-28, flow (day*cells/uL)			
N	73	6	79
Median	122.780	24.124	120.394
Q1, Q3	29.988, 317.241	6.791, 187.359	24.708, 304.551
Min, Max	2.064, 11982.070	5.334, 223.995	2.064, 11982.070
Geometric Mean (CV%)	101.063 (492.518)	30.981 (340.907)	92.383 (495.992)
CD8+			
Cmax, flow (cells/uL)			
N	74	5	79
Median	82.338	27.164	68.040
Q1, Q3	19.725, 294.017	14.912, 29.277	17.315, 287.745
Min, Max	0.241, 4417.860	1.386, 114.297	0.241, 4417.860
Geometric Mean (CV%)	68.198 (1014.377)	17.980 (354.527)	62.680 (985.494)
Tmax, flow (day)			

PK Parameters by Flow cytometry vs Dose Level - PK Analysis Set MCL			
	DL2S	**DL1S**	**Total**
	N=82	**N=6**	**N=88**
N	74	5	79
Median	10	13	10
AUC Day 0-28, flow (day*cells/uL)			
N	74	5	79
Median	573.685	151.736	526.022
Q1, Q3	137.268, 2084.734	69.088, 232.618	124.504, 2032.638
Min, Max	3.302, 21013.712	15.277, 458.882	3.302, 21013.712
Geometric Mean (CV%)	522.304 (645.185)	111.321 (212.072)	473.624 (642.002)

A high correlation between qPCR (transgene) and flow cytometry (CD3+ EGFRt+ T-cells) PK parameters was observed for Cmax, AUC(0-28), and Tmax, with correlation coefficients of 0.8585, 0.8848, and 0.5745, respectively.

Comparison with data from 3L+ LBCL in Study 017001

No apparent differences in transgene PK parameters were observed between R/R MCL and 3L+ LBCL in Study 017001 (Table 5). PK for subjects in 2L LBCL were also similar to those for subjects in 3L+ LBCL.

Table 5. Summary of liso-cel PK parameters in R/R MCL and 3L+LBCL

Parameter Statistic	**Study 017001**	
	R/R MCL **DL1S + DL2S** **N = 88**	**3L+ LBCL** **DL1S + DL2S + DL3S** **N = 261**
Cmax (copies/µg)		
n Median Q1, Q3	79 29335.0 9255.0, 136684.0	245 23928.2 8159.3, 78365.7
Tmax (days)		
n Median Q1, Q3	79 10.0 9.0, 14.0	245 12.0 10.0, 14.0

Parameter Statistic	Study 017001	
	R/R MCL **DL1S + DL2S** **N = 88**	**3L+ LBCL** **DL1S + DL2S + DL3S** **N = 261**
AUC(0-28) (day*copies/µg)		
n	79	245
Median	288556.8	213730.1
Q1, Q3	91758.9, 900207.6	74964.1, 662966.5

Note: n is the number of subjects who had PK parameters.

Persistence

For qPCR, persistence was defined as a transgene count greater than or equal to the LLOD (5 copies/reaction). Persistence of liso-cel transgene was observed up to Day 730.

Table 6. Summary of Persistence by qPCR Over Time vs Dose Level - qPCR PK Analysis Set MCL

	DL2S	DL1S	Total
Transgene, x/n (%)	N=82	N=6	N=88
Day 29	71/73 (97.3)	5/5 (100)	76/78 (97.4)
Day 60	53/57 (93.0)	3/3 (100)	56/60 (93.3)
Day 90	48/58 (82.8)	3/3 (100)	51/61 (83.6)
Day 180	28/42 (66.7)	2/2 (100)	30/44 (68.2)
Day 270	22/36 (61.1)	2/2 (100)	24/38 (63.2)
Day 365	22/34 (64.7)	2/2 (100)	24/36 (66.7)
Day 545	17/29 (58.6)	1/2 (50.0)	18/31 (58.1)
Day 730	9/25 (36.0)	1/1 (100)	10/26 (38.5)

1. The PK Analysis Set includes subjects in the Liso-cel-treated Analysis Set who have baseline and post-baseline PK measurements.
2. Persistence is defined as transgene count ≥ the lower limit of detection (5 copies per reaction).
3. Concentration values after the initiation of retreatment or additional cycles of liso-cel or after another anticancer treatment (including lymphodepletion) are excluded from the summaries.

Pharmacokinetic Parameters by Subgroup Analysis

No apparent differences in qPCR PK parameters by subgroups of age (⩾ 65 vs. < 65 years old), sex, race (White vs. others), pre-LDC SPD status (⩾ 50 vs. < 50 cm2), pre-LDC LDH status (⩾ 500 vs. < 500 U/L), Ki67 (⩾ 30 vs. < 30%), and TP53 mutation were observed (data not shown).

A potential association was observed between detection of blastoid morphology and lower Cmax and AUC(0-28). Median Cmax in subjects with blastoid morphology (n = 24) and subjects without blastoid morphology (n = 45) were 16372.0 and 54042.0 copies/µg, respectively (p = 0.0053). Median AUC(0-28) in subjects with blastoid morphology and subjects without blastoid morphology were 134762.3 and 394631.2 day*copies/µg, respectively (p = 0.0066).

Patients receiving a nonconforming product

At first infusion, 88 subjects (82 treated at DL2S and 6 treated at DL1S) who underwent leukapheresis received conforming product, and the remaining 4 (3 treated at DL2S and 1 treated at DL1S) received nonconforming product. Expansion was observed from all subjects. Cmax and AUC(0-28) by qPCR ranged from 327.0 to 53106.0 copies/µg and 1631.6 to 328785.7 day*copies/µg, respectively, which were generally lower than the median values of the all dose levels but within its ranges.

PK/efficacy and PK/safety Relationship

The relationship between PK parameters (Cmax, Tmax and AUC[0-28]) and dichotomous parameters such as BOR, CRS and iiNT were assessed by Wilcoxon tests. The relationship between PK parameters and multi-categorical parameters were assessed by Kruskal-Wallis tests. The relationship between PK parameters and time-to-event parameters were assessed by Cox proportional hazards models.

PK-efficacy relationships were evaluated in subjects who were in both the Liso-cel-treated Efficacy Analysis Set and PK Analysis Set, while PK safety relationships were evaluated in subjects who were in the PK Analysis Set (Table 7).

Table 7. Relationship Between Pharmacokinetic Parameters of Liso-cel and Clinical Efficacy and Safety, MCL Cohort, DL1S + DL2S

	Transgene			CD4+ EGFRt+			CD8+ EGFRt+		
Variable/ Statistic	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
Efficacy (assessed per IRC)									
Response (BOR of either CR or PR, versus non-response)									
Cmax									
N	67	8		67	8		68	7	
Median	31631.0	12444.0	0.0557	14.3	6.6	0.3154	82.3	29.3	0.3771
Q1, Q3	16603.0, 139924.0	3654.5, 34099.5		2.7, 50.3	1.5, 27.2		18.9, 281.7	12.1, 179.3	
Tmax									
N	67	8		67	8		68	7	
Median	10.0	14.0	0.1253	10.0	13.5	0.2513	10.0	10.0	0.6102
Q1, Q3	9.0, 14.0	10.0, 17.5		9.0, 14.0	10.0, 17.5		9.0, 14.0	10.0, 14.0	
AUC(0-28)									
N	67	8		67	8		68	7	
Median	309578.0	142461.5	0.1163	122.8	65.5	0.2467	540.5	232.6	0.3483
Q1, Q3	103329.7, 1089840.3	39903.5, 399860.0		26.9, 317.2	15.2, 183.4		151.9, 1946.3	124.5, 1407.2	
Complete Response (BOR of CR versus non-complete response)									
Cmax									
N	59	16		59	16		59	16	
Median	45068.0	12444.0	0.0099	16.8	3.5	0.0616	94.4	28.2	0.0284
Q1, Q3	17111.0, 149423.0	2383.5, 41257.5		3.3, 50.3	1.1, 27.2		24.7, 354.5	3.5, 138.1	
Tmax									
N	59	16		59	16		59	16	
Median	10.0	13.0	0.2222	10.0	14.0	0.0178	10.0	11.0	0.1903
Q1, Q3	9.0, 14.0	10.0, 17.0		9.0, 14.0	10.0, 21.0		9.0, 14.0	10.0, 14.0	
AUC(0-28)									
N	59	16		59	16		59	16	
Median	394631.2	142461.5	0.012	141.6	34.4	0.0635	601.9	197.2	0.024

	Transgene			CD4+ EGFRt+			CD8+ EGFRt+		
Variable/ Statistic	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
Q1, Q3	127193.0, 1357441.6	31967.0, 297004.2	8	30.1, 317.2	14.9, 183.4		220.7, 2084.7	51.8, 856.6	0
PFS									
Cmax Hazard ratio (95% CI)	0.60 (0.40, 0.91)		0.0157	0.40 (0.26, 0.62)		<.0001	0.53 (0.37, 0.76)		0.0005
AUC(0-28) Hazard ratio (95% CI)	0.56 (0.37, 0.86)		0.0076	0.37 (0.23, 0.60)		0.0001	0.50 (0.33, 0.74)		0.0006
DOR									
Cmax Hazard ratio (95% CI)	0.63 (0.41, 0.98)		0.0414	0.42 (0.27, 0.65)		0.0001	0.51 (0.35, 0.75)		0.0005
AUC(0-28) Hazard ratio (95% CI)	0.60 (0.38, 0.93)		0.0241	0.39 (0.24, 0.65)		0.0003	0.49 (0.32, 0.74)		0.0007
Safety									
CRS									
Cmax n Median Q1, Q3	50 42872.5 19685.0, 183107.0	29 17106.0 2287.0, 61058.0	0.0024	50 16.3 3.5, 60.3	29 9.7 1.4, 39.8	0.1047	50 105.6 33.9, 323.7	29 29.3 3.8, 196.2	0.0133
Tmax n Median Q1, Q3	50 10.0 9.0, 12.0	29 14.0 10.0, 15.0	0.0124	50 10.0 9.0, 14.0	29 14.0 10.0, 16.0	0.0049	50 10.0 9.0, 14.0	29 13.0 9.0, 16.0	0.1341
AUC(0-28) n Median Q1, Q3	50 375005.5 142331.5, 1534211.5	29 167235.2 33369.2, 498878.9	0.0038	50 142.8 32.0, 333.4	29 85.6 15.2, 195.2	0.0649	50 785.8 227.7, 2157.0	29 313.7 32.2, 1318.6	0.0176
iiNT									
Cmax n Median Q1, Q3	25 113596.0 31631.0, 235480.0	54 19683.5 5466.0, 61058.0	0.0006	26 52.7 15.8, 114.3	53 4.8 1.5, 22.8	<.0001	26 236.0 96.9, 641.5	53 34.0 7.9, 131.6	<.0001
Tmax n Median Q1, Q3	25 10.0 9.0, 12.0	54 10.0 9.0, 14.0	0.1789	26 10.0 9.0, 14.0	53 11.0 9.0, 14.0	0.1967	26 10.0 9.0, 12.0	53 10.0 10.0, 14.0	0.0635
AUC(0-28) n Median	25 900207.6	54 217964.6	0.0009	26 315.9	53 39.5	<.0001	26 1899.8	53 292.0	<.0001

	Transgene			CD4+ EGFRt+			CD8+ EGFRt+		
Variable/ Statistic	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
Q1, Q3	284430.4, 2170312.0	50383.9, 619493.4		122.8, 738.5	18.3, 173.0		774.4, 4176.9	83.1, 833.0	
iiNT Grade ≥ 3									
Cmax									
n	8	71		8	71		8	71	
Median	126760.0	25639.0	0.0224	84.6	11.0	0.0020	290.9	60.2	0.0541
Q1, Q3	49445.5, 2055100.0	8132.0, 115263.0		55.3, 117.5	2.4, 39.8		118.8, 543.0	15.3, 196.2	
Tmax									
n	8	71		8	71		8	71	
Median	12.0	10.0	0.7226	14.0	10.0	0.1315	10.0	10.0	0.8619
Q1, Q3	8.5, 17.5	9.0, 14.0		11.5, 14.0	9.0, 14.0		10.0, 13.5	9.0, 14.0	
AUC(0-28)									
n	8	71		8	71		8	71	
Median	1439165.1	269192.2	0.0062	717.2	82.5	0.0004	2425.4	473.8	0.0181
Q1, Q3	691457.7, 8406557.3	70874.4, 702938.1		445.7, 1474.8	23.5, 234.0		1430.2, 4229.8	106.2, 1714.9	

Immunogenicity

Immune responses to liso-cel were evaluated with an ATA assay to the ECD of liso-cel CAR, which binds to CD19, using a multi-tiered approach including a screening assay, a confirmatory assay, and a titer assay. Clinical plasma samples were analyzed for the presence of anti-liso-cel antibodies using a validated ECL immunoassay.

Sampling Timepoints for ATA evaluation were collected as follow: Pre-treatment Evaluation, Days 15, 29, 60, 90, 180, 270, 365, 545, 730.

Table 8. Anti-Therapeutic Antibodies vs Dose Level - Liso-cel-treated Analysis Set MCL

	DL2S N = 82	**DL1S N = 6**	**Total N = 88**
Prevalence of anti-therapeutic antibodies[a]			
Total subjects for evaluation	82	6	88
Yes, n (%)	11 (13.4)	0	11 (12.5)
No, n (%)	71 (86.6)	6 (100)	77 (87.5)
Incidence of anti-therapeutic antibodies[b]			
Total subjects for evaluation	80	6	86
Yes, n (%)	17 (21.3)	0	17 (19.8)
No, n (%)	63 (78.8)	6 (100)	69 (80.2)
Treatment-induced antibodies			

	DL2S N = 82	DL1S N = 6	Total N = 88
Total subjects for evaluation	70	6	76
Yes, n (%)	14 (20.0)	0	14 (18.4)
No, n (%)	56 (80.0)	6 (100)	62 (81.6)
Treatment-boosted antibodies			
Total subjects for evaluation	10	0	10
Yes, n (%)	3 (30.0)	0	3 (30.0)
No, n (%)	7 (70.0)	0	7 (70.0)

[a] Prevalence of anti-therapeutic antibodies is defined as the percentage of subjects with pre-existing antibodies that bind to liso-cel.

[b] Incidence of anti-therapeutic antibodies is defined as the percentage of subjects with treatment-induced or treatment-boosted antibodies that bind to liso-cel. In a subject without pre-existing antibodies, development of antibodies after first infusion of liso-cel is considered treatment-induced. In a subject with pre-existing antibodies, an increased level of antibodies after first infusion of liso-cel is considered treatment-boosted.

Table 9. Summary of Clinical Outcomes and PK Parameters by ATA

Variable/Statistic	Prevalence of ATA[a]		Incidence of ATA[b]	
	Yes	No	Yes	No
Cmax (copies/µg)				
N	10	69	16	63
Median	54357.5	29335.0	76117.0	25639.0
Q1, Q3	9255.0, 172071.0	14564.0, 115263.0	20811.0, 143053.5	8132.0, 115263.0
AUC(0-28) (day*copies/ug)				
N	10	69	16	63
Median	449932.7	288556.8	479454.1	269192.2
Q1, Q3	117687.8, 842036.3	91758.9, 900207.6	217964.6, 765618.8	70874.4, 914881.0
Response (per IRC), n (%)	8/11 (72.7)	61/72 (84.7)	14/14 (100.0)	55/67 (82.1)
Complete response (per IRC), n (%)	8/11 (72.7)	52/72 (72.2)	14/14 (100.0)	46/67 (68.7)
CRS any Grade, n (%)	5/11 (45.5)	49/77 (63.6)	9/17 (52.9)	43/69 (62.3)
CRS Grade ≥ 3, n (%)	0/11	1/77 (1.3)	0	0
iiNT any Grade, n (%)	4/11 (36.4)	23/77 (29.9)	4/17 (23.5)	22/69 (31.9)
iiNT Grade ≥ 3, n (%)	1/11 (9.1)	7/77 (9.1)	1/17 (5.9)	7/69 (10.1)

Table 9. Summary of Clinical Outcomes and PK Parameters by ATA

Variable/Statistic	Prevalence of ATA[a]		Incidence of ATA[b]	
	Yes	No	Yes	No
Hypersensitivity[c], n (%)	1/11 (9.1)	19/77 (24.7)	4/17 (23.5)	15/69 (21.7)
Hypersensitivity Grade ≥ 3, n (%)	0/11	2/77 (2.6)	0/17	1/69 (1.4)

[a] Prevalence of anti-therapeutic antibodies is defined as the percentage of subjects with pre-existing antibodies that bind to liso-cel.

[b] Incidence of anti-therapeutic antibodies is defined as the percentage of subjects with treatment-induced or treatment-boosted antibodies that bind to liso-cel. In a subject without pre-existing antibodies, development of antibodies after first infusion of liso-cel is considered treatment-induced. In a subject with pre-existing antibodies, an increased level of antibodies after first infusion of liso-cel is considered treatment-boosted.

[c] Hypersensitivity events were selected using pre-defined list of PTs. Hypersensitivity status is determined based on treatment-emergent events.

Among the four subjects receiving nonconforming product, one had pre-existing ATA.

2.4.3. Pharmacodynamics

Mechanism of action

Breyanzi is a CD19 directed genetically modified autologous cellular immunotherapy administered as a defined composition to reduce variability in CD8+ and CD4+ T cell dose. The CAR is comprised of a murine FMC63 monoclonal antibody-derived single chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4 1BB (CD137) costimulatory domain, and CD3 zeta activation domain. CD3 zeta signalling is critical for initiating T cell activation and antitumour activity, while 4 1BB (CD137) signalling enhances the expansion and persistence of Breyanzi. CAR binding to CD19 expressed on the cell surface of tumour and normal B cells induces activation and proliferation of CAR T-cells, release of pro-inflammatory cytokines, and cytotoxic killing of target cells.

Primary and secondary pharmacology

The clinical pharmacology of liso-cel has been evaluated in Study 017001 in subjects with R/R MCL. Pharmacodynamic objectives were exploratory objectives.

B-cell Aplasia

B-cell aplasia, defined as CD19 B-cells comprising less than 3% of peripheral blood lymphocytes, is an on-target effect of liso-cel. In the total Liso-cel-treated Analysis Set, (DL1S and DL2S, n = 88), an increase in the proportion of subjects with B-cell aplasia was observed from 58% of subjects at baseline to 98% of subjects by Month 2, with 69% of subjects maintaining B-cell aplasia through Month 12 (Table 10).

Table 10. B-cell Aplasia Incidence Over Time vs Dose Level – Liso-cel-Treated Analysis Set MCL

Visit Category	DL2S N=82	DL1S N=6	Total N=88
<3% CD19+ B-cells of lymphocytes	**n/N (%)**	**n/N (%)**	**n/N (%)**
Baseline	46/82 (56)	5/6 (83)	51/88 (58)
Day 4	46/66 (70)	5/5 (100)	51/71 (72)
Day 8	66/79 (84)	6/6 (100)	72/85 (85)
Day 11	62/68 (91)	6/6 (100)	68/74 (92)
Day 15	72/77 (94)	6/6 (100)	78/83 (94)
Day 22	70/75 (93)	6/6 (100)	76/81 (94)
Day 29	71/73 (97)	5/5 (100)	76/78 (97)
Month 2	57/58 (98)	3/3 (100)	60/61 (98)
Month 3	55/57 (96)	3/3 (100)	58/60 (97)
Month 6	35/42 (83)	2/2 (100)	37/44 (84)
Month 9	26/36 (72)	2/2 (100)	28/38 (74)
Month 12	22/33 (67)	2/2 (100)	24/35 (69)
Month 18	1/2 (50)	0	1/2 (50)

Concentration values after the initiation of retreatment or additional cycles of liso-cel or after another anticancer treatment (including lymphodepletion) are excluded from the summaries.

Baseline is defined as the last measurement prior to liso-cel infusion

n/N = (number of subjects with B-cell aplasia)/(number of subjects for evaluation).

Serum Immunoglobulins

IgG < 500 mg/dL was present in 40% of the subjects at baseline, increased to 68% of subjects by Month 6, and 53% of subjects at Month 24. Similar results were observed between dose levels (DL1S, DL2S), however the number of DL1S subjects was small (n = 6). The median IgG level was reduced from baseline for all post liso-cel infusion collections, consistent with the assessment of hypogammaglobulinemia. The analysis of serum IgG levels did not take into account potential confounding by the administration of IVIG for the treatment of hypogammaglobulinemia.

Pharmacodynamic-Safety Relationship

Pharmacodynamic-Safety relationships were evaluated in the Liso-cel-treated Analysis Set. Correlative analyses were performed to evaluate the relationships of baseline and peak values (ie, Cmax) of soluble biomarkers and CRP/ferritin with selective safety endpoints including CRS and iiNT.

The number of subjects with Grade ≥ 3 CRS (N<5) analyzed was insufficient to assess a relationship.

Soluble Biomarkers

A total of 37 soluble biomarkers were analyzed to examine changes in cytokine and chemokine levels following liso-cel infusion. Soluble biomarkers SAA, GM-CSF, IFN-g, IL-2, IL-4, IL-5, and IL-6 were the only analytes which demonstrated a Pharmacodynamic-safety Relationship. For soluble factors such as SAA, GM-CSF, IFN-g, IL-2, IL-5, and IL-6 where an increased trend after infusion was observed, peak elevation was noted at the Day 4 or 8 collections and decreased by Day 29.

No baseline soluble biomarker levels had an association comparing any grade CRS versus no CRS, or

any grade iiNT versus no iiNT, or Grade 3 or greater iiNT categories. Among the soluble biomarkers, Cmax of SAA, GM-CSF, IFN-γ, IL-2, IL-4, IL-5, and IL-6 were associated with any grade CRS versus no CRS, while only IL-2 was associated with any grade iiNT versus no iiNT.

C-reactive Protein (CRP) and Ferritin

Median post-infusion serum CRP for DL2S increased by Day 8 from Day 1 levels, although a wide interquartile range was observed, and then decreased by Day 29. Median post-infusion CRP in DL1S demonstrated an overall decrease from Day 1 levels, however, the number of DL1S subjects was small with wide interquartile ranges (n = 6).

Median serum ferritin observed for DL1S and DL2S had a slight upward trend from Day 1 levels between Day 11 and Day 22 but was equivalent by Day 29. However, a wide range of ferritin levels were observed at each timepoint within each dose level.

There were no associations in the baseline CRP or ferritin for subjects with any grade CRS versus subjects with no CRS, subjects with any grade iiNT versus subjects with no iiNT, nor in subjects with Grade 3 or higher iiNT versus subjects with no iiNT. There was an association of peak CRP, but not peak ferritin, in subjects with any grade CRS versus subjects with no CRS.

There were no associations of peak CRP or ferritin levels with iiNT status.

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology profile of liso-cel in subjects with R/R MCL has been characterized based on the results from clinical study 017001; subjects in the MCL Cohort received either DL1S (50×10^6 CAR+ T cells, 6 subjects) or DL2S (100×10^6 CAR+ T cells, 82 subjects).

The bioanalytical methods used in this application are the same as submitted in the initial MA.

The MAH submitted the bioanalytical reports for PK and ATA. The qPCR method shows an acceptable performance for all concentrations. Overall, this application makes use of previously validated methods with adequate performance or provided some partial validation where missing. This is considered acceptable.

The liso-cel concentration in the peripheral blood detected by qPCR exhibited a rapid expansion with a median Tmax of 10 days (range: 3 to 29 days). The median Tmax in DL1S is longer (17 days) compared to DL2S, however the number of subjects is smaller. The expansion declines up to 28 days after infusion in both DL1S and DL2S. Higher median Cmax and AUC0-28 by qPCR is observed in DL2S respect to DL1S, however the number of patients treated with DL1S was smaller. A large inter-subject variability is observed with both doses.

Flow cytometry-based PK assessment demonstrated the ability of CD4+ and CD8+ drug product components to expand following liso-cel infusion. A higher expansion of CD8+ EGFRt+ cells was observed compared with CD4+ EGFRt+ cells in both the DL1S and DL2S. The same trend in qPCR is observed in median Cmac and AUC0-28 of CD3+ EGFR+, CD4+ EGFR+, and CD8+ EGFR+ T-cells, with lower expansion in DL1S. This is expected due to the high correlation between qPCR (transgene) and flow cytometry.

In the current variation, the MAH submitted a comparison between R/R MCL DL1S+DL2S versus 3L+LBCL (pooling all three doses used in 017001 study (also object of the initial marketing authorization for Breyanzi)). Based on this comparison, the Cmax, AUC0-28 as well as Tmax are comparable between R/R MCL and 3L+LBCL.

A PK comparison at the same dose level in R/R MCL and DLBCL patients enrolled in study 017001 showed that PK parameters for DL2S dose (100×10^6 CAR+ T cells) are comparable (R/R MCL median Cmax 31631.0 copies/ug, median AUC0-28 329992.3 day*copies/ug, median Tmax 10.0 days; DLBCL cohort: median Cmax 25098.5 copies/ug, AUC0-28 229062.6 day*copies/ug, median Tmax 11 days).

For qPCR, persistence was defined as a transgene count greater than or equal to the LLOD (5 copies/reaction). Persistence of liso-cel transgene was observed up to Day 730.

The majority of subjects demonstrated long-term persistence of CAR+ T cells based on transgene detection in peripheral blood with 51 out of 61 patients had transgene persistence (82.8%) on Day 90; data on persistence is available up to Day 730 with 10 out of 26 (38.5%) showing transgene persistence. This is in line with data on persistence in the already approved indications.

The effect on PK of selected baseline demographic and disease characteristics in subjects receiving liso-cel was evaluated. A potential association between the presence of blastoid morphology and lower Cmax and AUC0-28 was observed. However, as reported in the efficacy section, ORR rates are between 80-90% but still clinically relevant in patients with blastoid morphology, in absence of a clear trend of lack of efficacy. The potential association between the presence of blastoid morphology and lower expansion could be affected by the small number of enrolled patients in that subgroup (N=16). No conclusion can be drawn on the effect of lower Cmax and AUC0-28 in patients with blastoid morphology.

Four subjects (3 treated at DL2S and 1 treated at DL1S) received a nonconforming product; their median Cmax and AUC0-28 are lower, however the ranges are included in that of subjects receiving the conforming product.

The relationship between PK and clinical efficacy and safety has been investigated. A potential relationship was observed between higher transgene PK parameters (Cmax and AUC[0-28]) and higher CR rate and longer PFS and DOR per IRC. No apparent relationship was observed between transgene PK parameters and response (BOR of either CR or PR, versus non-response).

A potential relationship was observed between higher transgene PK parameters (Cmax and AUC[0-28]) and higher incidence of any grade CRS, any grade iiNT and Grade ≥ 3 iiNT. The relationship between PK parameters and Grade ≥ 3 CRS was not assessed because the number of subjects with Grade ≥ 3 CRS (n = 1) was less than 5.

PK-efficacy/safety relationships were generally similar between R/R MCL and 3L+ LBCL. Some difference in PK-efficacy relationship between R/R MCL and 3L+ LBCL (ie, relationship between PK and response) could be due to a smaller number of subjects in the MCL Cohort relative to the DLBCL Cohort of Study 017001 and the high ORR observed in the MCL Cohort, resulting in a smaller number of subjects in certain subgroups (ie, non-responders).

The assessment of immune response to liso-cel was also performed and the prevalence and incidence of ATA in R/R MCL patients are in line with that observed in the already approved indications. In patients who received Breyanzi for MCL, pre-existing ATAs were detected in 13% (11/88) of patients, and treatment-induced or treatment-boosted ATAs were detected in 20% (17/86) of patients.

It was observed that median Cmax and AUC0-28 are higher in subject with pre-existing ATA or treatment-induced or treatment-boosted ATA. A similar trend has been already observed in LBCL patients. The effect of ATA on efficacy seems to suggest a better outcome in subjects who had treatment-induced or treatment-boosted ATA. It is suggest in the submitted dossier that it could be due to a longer follow-up of responders respect to non-responders since the median time to first positive ATA in subjects with treatment-induced ATA was 9.8 months. No clear conclusion can be done on this aspect.

<u>Pharmacodynamic</u>

The clinical pharmacology of liso-cel has been evaluated in Study 017001 in subjects with R/R MCL and pharmacodynamic objectives were exploratory objectives.

B-cell aplasia was observed in 58% of subjects at baseline increasing to 98% of subjects by Month 2, with 69% of subjects maintaining B-cell aplasia through Month 12. At baseline, 40% of subjects had IgG < 500 mg/dL which increased to 68% of subjects by Month 6 and remained above baseline through Month 24. However, there is a difference in baseline B-cell aplasia in the group of subjects administered with DL1S vs subjects administered with DL2S (baseline % of subjects with B-cell aplasia: DL1S = 83%; DL2S = 56%). Considering the small number of patients in DL1S group, no conclusion can be drawn on the significance of this difference and its impact on efficacy.

For soluble factors such as SAA, GM-CSF, IFN-γ, IL-2 and IL-5 where an increased trend after infusion was observed, peak elevation was observed at the day 4 or day 8 collection and decreased by Day 29. Peak levels of soluble biomarkers SAA, GM-CSF, IFN-γ, IL-2, IL-4, IL-5, and IL-6 were associated with any grade CRS, while only IL-2 was found to be associated with any grade iiNT. Peak CRP levels had an association with any grade CRS. The frequency of Grade ≥ 3 CRS was too low to assess any potential relationship with these events. No baseline soluble factor, CRP, or ferritin levels were associated with any grade CRS, any grade iiNT or Grade ≥ 3 iiNT.

2.4.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology of Breyanzi in R/R MCL has been well characterised, and can be considered adequate for the new indication.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Dosing recommendations were mainly based on results from Phase I Study 017001. The study comprises a Dose Finding (DF), Dose Expansion (DE) and Dose Confirmation (DC).

Dose-finding Group

Initially for dose-finding in the mantle cell lymphoma (MCL) cohort, eligible subjects were assigned to receive a liso-cel dose of 50×10^6 CAR+ T cells (DL1). Dose escalation/de-escalation in this study was guided by a modified continuous reassessment method (mCRM) that implemented Bayesian methodology to estimate the probabilities of DLT (P[DLT]) and CR (P[CR]). With each subject's information, the dose-toxicity and dose-response model was updated, and new P[DLT] and P[CR] was estimated. The P[DLT] and P[CR] based on investigator assessment, in conjunction with rules for enrolment and stopping, were used to determine the dose allocation for each subject. This trial was designed with an open enrolment feature, meaning that subjects were enrolled as they became available for the trial. The accrual rate into the trial was governed by allowing only a certain number of subjects enrolled with unknown DLT information per regimen.

Enrolment could have been stopped for early futility if no doses or schedules were determined to be either safe or effective. Prior to opening a new regimen for enrolment, the SRC reviewed the safety and efficacy data to provide recommendations to follow or override the mCRM algorithm's allocation of a subject or subjects.

Dose-expansion Groups

A dose regimen was allowed to continue from the dose-finding phase of the study to the dose-expansion phase for further safety and efficacy evaluation if it met early success criteria for enrolment suspension. The criteria were that it was likely to be safe (P[DLT < 0.33] > 0.7) and efficacious (P[CR

> 0.25] > 0.9). If multiple regimens continued to the DE phase, enrolment within DE groups was prioritized to the highest dose, unless the order of prioritization was changed or enrolment to an expansion group stopped in consultation with the steering committee (SC).

DLT assessment

In the DF and DE groups, DLTs were assessed from the time of liso-cel administration until day 28. In all groups, AEs and SAEs were collected.

Dose-confirmation Group for the MCL Cohort

Dose-Response for Efficacy and Safety Analysis for the DLBCL Cohort in Study 017001 and PK Comparison Across Indications have been conducted for extrapolation to the new indication.

The dose-response analysis for efficacy and safety performed for DLBCL Cohort were provided to the Agency during the initial marketing authorization application (MAA), EMEA/H/C/004731/0000.

Ad hoc analyses were conducted to explore the possible relationship of clinical outcomes for three of the dose regimens explored in the DLBCL Cohort of Study 017001:

DL1S: 50 × 10^6 CAR+ T cells (25 × 10^6 CD8+ CAR+ T cells and 25 × 10^6 CD4+ CAR+ T cells), single-dose regimen

DL2S: 100 × 10^6 CAR+ T cells (50 × 10^6 CD8+ CAR+ T cells and 50 × 10^6 CD4+ CAR+ T cells), single-dose regimen

DL3S: 150 × 10^6 CAR+ T cells (75 × 10^6 CD8+ CAR+ T cells and 75 × 10^6 CD4+ CAR+ T cells), single-dose regimen

Based on univariate analysis (EMEA/H/C/004731/0000), the administered dose of CAR+ viable T cells had no relationship with BOR over the dose range studied. There were no clear relationships between administered dose and other key clinical outcomes such as DOR, PFS, cytokine release syndrome (CRS), investigator-identified neurologic toxicity (iiNT), or incidence of Grade ≥ 3 infection.

Further analysis also showed no clear relationship between Cmax or AUC(0-28) and administered dose (44 to 156 ×10^6 CAR+ T cells) (EMEA/H/C/004731/0000).

In addition, more recent PK comparisons across indications show that there is no apparent difference in transgene PK parameters across R/R MCL, 3L+ LBCL, 2L LBCL, and 3L+ FL.

In agreement with the recommendation of the SC, based on the preliminary evidence for an efficacy dose-response, extrapolation from previous dose analysis in DLBCL, as well as acceptable safety in both DL1S and DL2S to date, **a recommended regimen of a single dose of 100 × 10^6 CAR+ T cells (DL2S) was selected for the MCL Cohort DC group**. The study enrolled subjects at this regimen for further testing in the DC group.

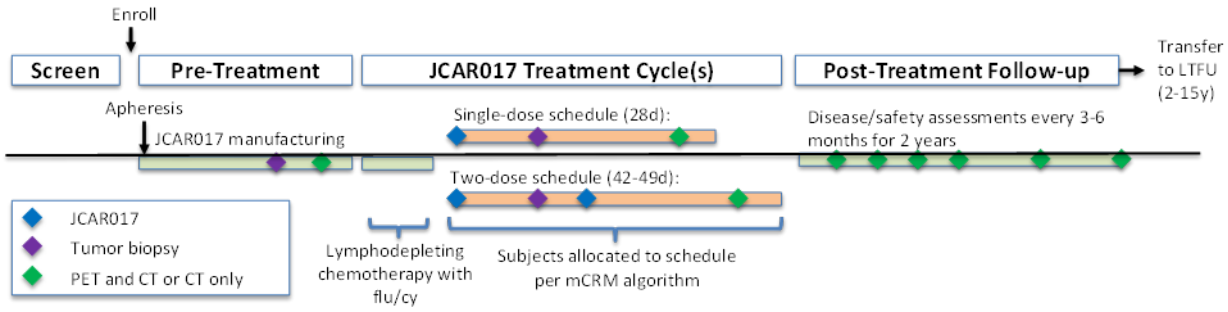
2.5.2. Main study

Title of Study

Phase 1, Multicenter, Open-Label Study of JCAR017, CD19-targeted Chimeric Antigen Receptor (CAR) T Cells, for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL)

Methods

Study 017001 design



Two disease-specific cohorts were enrolled in this study; the DLBCL cohort, object of the initial marketing authorisation (Breyanzi EPAR), and the Mantle Cell Lymphoma (MCL) cohort which included subjects with MCL having received ≥ 2 prior lines of systemic MCL therapy and having been treated with an alkylating agent, a BTKi, and rituximab (or other CD20-targeted agent).

The study consisted of 3 periods:

Pre-treatment period: After successful screening, eligible subjects were enrolled and underwent leukapheresis to enable liso-cel product generation. If necessary, anticancer therapy for disease control (ie, bridging therapy) was allowed while liso-cel was being manufactured (ie, during the period between screening and lymphodepletive chemotherapy (LDC); in this case, subjects were required to have PET-positive disease prior to treatment with LDC and liso-cel. All subjects were required to meet relevant eligibility criteria before liso-cel administration.

Treatment period: The treatment period included a lymphodepletive chemotherapy (LDC) with fludarabine and cyclophosphamide followed by 1 (single-dose schedule) or 2 (2 dose schedule) doses of liso-cel administered IV. Day 1 was defined as the day of first liso-cel administration. In the single-dose schedule, liso-cel was administered 2 to 7 days after completion of LDC. In the 2 dose schedule, subjects received the first dose as described above, and a second dose of liso-cel was given 14 days after the first dose of liso-cel (without further LDC between the 2 doses). The following dose levels were planned to be evaluated:

- **Dose Level 1 (DL1)**: 50 × 10^6 CAR+ T cells (25 × 10^6 CD8+ CAR+ T cells and 25 × 10^6 CD4+ CAR+ T cells); single and 2-dose regimens tested: **DL1S** and **DL1D**, respectively
- **Dose Level 2 (DL2)**: 100 × 10^6 CAR+ T cells (50 × 10^6 CD8+ CAR+ T cells and 50 × 10^6 CD4+ CAR+ T cells); single-dose regimen only: **DL2S**
- **Dose Level 3 (DL3)**: 150 × 10^6 CAR+ T cells (75 × 10^6 CD8+ CAR+ T cells and 75 × 10^6 CD4+ CAR+ T cells); single-dose regimen only: **DL3S**

In the MCL cohort, only DL1S and DL2S were eventually evaluated. As highlighted above, a recommended regimen of a single dose of 100 × 10^6 CAR+ T cells (DL2S) was selected for the MCL Cohort DC group. This target dose of liso-cel for MCL is the same as approved for the other indications, i.e., 100 × 10^6 CAR+ viable T cells (consisting of a target 1:1 ratio of CD4+ and CD8+ T cell components) within a range of 44 to 120 × 10^6 CAR+ viable T cells, administered by IV infusion.

The first response evaluation was performed at approximately 28 days after liso-cel infusion.

Post-treatment follow-up period: After Day 29, subjects entered the post-treatment follow-up period, and were followed on this study for safety, disease progression, and survival for 2 years at approximately 3, 6, 9, 12, 18 and 24 months after their last dose of liso-cel, including after disease progression and/or the initiation of additional anticancer therapies.

Long-term Follow-up: Upon discontinuation from the study, subjects who received liso-cel were asked to participate in a separate long-term follow-up study (Study GC-LTFU-001) for survival, long-term toxicity, and viral vector safety for up to 15 years post-last dose of liso-cel per health authority guidance on viral vector-based gene therapy products.

Study participants

Inclusion and exclusion criteria

Main inclusion criteria

Subjects must meet all of the following criteria to be enrolled into this study:

- Age ≥18 years at the time of consent
- MCL diagnosis, confirmed with cyclin D1 expression or evidence of t(11;14) by cytogenetics, fluorescent in situ hybridization [FISH], or PCR) with relapsed or refractory disease after at least 2 prior lines of systemic MCL therapy). Subjects must have been treated with an alkylating agent, Bruton's tyrosine kinase inhibitor (BTKi), and rituximab (or other CD20-targeted agent).
- Archived tumor biopsy tissue available from the last relapse and corresponding pathology report available or, if at least one tumor-involved site is deemed accessible at time of screening, willing to undergo pre-treatment biopsy (excisional when possible) for disease confirmation. If the subject has never had a CR, a sample from the most recent biopsy is acceptable.
- Positron emission tomography (PET)-positive disease according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson, 2014)
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
- Adequate organ functions including:
    - adequate bone marrow function to receive lymphodepleting as assessed by the investigator
    - Serum creatinine ≤ 1.5 x age-adjusted upper limit of normal (ULN) OR calculated creatinine clearance (Cockcroft and Gault) > 30 mL/min/1.73 m^2 and
    - Alanine aminotransferase (ALT) ≤ 5 x ULN and total bilirubin < 2.0 mg/dL (or< 3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver)
    - adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram or multiple uptake gated acquisition (MUGA) scan performed within 1 month of determination of eligibility
- The study included patients with prior autologous and/or allogeneic HSCT in the absence of acute or chronic graft versus-host disease (GVHD)
- Subjects who have received previous CD19-targeted therapy must have CD19-positive lymphoma confirmed on biopsy since completing the prior CD19-targeted therapy.

Main exclusion criteria

- Subjects with central nervous system (CNS)-only involvement by malignancy (note: subjects with secondary CNS involvement are allowed on study)

- History of another primary malignancy not in remission for at least 2 years.
- Treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis
- Subjects with uncontrolled and or active infections
- Presence of Graft Versus Host Disease (GVHD)

Treatments

Pre-treatment period

Leukapheresis

A leukapheresis collection was performed on each subject to obtain a sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the production of the JCAR017 investigational product. In case of technical issues during the procedure or in the processing of the product such that it cannot be used for JCAR017 administration, a subsequent collection procedures were performed.

Anticancer Treatments between Leukapheresis and Lymphodepleting (Bridging therapy)

If necessary, anticancer treatment was allowed for disease control while JCAR017 is being produced (i.e., after leukapheresis and prior to lymphodepleting chemotherapy); low dose chemotherapy (e.g., vincristine, rituximab, cyclophosphamide ≤ 300 mg/m2) is allowed if completed at least 7 days prior to the start of lymphodepleting chemotherapy. Local radiation was allowed to a single lesion or subset of lesions if other un-irradiated PET-positive lymphoma lesions are present. If anticancer treatment is necessary during this time, the pre-treatment PET and CT assessments and other pre-treatment study procedures must have been performed after the completion of the anticancer treatment.

Treatment period

Lymphodepleting Therapy

Subjects received fludarabine (30 mg/m2/day for 3 days) plus cyclophosphamide (300 mg/m2/day for 3 days) prior to treatment with JCAR017. Lymphodepleting chemotherapy must be completed between 2 and 7 days before JCAR017 administration.

Liso-cel Treatment

Liso-cel is comprised of autologous CD4+ and CD8+ T cells that express a CD19-specific CAR, provided as frozen cell suspensions for IV administration and in 2 individually formulated CD4+ and CD8+ T-cell suspensions in media containing DMSO for direct IV administration in equal CAR+ T cell quantities into the subject. The dose of JCAR017 was in between 50 and 150 x 10^6; only patients treated with a target dose of 50 or 100 x 10^6 were included in the analysis set.

Post treatment period

Prophylactic or treatment measures for the management of CRS, neurotoxicity and other Adverse Events were allowed if considered necessary by treating clinicians.

Objectives

Study assessment

Efficacy assessments of response and progression were performed both by investigators and by an IRC. Disease evaluation at baseline and at response was determined according to the Lugano 2014 criteria.

Response Category[c]	PET-CT-Based Criteria[b]
CR	Score 1, 2, or 3[a] with or without residual mass No evidence of FDG-avid disease in marrow[d]
PR	Score 4 or 5[a] with reduced uptake compared with baseline and residual masses of any size Bone marrow with residual uptake higher than in normal marrow but reduced compared with baseline (Diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in marrow in the context of a nodal response, should consider further evaluation with MRI, biopsy, or interval scan.
SD	Score 4 or 5[a] with no significant change in FDG uptake from baseline Bone marrow unchanged from baseline
PD	Score 4 or 5[a] with an increase in intensity of uptake from nadir New FDG-avid foci consistent with lymphoma (may need biopsy or repeat scan if uncertain about etiology of foci)

a. Based on the Deauville 5-point Scale: 1: no uptake; 2: uptake ≤ mediastinum; 3: uptake > mediastinum ≤ liver; 4: moderately increased uptake > liver; 5: markedly increased uptake > liver and/or new lesions related to lymphoma; X: new areas of uptake unlikely to be related to lymphoma

b. CT scans alone that are done per protocol, can be used to follow subjects for ongoing response in the absence of PET.

c. If BMA/BMB performed, assessment should be by morphology. If indeterminate then IHC should be used (Cheson, 2014).

d. For subjects in the MCL cohort who have evidence of bone marrow lymphoma involvement prior to LDC infusion based on the BMA/BMB or on PET scan performed closest to and prior to LDC, if the post-infusion BMA/BMB documenting no lymphoma involvement is done >28 days post the PET scan documenting first CR, then that response assessment should be downgraded to PR and the result of the BMA/BMB negative for lymphoma involvement should be applied to the subsequent response assessment (including PET scan). For BMA/BMB results, the assessment window will be extended to + 42 days if there are no subsequent response assessment time points. This + 42-day window will only apply to overall assessments associated with the subject's last response assessment time point

Assessment of bone marrow involvement by lymphoma in the MCL cohort required a post-infusion bone marrow aspirate/bone marrow biopsy (BMA/BMB), performed within the visit window and up to a maximum of 28 days after the PET confirming CR.

Table 11. BMA/BMB Requirements in MCL Cohort

Baseline		Post-Baseline
BM involvement by PET	**BM involvement by BMA/BMB**	**To confirm CR assessed by PET scan**
Yes	Yes	Require BMA/BMB
Yes	No or Missing	Require BMA/BMB
No	Yes	Require BMA/BMB
No	No	No BMA/BMB required
No	Missing	Require BMA/BMB if subject has prolonged cytopenia (laboratory-based Grade ≥ 3 anemia, neutropenia or thrombocytopenia at the Day 29 visit) that has not resolved to Grade ≤2 on or before the Day 90 visit

BMA/BMB = Bone marrow aspirate/bone marrow biopsy; CR = Complete remission; MCL = Mantle Cell Lymphoma; PET = Positron emission tomography.

The evaluation of response was in charge of an Independent Review Committee (IRC).

Outcomes/endpoints

Primary Endpoint

Table 12. Primary efficacy endpoint for Study 017001 MCL Cohort

Objective	Endpoint	Endpoint Description
Primary		
To assess the antitumor activity of liso-cel	ORR	The ORR was defined as the proportion of subjects with a Best Overall Response (BOR) of either CR or PR. The BOR was the best disease response recorded from the time of liso-cel infusion until disease progression, the start of another anticancer therapy, HSCT or end of study (EOS).

Estimands for the primary objective

Population	Adult patients with relapsed or refractory mantle cell lymphoma after at least 2 lines of systemic therapy.
Treatment condition<s>	Assignment to liso-cel, single administration, in a single arm trial
Endpoint (variable)	ORR: proportion of subjects with a BOR of either CR or PR which is assessed by PET-CT by IRC using the 2014 Lugano Classification
Population-level summary	Overall response rate is defined as proportion of subjects with an IRC assessed BOR of either CR or PR.
Intercurrent events and strategy to handle them	
Subsequent Anti-cancer Therapy	**Strategy** While-on-treatment **Rationale** Assessments before the intercurrent event will be included
HSCT	**Strategy** While-on-treatment **Rationale** Assessments before the intercurrent event will be included
Progression Assessed by IRC	**Strategy** While on treatment **Rationale** Assessment after the intercurrent event will be included

Death	**Strategy** While on treatment **Rationale** Assessment before the intercurrent event will be included

Secondary Endpoints

Table 13 Secondary efficacy endpoints/PRO Objectives and Endpoints for Study 017001 MCL Cohort

Objective	Endpoint	Endpoint Description
To assess the rate of CR and durability of antitumor activity of liso-cel	CR rate	CR rate was defined as the proportion of subjects with a BOR of CR from the time of the liso-cel infusion until disease progression, or the start of another anticancer therapy or HSCT or EOS.
	DOR	DOR was defined as the interval from the first documentation of CR or PR to the earlier date of disease progression or death due to any cause. The first documentation of CR or PR was defined as the latest of all dates of required measurements to establish the response.
To estimate the PFS and OS of subjects treated with liso-cel	PFS	PFS was defined as the time from the date of the liso-cel infusion to the earlier date of disease progression or death due to any cause. The progression date was defined as the earliest date of all assessments that lead to a progression.
	PFS ratio	PFS ratio was defined as the ratio of PFS to the most recent line of therapy (including systemic treatments, radiotherapy, and HSCT prior to liso-cel) to the PFS on liso-cel based on investigator assessment. The PFS to the most recent line of therapy prior to liso-cel was the time from the start date of the most recent line of therapy prior to liso-cel to the date of progression or informed consent if date of progression is entirely missing.
	OS	OS was defined as the interval from the date of the liso-cel infusion to the date of death due to any cause. The OS analysis included all available survival information with long-term follow-up data.
To assess HRQoL and health economics and outcome research	HRQoL	Measurement of HRQoL changes as assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 and the EuroQol instrument EQ-5D-5L.

Table 13 Secondary efficacy endpoints/PRO Objectives and Endpoints for Study 017001 MCL Cohort

Objective	Endpoint	Endpoint Description
	Hospital resource utilization	Numbers of ICU inpatient days and non-ICU inpatient days and reasons for hospitalization.

First key secondary endpoint: complete response (CR) rate

Population	Adult patients with relapsed or refractory mantle cell lymphoma after at least 2 lines of systemic therapy.
Treatment condition<s>	Assignment to liso-cel, single administration, in a single arm trial
Endpoint (variable)	CRR: proportion of subjects with a BOR of CR after liso-cel infusion which is assessed by PET-CT by IRC using the 2014 Lugano Classification
Population-level summary	Complete response rate is defined as proportion of subjects with an IRC assessed BOR of CR.
Intercurrent events and strategy to handle them	
Subsequent anticancer therapy	**Strategy** While on treatment **Rationale** Assessments before the intercurrent event will be included
HSCT	**Strategy** While on treatment **Rationale** Assessments before the intercurrent event will be included
Progression assessed by IRC	**Strategy** While on treatment **Rationale** Assessments after the intercurrent event will be included
Death	**Strategy** While on treatment **Rationale** Assessments before the intercurrent events will be included.

Second key secondary endpoint: Duration of response (DOR)

Population	Adult patients with relapsed or refractory mantle cell lymphoma after at least 2 lines of systemic therapy.
Treatment condition<s>	Assignment to liso-cel, single administration, in a single arm trial
Endpoint (variable)	DOR: time from first response (CR or PR) to disease progression or death from any cause, whichever occurs first up to 60 months after liso-cel infusion (EOS), which is assessed by IRC using the Lugano 2014 Classification
Population-level summary	Median DOR with 95% CI
Intercurrent events and strategy to handle them	
Received a subsequent anti-cancer therapy (including systemic therapy, radiotherapy) or proceed to HSCT before PD or death	**FDA censoring** **Strategy** While on treatment **Rationale** Censor at last adequate response assessment before the intercurrent event.
	Sensitivity analysis (EMA censoring rules) **Strategy** Treatment policy **Rationale** All data collected are used regardless of whether the intercurrent event occurs (ie, a subject achieving PD after the intercurrent event is counted as progressed and if the subject dies after the intercurrent event, this is also considered an event for DOR)
Received retreatment before PD or death	**FDA censoring** **Strategy** While-on-treatment **Rationale** Censor at last adequate response assessment before the intercurrent event**.**
	Sensitivity analysis (EMA censoring)

	Strategy While on treatment **Rationale** Censor at last adequate response assessment before the intercurrent event.

DOR was assessed based on the IRC evaluations for subjects who achieved a CR or PR using the Lugano 2014 criteria. A description of the censoring rules used for this application is found in Table 14. Sensitivity analyses were performed without censoring HSCT and without censoring new anticancer therapy, HSCT and missing at least two consecutive scheduled disease assessments

Table 14. Censoring rules for DOR and PFS

Scenario	EMA Guidelines		FDA Guidelines	
	Censor/ Event	Date	Censor/ Event	Date
Death or PD	Event	Earlier of PD or death	Event	Earlier of PD or death
Start new subsequent anti-lymphoma therapy before PD or death	Event	Earlier of PD or death	Censor	Last adequate assessment date before starting new subsequent anti-lymphoma therapy
Experienced an event after missing at least 2 consecutive scheduled disease assessments	Event	Earlier of PD or death	Censor	Last adequate assessment date before 2 consecutive missing assessment timepoints
No documented PD and No Death	Censor	Last adequate assessment date on or prior to the earliest censoring event	Censor	Last adequate assessment date on or prior to the earliest censoring event

Censoring rules based on EMA guidance (2013) for cancer trial endpoints and FDA Guidance (2007)

Sensitivity analyses

Sensitivity analyses of primary and secondary efficacy endpoints, including ORR, CR rate, DOR, PFS, and OS, was performed based on:

- the Leukapheresed (ITT) Set
- the response determined by investigator
- Liso-cel-treated Efficacy Analysis Set

All the subjects in the ITT Set were used for the purpose of the ITT analyses. In the ITT analysis of ORR and CR rate, a subject in the ITT Set who achieved a BOR of CR or PR was considered a responder. A subject in the ITT Set who did not receive CAR-T cell product was considered not evaluable (ie, a non-responder). In the ITT analyses of PFS and OS, the date of the first leukapheresis

served as the reference date instead of the date of the first liso-cel infusion. The ITT analyses of the primary and secondary efficacy endpoints were presented by assigned dose level and overall.

The analysis methods for all sensitivity analyses were the same as described for the primary analysis for the corresponding endpoints.

Post-hoc sensitivity analyses for DOR, PFS and OS were conducted to evaluate the impact of COVID-19 related deaths on the above-mentioned time to event endpoints, censoring the subjects who died in ongoing CR as discontinued from the study for DOR and PFS and alive for OS, and censoring the subject who died after experiencing PD as alive for OS.

Subgroup analyses

Efficacy subgroup analyses were performed based on the following variables:

- Age: < 65 versus ≥ 65 years and < 75 versus ≥ 75 years at the time of the first liso-cel infusion
- Sex: male versus female
- Ethnicity: Hispanic or Latino versus not Hispanic or Latino
- Race: white versus other races
- Prior HSCT status: yes versus no
- Prior response status: refractory vs relapsed to last prior therapy. The status is refractory if a subject achieved less than a CR to last prior therapy; otherwise the status is relapsed
- Response to prior chemotherapy, defined as: chemorefractory vs chemosensitive to last prior chemotherapy-containing therapy. The status is chemorefractory if a subject achieved SD or PD to last chemotherapy-containing regimen or relapsed <12 months after ASCT; otherwise the status is chemosensitive
- CNS disease status: known CNS disease vs no known CNS disease at the time of the first liso-cel infusion
- Ki67 proliferation index: ≥ 30% versus < 30%
- TP53 mutations: yes versus no
- Blastoid morphology: yes versus no

Subgroup analyses were performed for the primary and secondary efficacy endpoints. Forest plots were only generated for ORR and CRR. Some groupings of classes were considered if there were too few subjects in some subgroups.

Data from subjects treated with nonconforming product were analyzed separately from those treated with liso-cel and were excluded from the primary efficacy analysis.

Sample size

The ORR and CR rates in patients with MCL who have received 1 or more prior therapies are low, 18% to 64% and 7% to 35%, respectively (Chiappella 2009, Chiappella 2015, Witzig 2017, Martin 2016, Morschhauser 2013, Andorsky 2016, Wang 2015). Based on a meta-analysis using random-effects model, the estimated ORR is 40% (95% CI: 28, 55) and CR is 18% (95% CI: 10, 30).

For MCL cohort, based on the null hypothesis of primary efficacy endpoint ORR ≤ 40% and an alternative hypothesis of ORR > 40%, being powered for ORR = 65%, a sample size of 50 subjects in the MCL primary analysis set (PAS) from the Dose Finding, Dose Expansion and Dose Confirmation

groups will provide 93% power to demonstrate statistical significance based on an exact test at a 1-sided significance level of 0.025. For the key secondary efficacy endpoint of CR rate, based on the null hypothesis of CR rate ≤18% and an alternative hypothesis of CR rate > 18%, being powered for CR rate = 40%, 50 subjects will provide 97% power to demonstrate statistical significance based on an exact test at a 1-sided significance level of 0.025. The key secondary hypothesis (regarding CR rate) will only be tested at the same significance level as for the ORR if the primary hypothesis for ORR is rejected.

Randomisation

Not applicable as the study is a single arm trial

Blinding (masking)

Not applicable as the study is an open label study

Statistical methods

The MCL cohort consisted of subjects with R/R disease having received ≥ 2 prior lines of systemic MCL therapy including an alkylating agent, BTKi, and rituximab (or other CD20-targeted agent). Prior to Protocol Amendment 7, subjects were required to have received at least 1 prior therapy.

The statistical analysis plan (SAP) is based on Amendment 07 of the study protocol, dated 19 December 2019.

The primary efficacy endpoint was ORR, the key secondary endpoint was CR rate, and the secondary efficacy endpoints included DOR and PFS based on the Lugano 2014 criteria. The findings of the IRC were considered primary for these efficacy endpoints.

The hypothesis testing was planned to be done at the time of the primary analysis and to be conducted on the MCL PAS based on the IRC assessments at a one-sided significance level of 0.025.

The primary analysis for the MCL Cohort was to occur after at least 50 subjects in the MCL PAS from DE, DF, and DC group of MCL treated at the recommended regimen; these subjects had been followed for at least 6 months from first response or until death, disease progression, or withdrawal from study.

Based on health authority feedback received in April 2021 to provide data for registration from at least 60 subjects treated with liso-cel who had at least 6 months follow-up for DOR, it was decided to perform the primary analysis once a minimum of 70 subjects were treated and had at least 6 months follow-up from the first objective response.

Hypothesis Testing

The primary analysis conducted on the MCL PAS based on the IRC assessments was planned for this study at one-sided significance level of 0.025.

Two hypothesis tests were performed in the following sequential order for primary endpoint (ORR) and key secondary endpoint (CR):

H_0: ORR ≤ 40% versus H_1: ORR > 40%; 2) H_0: CR rate ≤ 18% versus H_1: CR rate > 18%

The null hypothesis was rejected if the p-value was less than 0.025. Only after rejecting the null hypothesis in the first hypothesis test, the second hypothesis testing could be performed. A p-value and the 2-sided 95% exact CI based on the Clopper-Pearson method for the ORR and CR rate were provided.

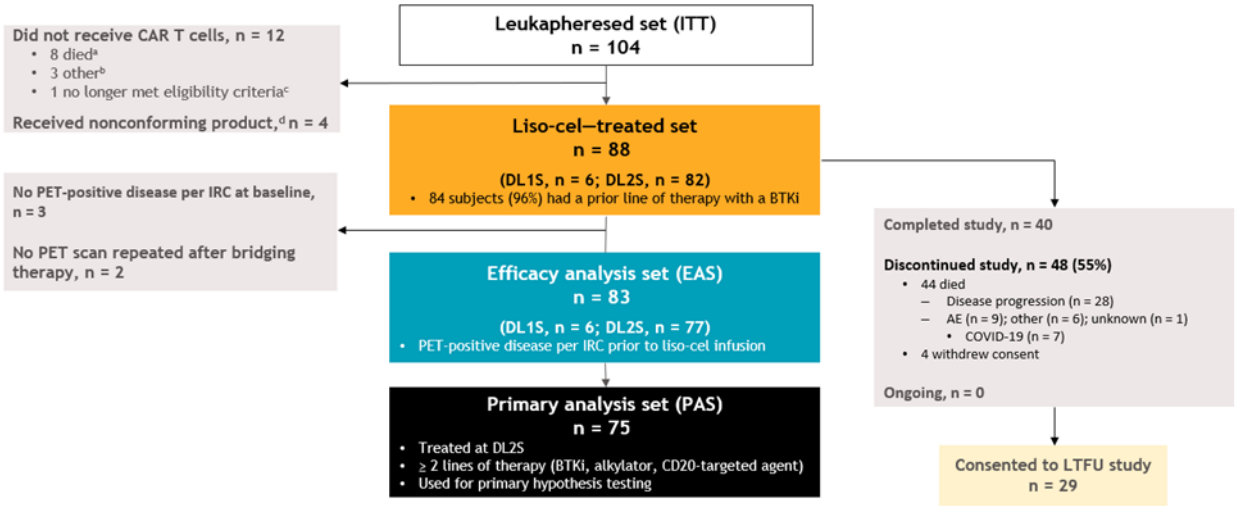
Results of these hypothesis testing analyses were reported in the 017001 Addendum 02 CSR (data cut off 19-Jan-2023) and showed that both endpoints were met. Hypothesis testing was not repeated at the final analysis (data cut off 16-May-2024).

The updated efficacy analysis was based on the MCL PAS and MCL Liso-cel-treated Efficacy Analysis set from the 16-May-2024 data cut.

For binary endpoints (ORR and CR rate), the frequency distribution (n, %) was provided along with the 2-sided 95% exact CI based on Clopper-Pearson method. For time-to-event endpoints (DOR, PFS, and OS), the KM product limit method was used to estimate the survival function. Event rates at specific time points were estimated from KM curves. Medians together with two-sided 95% CIs were calculated. 95% CIs for all endpoints were two sided.

Results

Participant flow



[a] Six patients died because of disease progression, 1 because of an AE, and 1 because of other reasons;

[b] One patient was ineligible due to second primary malignancy before LDC and 2 patients remained in ongoing CR after receipt of bridging therapy;

[c] 1 subject underwent leukapheresis and was retrospectively determined to have met exclusion criteria 2 regarding prior malignancies (this subject was discontinued prior to receiving LDC and liso-cel infusion).

[d] Defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but was considered appropriate for infusion.

Recruitment

A total of 105 subjects were screened for the MCL cohort at 14 sites in the US; as of the 16-May-2024 data cut-off, 40 (45.5%) subjects in the Liso cel-treated Analysis Set had completed the study and 0 were ongoing.

Conduct of the study

The original protocol for this study was dated 21-May-2015. As of the data cutoff date of 19 January 2023 for the addendum 2 CSR and the 16-May-2024 for this closeout CSR, 8 protocol amendments and 2 administrative letters were filed during the conduct of the study.

Table 15. summary key changes to protocol 017001

Document (Amendment)/Date	Summary of Key Changes
Amendment 1/ 24-Sep-2015	• Corrected and completed eligibility criteria for adequate renal function • Provided additional information for continued liso-cel treatment (additional cycles) in subjects who achieve a response following liso-cel therapy. (Note, the option for additional cycles was removed in Amendment 6.) • Modified language to require consultation with Sponsor if delay in starting LDC is more than 14 days • Made local analysis of cytokines an optional evaluation • Provided additional dosing recommendations for administration of LDC • Added instructions to administer the neuropsychological test at the EOS visit for subjects who withdraw more than 2 months after the Day 90 visit and before Day 180 • Specified conditions under which assessment of immunoglobulins is not required • Specified that neuropsychological tests will only be administered to English-speaking subjects • Added details regarding number of subjects enrolled in the regimen-finding portion of the study, the number of subjects within each disease cohort, and the number of subjects that may be added to a given dose regimen for further evaluation • Updated the simulation report to include the hierarchical dose-response model, simulation results, and model operating characteristics by borrowing efficacy data across disease cohorts.
Amendment 2/ 14-Mar-2016	• A second group of subjects may be enrolled and treated at a higher dose of liso-cel (100×10^6 CAR+ T cells) on the single- and 2 dose schedules if acceptable safety is observed among at least 6 subjects treated with 50×10^6 CAR+ T cells (Group A) on a single-dose schedule. • The planned maximum sample size was increased from 70 to 90 subjects. • Language regarding possible exploration of alternative doses or schedules of LDC was removed. • Updated clinical data from patients with ALL and NHL who were treated with JCAR014 in the Fred Hutchinson 2639 study (NCT # 01865617). • A separate Bayesian adaptive design simulation report for Dose Level 2 (Group B) was added.
Amendment 3/ 29-Jun-2016	• Allowed for a third, higher liso-cel dose level (150×10^6 CAR+ T cells) • Allowed for expansion groups to be opened at a dose level once that level has been shown likely to be safe and efficacious during the dose-finding portion of the study • Made efficacy a primary endpoint rather than secondary • Updated the sample size of the study and other statistical methods as a result of the above changes

Document (Amendment)/Date	Summary of Key Changes
	• Added an SC to be responsible for overseeing the conduct and scientific validity and integrity of the trial, and clarified the role of the SRC • Specified that efficacy evaluations will be performed both by the investigator and by a central IRC • Lengthened the follow-up time on this study to 2 years before subjects enroll in the long term follow up study, and added appropriate evaluations for this time period • Clarified that subjects with PMBCL are allowed • Changed inclusion criteria to no longer allow subjects with relapse within 1 year of frontline chemo-immunotherapy and not eligible for auto-HSCT (ie, disallowed second-line transplant ineligible subjects) • Specified that subjects must have archived tumor biopsy tissue available or, if at least one tumor-involved site is deemed accessible at time of screening, willing to undergo biopsy for disease confirmation at baseline • Added an exclusion for prior CAR T-cell or other genetically-modified T cell therapy • Clarified that steroids can be used after lack of response, subsequent therapy for lymphoma, or 1 year following liso-cel treatment • Included additional information regarding MAS • Clarified the timing of pre-treatment PET and CT scans • Removed optional blood draws for cytokines • Expanded definitions of relationship to study drug. The previous definitions of relationship to study drug focused on the time course of the event with regards to liso-cel treatment. The updated definitions allow a causal relationship for any reason. With the longer duration of this study, this change allows for long-term sequelae to be assessed more accurately.
Amendment 4/ 05-Jan-2017	• Defined a more homogeneous PAS for efficacy analyses. • Added provision for a DC group to further test the safety and efficacy at a recommended dose regimen already estimated to be safe and effective. • Added a prespecified interim analysis after approximately 50 subjects in the PAS have been followed for at least 3 months or until death, disease progression, or withdrawal from study, and the primary analysis after at least 75 subjects in the PAS have been treated and the last subject has been followed for at least 6 months or until death, disease progression, or withdrawal from study. A final analysis will be carried out after all subjects have completed or discontinued the study due to any reason. No formal hypothesis testing will be performed at the final analysis. • Added chemorefractory subgroup and an efficacy hypothesis for this subgroup. • Changed CR and DOR from primary to secondary endpoints, changed assessment of CR using Bayesian methods to exploratory, and added PFS ratio as a secondary endpoint.

Document (Amendment)/Date	Summary of Key Changes
	• Added subgroup analyses for safety and efficacy analyses. • Clarified that all subjects in the DLBCL Cohort must have relapsed or refractory disease after at least 2 lines of therapy or after autologous HSCT and clarified definition of DLBCL subjects with regard to current WHO guidelines. • Allowed subjects with CNS involvement of their lymphoma, and excluded subjects with CNS-only disease. • Added HRQoL and HEOR as secondary objectives. • Added guidance for administration of liso-cel in an outpatient setting when appropriate. • Updated information regarding potential risks and management of treatment toxicities to align with the current IB, including updating the CRS management algorithm • Updated the safety reporting rules (including increasing the reporting period for all AEs from 30 to 90 days following liso-cel infusion and specifying that all AE/SAEs will be collected for 30 days following initiation of new noncytotoxic anticancer therapy). • Clarified that investigational product includes both LDC and liso-cel.
Amendment 5/ 14-Aug-2017	• Allowed for more than 1 dose confirmation group, and added reference to stopping rules for a dose confirmation group were implemented to help detect safety and futility signals that may have occurred during the course of a DC group. • Amended the timing of the prespecified interim analysis to occur when the following conditions were met: 1) at least 75 subjects in the PAS have been treated at 1 recommended regimen across the DF, DE, and DC groups; 2) approximately the first 50 subjects treated in the DC group of the PAS have been followed for at least 3 months, or until death, disease progression, or withdrawal from the study; 3) at least the first 20 subjects treated in the DC group of the PAS have been followed for at least 6 months or until death, disease progression, or withdrawal from the study. • Added safety and futility monitoring boundaries for DC group • Excluded further enrollment of subjects with ECOG performance status of 2 at screening • Updated CRS management algorithm and guidance regarding NT based on most recent data. More specific language was added regarding actions to be taken in cases of potential CRS, especially for Grade 1 and 2 events. • Changed DL 1 to 25 × 10^6 CAR+ T cells (previously was 10 × 10^6 CAR+ T cells). • Updated PAS to exclude FL3B and DLBCL transformed from indolent histologies, as well as those with ECOG performance status of 2 or prior allo-HSCT • Specified evaluations needed in subjects who receive leukapheresis but no treatment
Amendment 6/ 13-Apr-2018	• Implemented larger windows around the Day 180 and Day 270 PET and CT scans to allow for more flexibility in the timing of scans and allow collection of follow-up response data 6 months from first response.

Document (Amendment)/Date	Summary of Key Changes
	• Added sentence to emphasize that fludarabine doses should be adjusted in subjects with renal insufficiency, in accordance with the fludarabine label • Changed the PK objective from primary to secondary • Refined CRS and NT management algorithms to be consistent with letter previously sent to sites • Added guidance regarding subject clinical stability prior to liso-cel administration • Removed the possibility of additional cycles for subjects who responded to liso-cel but did not achieve CR • Added flexibility to enrollment numbers to ensure adequate enrollment for the PAS
Amendment 7/ 19-Dec-2019	• Updated inclusion criterion to specify that subjects must have failed 2 lines of prior systemic therapy and have been treated with an alkylating agent, Bruton's tyrosine kinase inhibitor, and rituximab (or other CD20-targeted agent) • Defined and allowed inclusion of a dose-confirmation group for the MCL cohort • Updated the definition of the MCL primary analysis set, study duration, timing of analysis, statistical methods, sample size, and power calculations.
Amendment 8/ 30-Aug-2021	• Included the requirement of having a post-baseline assessment to confirm CR in MCL subjects with a baseline bone marrow involvement by imaging or bone marrow biopsy, or a delayed recovery of prolonged cytopenia in subjects with missing baseline bone marrow biopsy.

Impact of COVID-19 Pandemic

Two Dear Investigator Letters (dated 13-Mar-2020 and 19-Mar-2020) were sent to the sites detailing the required adjustments to the conduct of the study due to the pandemic and outlined the temporary suspension of screening, enrolment, and apheresis in all cellular therapy trials conducted by the Sponsor. A follow-up Dear Investigator Letter dated 27-Apr-2020 described the conditions to resume screening and consent for new subjects at the clinical sites, outlining study conduct considerations and approaches to protect the safety of study subjects and personnel, and to ensure scientific integrity, in light of the potential impact of COVID-19 disruptions to the study. The dear Investigator Letters were also submitted to regulatory health authorities and/or the ethics committees. As a result of these guidance, study enrolment was on hold for approximately 2 months and resumed in May 2020. As of

the data cutoff date of 19-Jan-2023 for the addendum 2 CSR, the study and the COVID-19 pandemic were still ongoing. At the time of the final analysis (data cutoff date of 16-May2024) WHO had already declared an end to the global Public Health Emergency for COVID-19 (05-May-2023).

Protocol deviations

- **GCP deviation and serious breach**

The contract research organisation, which provided eCOA services for the study, experienced a cybersecurity event on 20-Sep- 2020 that resulted in taking their clinical servers offline while the event was investigated and effectively controlled. While the CRO servers were offline, CRO provided a series of communications including mitigations for continuity to Sponsor and site staff. Upon restoring CRO's servers on 01-Oct-2020, all data were uploaded to the clinical database. Based on the scope of the cybersecurity event, and because the data transmissions were simply delayed and there was no safety reporting impacted, Sponsor has determined that the cybersecurity event had no impact on patient safety or data integrity.

No GCP deviations impacting the study were reported.

Table 16. Summary of major protocol deviations - Liso-cel-treated Analysis Set

	DL2S N = 82	DL1S N = 6	Total N = 88
Subjects with Major Protocol Deviations, n (%)	6 (7.3)	0	6 (6.8)
Study Treatment Deviation, n (%)	4 (4.9)	0	4 (4.5)
Prohibited Medications Deviation, n (%)	1 (1.2)	0	1 (1.1)
Study Procedure Deviation, n (%)	1 (1.2)	0	1 (1.1)
Number of subjects with, n (%)			
One major protocol deviation	6 (7.3)	0	6 (6.8)

Baseline data

Table 17. Demographic and Baseline Characteristics - PAS, Liso-cel-treated Analysis Set and the Leukapheresed Set (ITT) MCL

	PAS DL2S N = 75	Liso-cel-treated Analysis Set (DL2S+DL1S) N = 88	Leukapheresed Set (ITT) (DL2S+DL1S) N = 104
Age (years)[a]			
N	75	88	104
Median	69.0	68.5	68.0
Min, Max	36, 86	36, 86	36, 86
Age Group, n (%)			
< 65 years	20 (26.7)	24 (27.3)	33 (31.7)
≥ 65 years	55 (73.3)	64 (72.7)	71 (68.3)
< 75 years	60 (80.0)	70 (79.5)	82 (78.8)

Table 17. Demographic and Baseline Characteristics - PAS, Liso-cel-treated Analysis Set and the Leukapheresed Set (ITT) MCL

	PAS DL2S N = 75	Liso-cel-treated Analysis Set (DL2S+DL1S) N = 88	Leukapheresed Set (ITT) (DL2S+DL1S) N = 104
≥ 75 years	15 (20.0)	18 (20.5)	22 (21.2)
Sex, n (%)			
Male	56 (74.7)	67 (76.1)	81 (77.9)
Female	19 (25.3)	21 (23.9)	23 (22.1)
Race Group, n (%)			
White	65 (86.7)	77 (87.5)	90 (86.5)
Others: Include Other Races	7 (9.3)	8 (9.1)	11 (10.6)
Unknown or Missing	3 (4.0)	3 (3.4)	3 (2.9)
Race, n (%)			
American Indian or Alaska Native	0	0	1 (1.0)
Asian	4 (5.3)	5 (5.7)	6 (5.8)
Black or African American	2 (2.7)	2 (2.3)	3 (2.9)
Native Hawaiian or Other Pacific Islander	1 (1.3)	1 (1.1)	1 (1.0)
White	65 (86.7)	77 (87.5)	90 (86.5)
Not Reported	3 (4.0)	3 (3.4)	3 (2.9)
Ethnicity, n (%)			
Hispanic or Latino	4 (5.3)	4 (4.5)	5 (4.8)
Not Hispanic or Latino	68 (90.7)	81 (92.0)	96 (92.3)
Unknown	3 (4.0)	3 (3.4)	3 (2.9)
Screening ECOG, n (%)			
0	41 (54.7)	48 (54.5)	56 (53.8)
1	34 (45.3)	40 (45.5)	47 (45.2)
2	0	0	1 (1.0)
Pre-LDC ECOG score, n (%)[b]			

Table 17. Demographic and Baseline Characteristics - PAS, Liso-cel-treated Analysis Set and the Leukapheresed Set (ITT) MCL

	PAS DL2S N = 75	**Liso-cel-treated Analysis Set (DL2S+DL1S) N = 88**	**Leukapheresed Set (ITT) (DL2S+DL1S) N = 104**
0	37 (49.3)	41 (46.6)	42 (40.4)
1	37 (49.3)	45 (51.1)	49 (47.1)
2	0	1 (1.1)	1 (1.0)
3[c]	1 (1.3)	1 (1.1)	1 (1.0)
LDH prior to LDC, U/L			
N	75	88	93
Median	235.0	233.5	236.0
Min, Max	78, 4651	78, 4651	78, 4651
≥ 500 U/L, n (%)[d]	7 (9.3)	10 (11.4)	11 (11.8)
< 500 U/L, n (%)[d]	68 (90.7)	78 (88.6)	82 (88.2)
SPD per IRC prior to LDC, cm^2			
N	71	80	84
Median	11.760	13.855	14.590
Min, Max	0.66, 77.20	0.66, 99.51	0.66, 99.51
≥ 50 cm^2, n (%)[d]	4 (5.6)	7 (8.8)	8 (9.5)
< 50 cm^2, n (%)[d]	67 (94.4)	73 (91.3)	76 (90.5)
Baseline CRP, mg/L			
N	75	87	91
Median	14.300	15.000	15.500
Min, Max	0.25, 1444.00	0.25, 1444.00	0.25, 1444.00
< 20 mg/L, n (%)[d]	50 (66.7)	53 (60.9)	54 (59.3)
≥ 20 mg/L, n (%)[d]	25 (33.3)	34 (39.1)	37 (40.7)
Screening LVEF, n (%)			
N	75	88	104
Median	60.0	60.0	60.0
Min, Max	45, 88	45, 88	45, 88

Table 17. Demographic and Baseline Characteristics - PAS, Liso-cel-treated Analysis Set and the Leukapheresed Set (ITT) MCL

	PAS DL2S N = 75	Liso-cel-treated Analysis Set (DL2S+DL1S) N = 88	Leukapheresed Set (ITT) (DL2S+DL1S) N = 104
≥ 40 to < 50%, n (%)[d]	4 (5.3)	5 (5.7)	5 (4.8)
≥ 50%, n (%)[d]	71 (94.7)	83 (94.3)	99 (95.2)
Pre-LDC CrCl, n (%)			
N	74	87	92
Median	80.679	79.688	80.679
Min, Max	39.93, 195.66	39.93, 195.66	39.93, 195.66
< 60 mL/min, n (%)[d]	17 (23.0)	19 (21.8)	19 (20.7)
≥ 60 mL/min, n (%)[d]	57 (77.0)	68 (78.2)	73 (79.3)

Baseline is the last observation collected on or prior to the date of the first product infusion

[a] Age (years)=(date of first liso-cel infusion – date of birth + 1) / 365.25 (rounded down to an integer).

[b] Pre-LDC ECOG score is the most recent ECOG score prior to the start of lymphodepleting chemotherapy.

[c] Note: this subject [redacted]

[d] Percentages are based on number of subjects with non-missing results.

Table 18. Baseline Disease Characteristics - PAS, Liso-cel-treated Analysis Set and the Leukapheresed Set (ITT) MCL

	PAS DL2S N = 75	Liso-cel-treated Analysis Set (DL2S+DL1S) N = 88	Leukapheresed Set (ITT) (DL2S+DL1S) N = 104
Ki67 proliferation fraction (%)			
N	68	81	97
Median	60.00	60.00	65.00
Min, Max	5.0, 95.0	5.0, 95.0	5.0, 100.0
≥ 30%	56 (74.7)	66 (75.0)	82 (78.8)
< 30%	12 (16.0)	15 (17.0)	15 (14.4)
TP53 mutation			
Yes	18 (24.0)	20 (22.7)	25 (24.0)
No	30 (40.0)	34 (38.6)	37 (35.6)

Table 18. Baseline Disease Characteristics - PAS, Liso-cel-treated Analysis Set and the Leukapheresed Set (ITT) MCL

	PAS DL2S N = 75	Liso-cel-treated Analysis Set (DL2S+DL1S) N = 88	Leukapheresed Set (ITT) (DL2S+DL1S) N = 104
Indeterminate	2 (2.7)	4 (4.5)	6 (5.8)
Not Done	25 (33.3)	30 (34.1)	36 (34.6)
Blastoid morphology			
Yes	21 (28.0)	27 (30.7)	30 (28.8)
No	43 (57.3)	48 (54.5)	55 (52.9)
Not Done	11 (14.7)	13 (14.8)	19 (18.3)
Complex karyotype			
Yes	23 (30.7)	26 (29.5)	30 (28.8)
No	29 (38.7)	35 (39.8)	40 (38.5)
Indeterminate	4 (5.3)	4 (4.5)	4 (3.8)
Not Done	19 (25.3)	23 (26.1)	30 (28.8)
Refractory or Relapsed[a], n (%)			
Refractory	49 (65.3)	58 (65.9)	70 (67.3)
Relapsed	26 (34.7)	30 (34.1)	34 (32.7)
Prior BTKi	75 (100)	84 (95.5)	98 (94.2)
Refractory to BTKi[a]	41 (54.7)	47 (53.4)	55 (52.9)
Prior ibrutinib	58 (77.3)	66 (75.0)	74 (71.2)
Refractory to ibrutinib[a]	30 (40.0)	35 (39.8)	41 (39.4)
Prior venetoclax	24 (32.0)	24 (27.3)	31 (29.8)
Refractory to venetoclax[a]	17 (22.7)	17 (19.3)	22 (21.2)
Prior alkylator	75 (100)	88 (100)	104 (100)
Prior bendamustine	49 (65.3)	55 (62.5)	65 (62.5)
Prior anthracycline	54 (72.0)	65 (73.9)	75 (72.1)
Chemorefractory or chemosensitive[b], n (%)			
Chemorefractory	22 (29.3)	28 (31.8)	34 (32.7)

Table 18. Baseline Disease Characteristics - PAS, Liso-cel-treated Analysis Set and the Leukapheresed Set (ITT) MCL

	PAS DL2S N = 75	Liso-cel-treated Analysis Set (DL2S+DL1S) N = 88	Leukapheresed Set (ITT) (DL2S+DL1S) N = 104
Relapse <12 m after ASCT	3 (4.0)	3 (3.4)	5 (4.8)
Last Chemo	19 (25.3)	25 (28.4)	29 (27.9)
Chemosensitive	53 (70.7)	60 (68.2)	70 (67.3)
Active CNS disease at first liso-cel infusion			
Yes	7 (9.3)	7 (8.0)	7 (6.7)
No	68 (90.7)	81 (92.0)	87 (83.7)
Not available	0	0	10 (9.6)
Best prior response[c]			
Complete response	63 (84.0)	71 (80.7)	83 (79.8)
Partial response	9 (12.0)	12 (13.6)	13 (12.5)
Stable disease	1 (1.3)	2 (2.3)	3 (2.9)
Progressive disease	2 (2.7)	3 (3.4)	5 (4.8)
Months from eligible diagnosis to first liso-cel infusion[d]			
N	75	88	92
Median	67.90	63.75	67.35
Min, Max	3.9, 299.5	3.9, 299.5	3.9, 299.5

[a] Relapsed vs Refractory is defined as best response of CR vs best response of PR, SD, or PD to last systemic or transplant treatment with curative intent. Determined by the response to the CRF question "Was disease relapsed or refractory to last therapy?". Refractory to prior BTKi, ibrutinib, or venetoclax is defined as any response to prior BTKi, ibrutinib, or venetoclax is less than PR.

[b] Chemorefractory is defined as experiencing SD or PD to last chemo-containing regimen or relapsed <12 months after ASCT; otherwise, it is chemosensitve.

[c] Best prior response is the best response to any prior therapy.

[d] Eligible diagnosis is defined as a subject's mantle cell lymphoma diagnosis which met eligibility for the clinical trial. The date of this diagnosis captured in the database is used for calculating the time from diagnosis. When diagnosis dates are partial, imputed diagnosis dates have been used to calculate duration to liso-cel infusion.

Table 19. Prior Treatments - PAS, Liso-cel-treated Analysis Set and the Leukapheresed Set (ITT) MCL

	PAS (DL2S) N=75	Liso-cel-treated Analysis Set (DL2S+DL1S) N=88	Leukapheresed Set (ITT) (DL2S+DL1S) N=104
Prior treatment[a], n (%)			
Hematopoietic stem cell transplant	24 (32.0)	29 (33.0)	36 (34.6)
Allogeneic	4 (5.3)	6 (6.8)	8 (7.7)
Autologous	22 (29.3)	26 (29.5)	33 (31.7)
Radiotherapy	22 (29.3)	24 (27.3)	28 (26.9)
Systemic Treatment	75 (100)	88 (100)	104 (100)
Number of prior systemic treatments[b]			
N	75	88	104
Mean (StD)	3.8 (1.99)	3.7 (1.94)	3.7 (1.91)
Median	3.0	3.0	3.0
Min, Max	2, 11	1, 11	1, 11
Number of prior systemic treatments[b], n (%)			
1 prior regimen	0	2 (2.3)	2 (1.9)
2 prior regimens	25 (33.3)	29 (33.0)	32 (30.8)
3 prior regimens	17 (22.7)	19 (21.6)	27 (26.0)
4 prior regimens	9 (12.0)	12 (13.6)	13 (12.5)
≥ 5 prior regimens	24 (32.0)	26 (29.5)	30 (28.8)

Intrathecal (IT) chemotherapy is not calculated in the systemic lines of prior treatment, if given [a] Only regimens post diagnosis of MCL are included. Bridging anticancer therapy for disease control was not counted as a prior systemic regimen unless the outcome was complete response.

HSCT was not included as systemic therapy

Table 20. Summary of Anticancer Treatment for Disease Control (Bridging Therapy) - PAS, Liso-cel-treated Analysis Set and the Leukapheresed Set (ITT) MCL

	PAS (DL2S) N=75	Liso-cel-treated Analysis Set (DL2S+DL1S) N=88	Leukapheresed Set (ITT) (DL2S+DL1S) N=104
Anticancer Treatment[a], n (%)			
Yes	49 (65.3)	58 (65.9)	69 (66.3)
No	26 (34.7)	30 (34.1)	35 (33.7)
Type of Treatment[b], n (%)			
Systemic Treatment only	35 (71.4)	42 (72.4)	51 (73.9)
Radiotherapy only	3 (6.1)	3 (5.2)	3 (4.3)
Both	11 (22.4)	13 (22.4)	15 (21.7)

Bridging therapies are included in this table unless the outcome is complete response

[a] CRF captured new anticancer treatment for disease control that was started after consent and prior to lymphodepleting chemotherapy. The percentage is calculated based on the number of subjects in each treatment arm.

[b] The denominator is the number of subjects who received anticancer treatment.

Among the 88 subjects in the Liso cel-treated Analysis Set, 86 subjects were retrospectively confirmed by the central pathology laboratory as MCL diagnosis. Only 1/86 subject had received prior CD19-targeted therapy.

Numbers analysed

Table 21. Study 017001 MCL Cohort - Protocol-defined Analysis Sets and Populations

Analysis set	Definition	DL2S n (%)	DL1S n (%)	Total N (%)
Leukapheresed Set (ITT) (n)	All subjects who signed informed consent, who met all inclusion/exclusion criteria, and underwent leukapheresis.	94	10	104
Liso-cel-treated Analysis Set (n)	All subjects who received at least one dose of conforming liso-cel cell product.	82 (87.2)	6 (60.0)	88 (84.6)

Table 21. Study 017001 MCL Cohort - Protocol-defined Analysis Sets and Populations

Analysis set	Definition	DL2S n (%)	DL1S n (%)	Total N (%)
Liso-cel-treated Efficacy Analysis Set (EAS) (n)	All subjects in the MCL Cohort and Liso-cel-treated Analysis Set who had PET-positive disease present per IRC before liso-cel administration. Those subjects without baseline PET/CT disease assessment repeated after anticancer therapy for disease control and before liso-cel administration were excluded. Included subjects treated with DL1S and DL2S.	77 (81.9)	6 (60.0)	83 (79.8)
Liso-cel-treated Primary Analysis Set (PAS)[a] (n)	**All subjects in the MCL Cohort and Liso-cel-treated Analysis who met all of the following:** **PET-positive disease at baseline per IRC assessment** **Failed at least 2 prior lines of systemic therapy including an alkylating agent, a BTKi, and rituximab (or other CD20-targeted agent)** **Received DL2S (ie, recommended regimen)**		**0**	**75 (72.1)**
Pharmacokinetic Analysis Set (n)	All subjects in Liso-cel-treated Analysis Set who had the necessary baseline and on-study PK measurements to provide interpretable results for the specific parameters of interest.	82 (87.2)	6 (60.0)	88 (84.6)
PRO/QoL QLQ-C30 Evaluable Set	Subjects in the Liso-cel-treated Analysis Set who had a baseline and at least one post baseline assessment that was analyzable.	68 (72.3)	1 (10.0)	69 (66.3)

Extent of exposure

Lymphodepleting Chemotherapy

In all subjects (total, DL1S+DL2S) in the Liso-cel-treated Analysis Set, most subjects (71.6%) received the full specified dose of fludarabine or cyclophosphamide at the planned time. In the Liso-cel-treated Analysis Set, the median time from last LDC to liso-cel treatment was 4.0 days (range: 3 to 13 days), which was consistent with the protocol, with only 1 subject that received liso-cel infusion beyond the protocol specified window of 7 days, following the completion of LDC.

Manufacturing

Table 22. Manufacturing Summary – Leukapheresed set MCL

	DL2S N=94	DL1S N=10	Total N=104
Time from Leukapheresis to liso-cel Product Availability (Day) [a]			
N			88
Mean (StD)			27.8 (12.20)
Median			24.5
Q1, Q3			21.0, 28.5
Min, Max			17, 80
Time from Leukapheresis to liso-cel Infusion (Day) [a]			
N	82	6	88
Mean (StD)	53.5 (65.85)	53.2 (10.50)	53.5 (63.59)
Median	38.0	53.5	39.0
Q1, Q3	32.0, 46.0	43.0, 57.0	33.0, 48.0
Min, Max	28, 489	42, 70	28, 489

a Data from non-conforming product will not be included in the calculation.

Liso-cel Treatment in the PAS

Table 23. Liso-cel exposure – PAS MCL

- **At cut-off date 19 January 2023:**

	DL2S N = 74
CD8 dose (10^6 cells)	
N	2
Mean (StD)	49.8 (0.07)
Median	49.8
Q1, Q3	49.8, 49.9
Min, Max	50, 50
CD4 volume infused (mL)	
N	2
Mean (StD)	2.15 (0.354)
Median	2.15
Q1, Q3	1.90, 2.40
Min, Max	1.9, 2.4
CD4 dose (10^6 cells)	
N	2
Mean (StD)	49.6 (0.62)
Median	49.6
Q1, Q3	49.2, 50.1
Min, Max	49, 50
Total volume infused (mL)	
N	2
Mean (StD)	5.15 (2.333)
Median	5.15
Q1, Q3	3.50, 6.80
Min, Max	3.5, 6.8
Total dose (10^6 cells)	
N	2
Mean (StD)	99.4 (0.69)
Median	99.4
Q1, Q3	98.9, 99.9
Min, Max	99, 100

[a] After the DBL, a data entry error was found for 1 subject for the infused volume of the CD8 component. This subject was administered the assigned DL2S CD8 component dose of 50×10^6 CAR T cells, and actually received a total dose of $\geq 90 \times 10^6$ CAR+ viable T cells.

- **At cut-off date 16 May 2024:**

	DL2S N = 75
Cycle 1, Dose 1	
CD8 volume infused (mL)	
N	75
Mean (StD)	2.98 (1.940)
Median	2.40
Q1, Q3	1.70, 3.60
Min, Max	1.0, 13.5
CD8 dose (10^6 cells)	
N	75
Mean (StD)	48.5 (5.21)
Median	49.8
Q1, Q3	49.4, 50.3
Min, Max	22, 56
CD4 volume infused (mL)	
N	75
Mean (StD)	1.97 (0.644)
Median	1.80
Q1, Q3	1.50, 2.40
Min, Max	0.9, 3.9

	DL2S N = 75
CD4 dose (10^6 cells)	
N	75
Mean (StD)	49.0 (2.75)
Median	49.4
Q1, Q3	49.0, 50.4
Min, Max	35, 52
Total volume infused (mL)	
N	75
Mean (StD)	4.95 (2.191)
Median	4.50
Q1, Q3	3.40, 6.20
Min, Max	2.1, 16.1
Total dose (10^6 cells)	
N	75
Mean (StD)	97.5 (7.62)
Median	99.6
Q1, Q3	98.6, 100.3
Min, Max	62, 103
Ratio of CD4:CD8 Dose Administered	
N	75
Mean (StD)	1.02 (0.123)
Median	1.00
Q1, Q3	0.98, 1.02
Min, Max	0.8, 1.8
Subjects received additional cycles, n (%)	0
Subjects received retreatment, n (%)	2 (2.7)
Retreatment	
CD8 volume infused (mL)	
N	2
Mean (StD)	3.00 (1.980)
Median	3.00
Q1, Q3	1.60, 4.40
Min, Max	1.6, 4.4

	DL2S N = 75
CD8 dose (10^6 cells)	
N	2
Mean (StD)	49.8 (0.07)
Median	49.8
Q1, Q3	49.8, 49.9
Min, Max	50, 50
CD4 volume infused (mL)	
N	2
Mean (StD)	2.15 (0.354)
Median	2.15
Q1, Q3	1.90, 2.40
Min, Max	1.9, 2.4
CD4 dose (10^6 cells)	
N	2
Mean (StD)	49.6 (0.62)
Median	49.6
Q1, Q3	49.2, 50.1
Min, Max	49, 50
Total volume infused (mL)	
N	2
Mean (StD)	5.15 (2.333)
Median	5.15
Q1, Q3	3.50, 6.80
Min, Max	3.5, 6.8
Total dose (10^6 cells)	
N	2
Mean (StD)	99.4 (0.69)
Median	99.4
Q1, Q3	98.9, 99.9
Min, Max	99, 100

Outcomes and estimation

Primary Efficacy Endpoint - Overall Response Rate per IRC Assessment in the PAS

Table 24. Overall Response Rate - IRC Assessment - PAS MCL

	DL2S N=75
BOR[a], n (%)	
CR	56 (74.7)
PR	9 (12.0)
SD	5 (6.7)
Non-PD	0
PD	1 (1.3)
NE	4 (5.3)
ORR, n (%)	
CR+PR	65 (86.7)

Table 24**. Overall Response Rate - IRC Assessment - PAS MCL**

	DL2S N=75
95% CI[b]	76.8, 93.4
CR Rate, n (%)	
CR	56 (74.7)
95% CI[b]	63.3, 84.0
Partial Response Rate, n (%)	
PR	9 (12.0)
95% CI[b]	5.6, 21.6

Data cutoff: of 16-May-2024 (median follow-up 19.53 months)

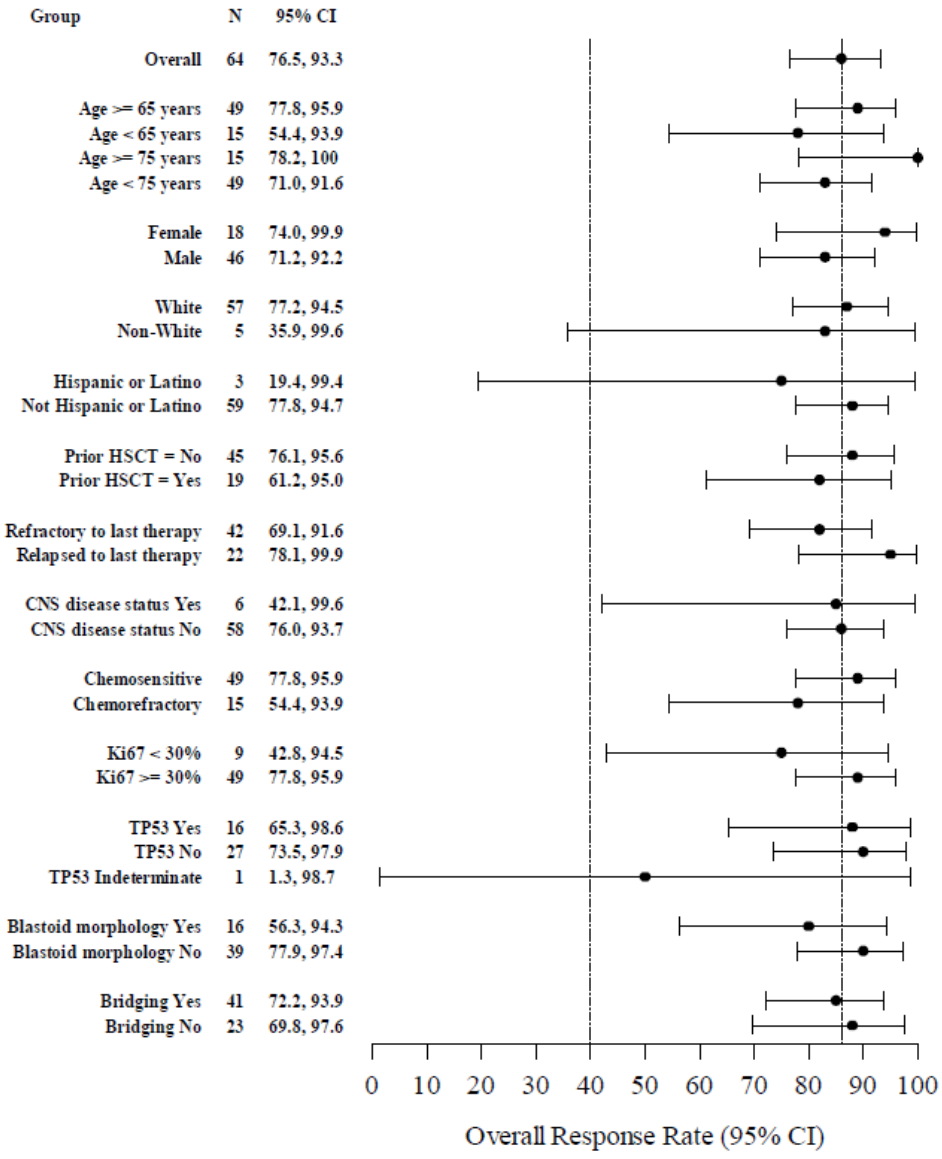
[a] BOR is the best disease response recorded from the time of the final liso-cel infusion of the initial cycle until disease progression, end of study, the start of another anticancer therapy or HSCT.

[b] 2-sided 95% exact Clopper-Pearson CIs.

Subgroup analysis for the primary endpoint of ORR

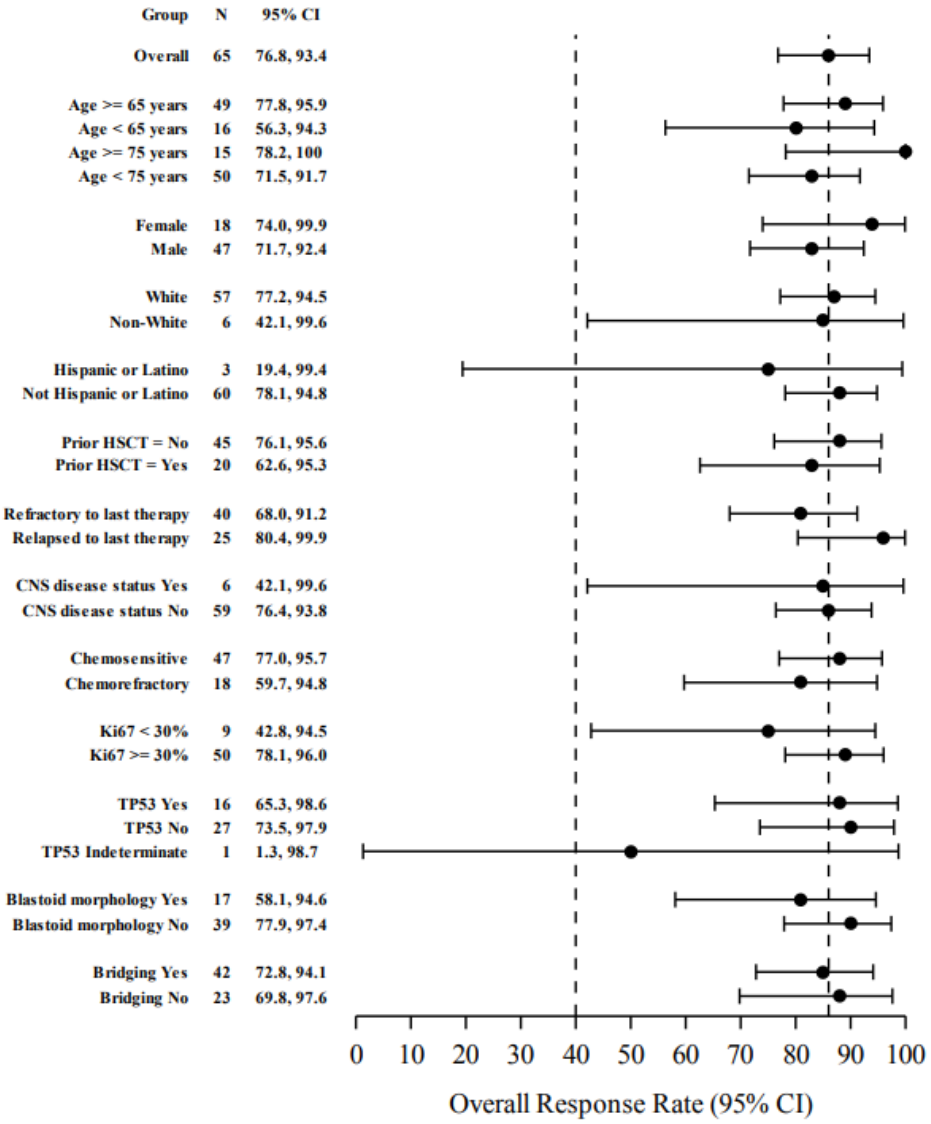
Figure 4. Forest Plot of Overall Response Rate (ORR) - IRC Assessment – PAS MCL

- **At cut-off date 19 January 2023:**



ORR and 2-sided 95% exact Clopper-Pearson confidence intervals are displayed.

- **At cut-off date 16 May 2024:**



ORR and 2-sided 95% exact Clopper-Pearson confidence intervals are displayed.

Sensitivity Analyses of ORR

Table 25. Sensitivity Analyses of ORR - Liso-cel-treated Efficacy Analysis Set and Leukapheresed Set MCL

- **At cut-off date 16 May 2024:**

	DL2S	DL1S	Total
Investigator Assessment - Liso-cel-treated Efficacy Analysis Set MCL			
All Subjects, N	77	6	83
ORR, n (%)	66 (85.7)	3 (50.0)	69 (83.1)
95% CI [a]	75.9, 92.6	11.8, 88.2	73.3, 90.5
IRC Assessment - Leukapheresed Set MCL			
All Subjects, N	94	10	104
ORR, n (%)	70 (74.5)	3 (30.0)	73 (70.2)
95% CI [a]	64.4, 82.9	6.7, 65.2	60.4, 78.8

[a] 2-sided 95% exact Clopper-Pearson confidence intervals.

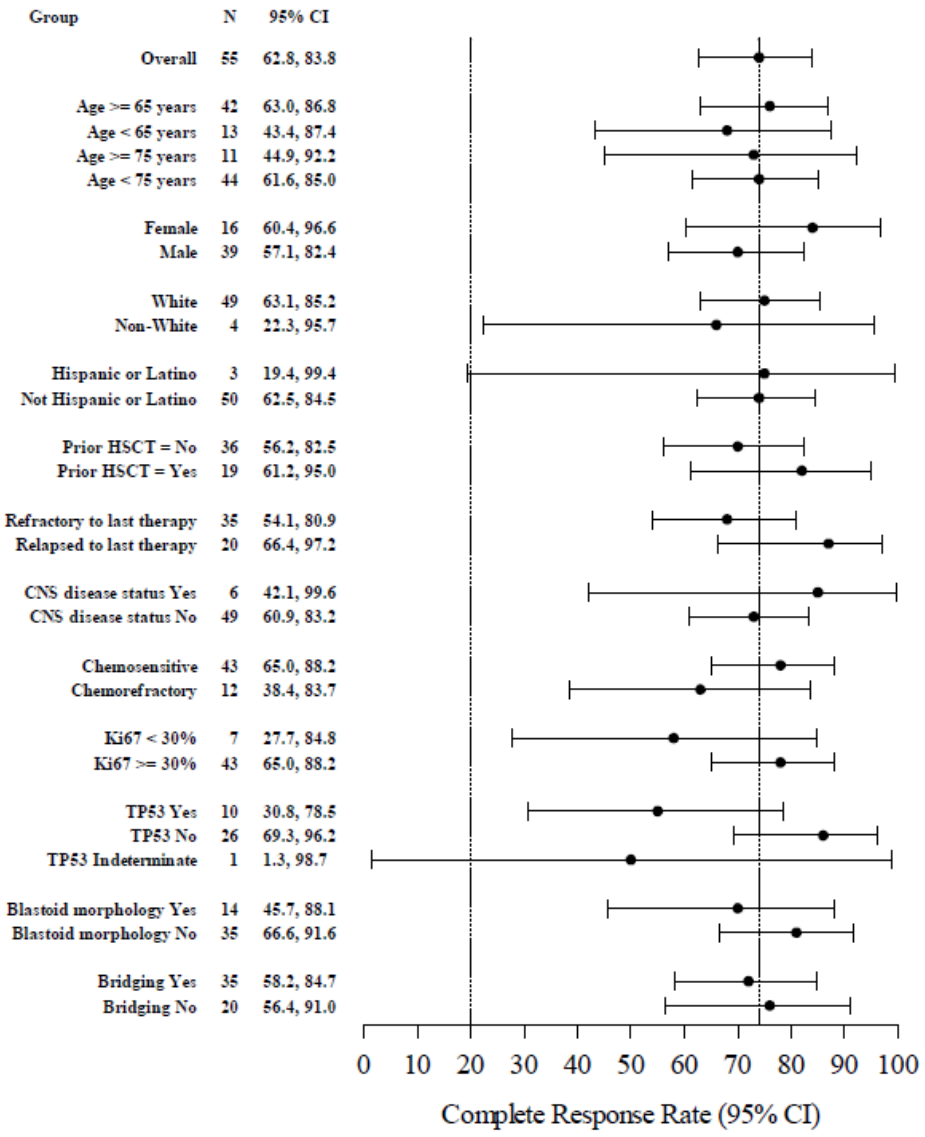
Secondary efficacy endpoint: Complete Response Rate (CRR)

Because the null hypothesis for the first hypothesis test of H0: ORR ≤ 40% versus H1: ORR > 40% was rejected, the second hypothesis H0: CR rate ≤ 18% versus H1: CR rate > 18% was tested. The study met its key secondary efficacy endpoint and rejected the null hypothesis of CR rate ≤ 18% (p <0.0001) in the MCL Cohort PAS. The IRC-assessed CR rate was 74.7% (95% CI: 63.3, 84.0) (see table of ORR above).

Subgroup Analysis of CR rate

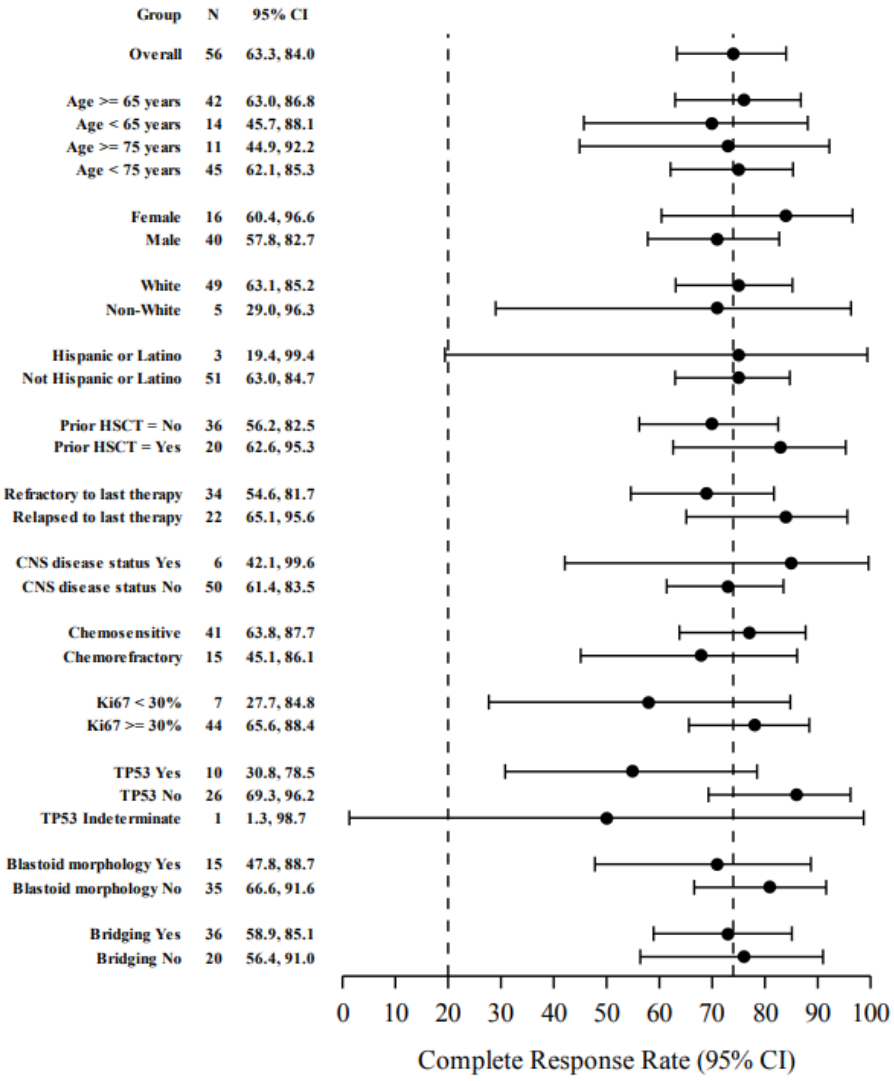
Figure 5. Forest Plot of Complete Response Rate - IRC Assessment - PAS MCL

- **At cut-off date 19 January 2023:**



CRR and 2-sided 95% exact Clopper-Pearson confidence intervals are displayed.

- **At cut-off date 16 May 2024:**



CRR and 2-sided 95% exact Clopper-Pearson confidence intervals are displayed.

Sensitivity analyses of CRR

Table 26. Sensitivity Analyses of CR Rate - Liso-cel-treated Efficacy Analysis Set and Leukapheresed Set MCL

- **At cut-off date 16 May 2024:**

	DL2S	DL1S	Total
Investigator Assessment - Liso-cel-treated Efficacy Analysis Set MCL			
All Subjects, N	77	6	83
CR rate, n (%)	58 (75.3)	2 (33.3)	60 (72.3)
95% CI [a]	64.2, 84.4	4.3, 77.7	61.4, 81.6
IRC Assessment - Leukapheresed Set MCL			
All Subjects, N	94	10	104
CR rate, n (%)	61 (64.9)	3 (30.0)	64 (61.5)
95% CI [a]	54.4, 74.5	6.7, 65.2	51.5, 70.9

[a] 2-sided 95% exact Clopper-Pearson CIs

In the Liso-cel-treated Efficacy Analysis Set, IRC assessed CR rate was 75.3% (95% CI: 64.2, 84.4) for DL2S, 33.3% (95% CI: 4.3, 77.7) for DL1S, and 72.3% (95% CI: 61.4, 81.6) for the total population (DL1S+DL2S).

Secondary Efficacy Endpoint: Duration of Response

Table 27. Duration of Response (DOR) - IRC Assessment - EMA Censoring - PAS MCL

- **At cut-off date 16 May 2024:**

	DL2S N = 75
Subjects Achieved CR or PR, n	65
Progression or Death, n (%) [c]	39 (60.0)
Progression	**28 (43.1)**
Death	11 (16.9)
Censored, n (%) [c]	26 (40.0)
Ongoing	0
Completed the study	24 (36.9)
Discontinued the study	2 (3.1)
Received liso-cel retreatment	0
Duration of Response (Months)	
Median (95% CI) [a]	11.3, 5.7-24.0
Q1, Q3	2.6, 24.0
Min, Max	0.0+, 24.0

Table 27. Duration of Response (DOR) - IRC Assessment - EMA Censoring - PAS MCL

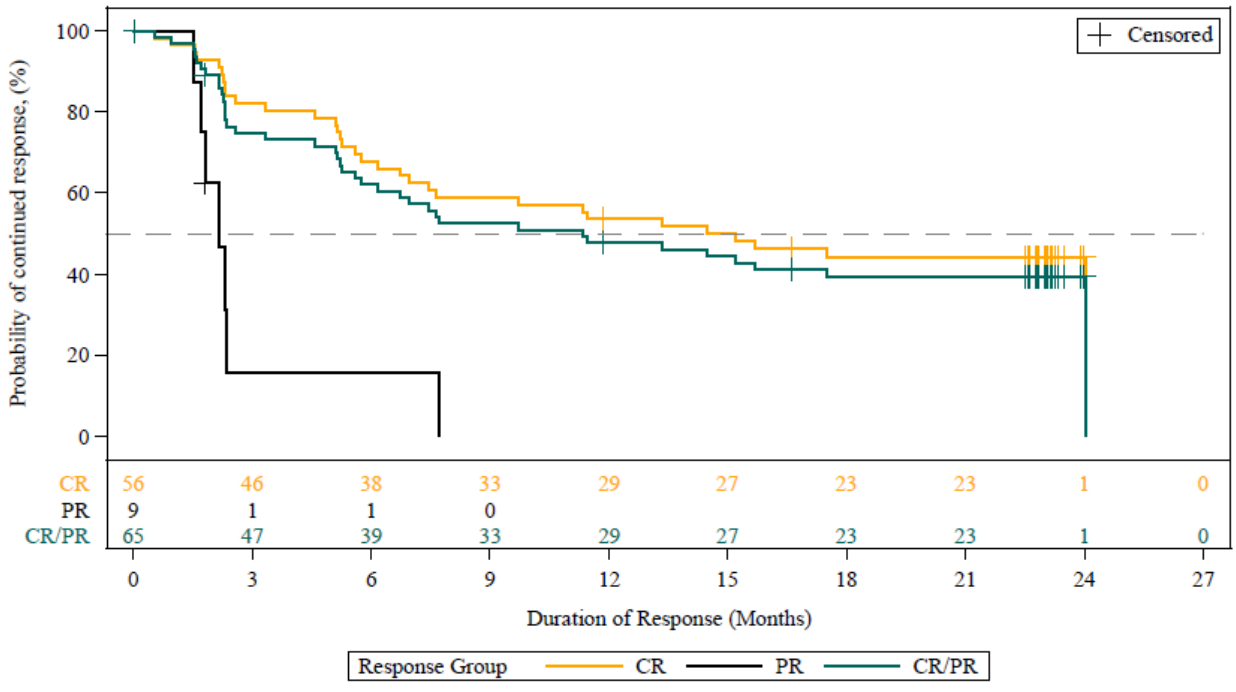
- **At cut-off date 16 May 2024:**

	DL2S **N = 75**
Probability of Continued Response Post-initial Response, %	
≥ 6 months	62.0
95% CI [a]	48.9-72.7
≥ 12 months	47.7
95% CI [a]	35.0-59.3
≥ 18 months	39.4
95% CI [a]	27.4-51.2
≥ 24 months	39.4
95% CI [a]	27.4-51.2
Follow-up (Months)	
Median (95% CI) [b]	23.0, 22.8-23.1
Min, Max	0.0+, 24.0

[a] KM method is used to obtain 2-sided 95% CIs. [b] Reverse KM method is used to obtain the median follow-up and its 95% CIs. [c] Denominator is number of subjects achieved CR or PR. [+] Censored.

Figure 6. Duration of Response - IRC Assessment - EMA Censoring - PAS MCL

- **At cut-off date 16 May 2024:**



DOR in the Liso-cel-treated Efficacy Analysis Set

Table 28. Duration of Response (DOR) - IRC Assessment - EMA Censoring - Liso-cel-treated Efficacy Analysis Set MCL

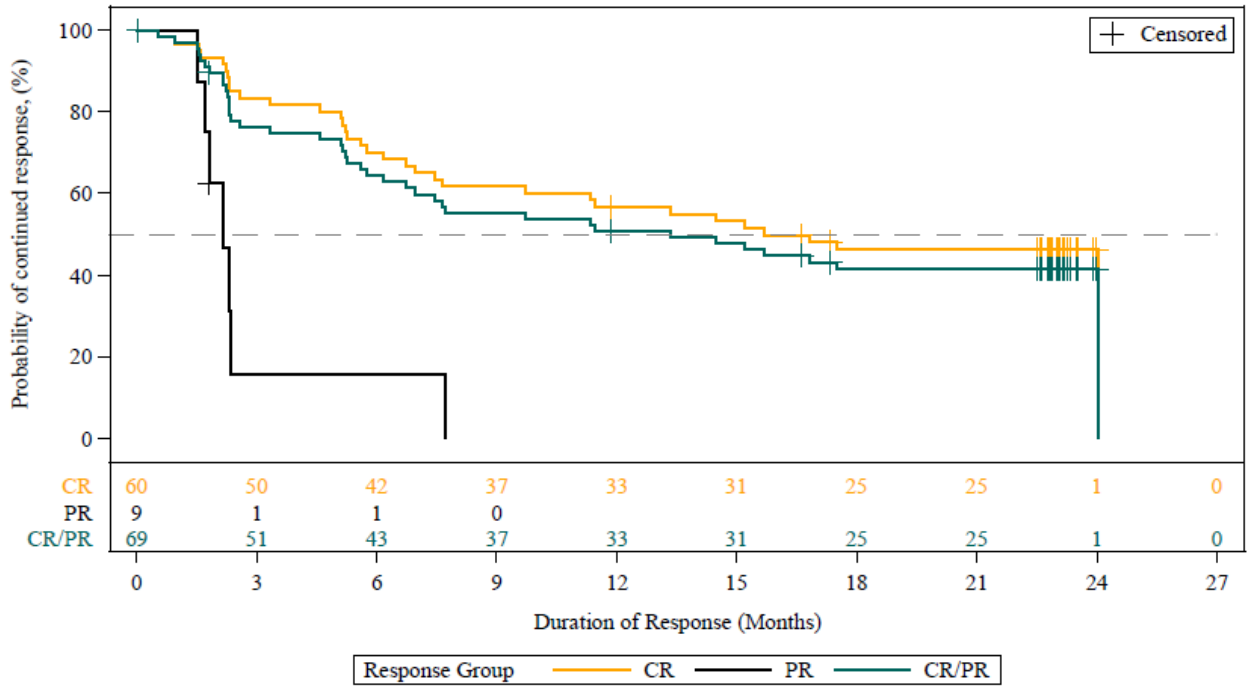
- At cut-off date 16 May 2024:

	DL2S N = 77	**DL1S N = 6**	**Total N = 83**
Subjects Achieved CR or PR, n	67	2	69
Progression or Death, n (%) [c]	40 (59.7)	0	40 (58.0)
Progression	29 (43.3)	0	29 (42.0)
Death	11 (16.4)	0	11 (15.9)
Censored, n (%) [c]	27 (40.3)	2 (100)	29 (42.0)
Ongoing	0	0	0
Completed the study	25 (37.3)	2 (100)	27 (39.1)
Discontinued the study	2 (3.0)	0	2 (2.9)
Received liso-cel retreatment	0	0	0
Duration of Response (Months)			
Median, 95% CI [a]	11.5, 6.2-24.0	NR, NR-NR	13.3, 6.7-24.0
Q1, Q3	3.3, 24.0	NR, NR	3.3, 24.0
Min, Max	0.0+, 24.0	17.3+, 22.9+	0.0+, 24.0
Probability of Continued Response Post-initial Response, %			
≥ 6 months	63.2	100.0	64.3
95% CI [a]	50.3-73.6	NR-NR	51.6-74.4
≥ 12 months	49.3	100.0	50.8
95% CI [a]	36.7-60.7	NR-NR	38.4-62.0
≥ 18 months	39.7	100.0	41.4
95% CI [a]	27.7-51.3	NR-NR	29.5-52.9
≥ 24 months	39.7	NR	41.4
95% CI [a]	27.7-51.3	NR-NR	29.5-52.9
Follow-up (Months)			
Median, 95% CI [b]	23.0, 22.8-23.1	20.1, 17.3-22.9	22.9, 22.8-23.1
Min, Max	0.0+, 24.0	17.3+, 22.9+	0.0+, 24.0

[a] KM method is used to obtain 2-sided 95% CIs. [b] Reverse KM method is used to obtain the median follow-up and its 95% CIs. [c] Denominator is number of subjects achieved CR or PR. [+] Censored.

Figure 7. Duration of Response - IRC Assessment - EMA Censoring - Liso-cel-treated Efficacy Analysis Set MCL

- **At cut-off date 16 May 2024:**



Sensitivity Analysis of DOR

The results for sensitivity analyses of DOR using EMA censoring rules were:

- Investigator-assessed median DOR in the PAS was 11.3 months (95% CI: 5.7, 23.3).
- IRC-assessed median DOR in the Leukapheresed Set was 15.2 months (95% CI: 7.0, 24.0).

Other Secondary Efficacy Endpoint: Progression Free Survival (PFS)

Table 29. Progression-Free Survival (PFS) - IRC Assessment - EMA Censoring - PAS MCL

- **At cut-off date 16 May 2024:**

	DL2S **N = 75**
PFS Events, n (%)	48 (64.0)
Progression	30 (40.0)
Death	18 (24.0)
Censored, n (%)	27 (36.0)
Ongoing	0

Table 29. Progression-Free Survival (PFS) - IRC Assessment - EMA Censoring - PAS MCL

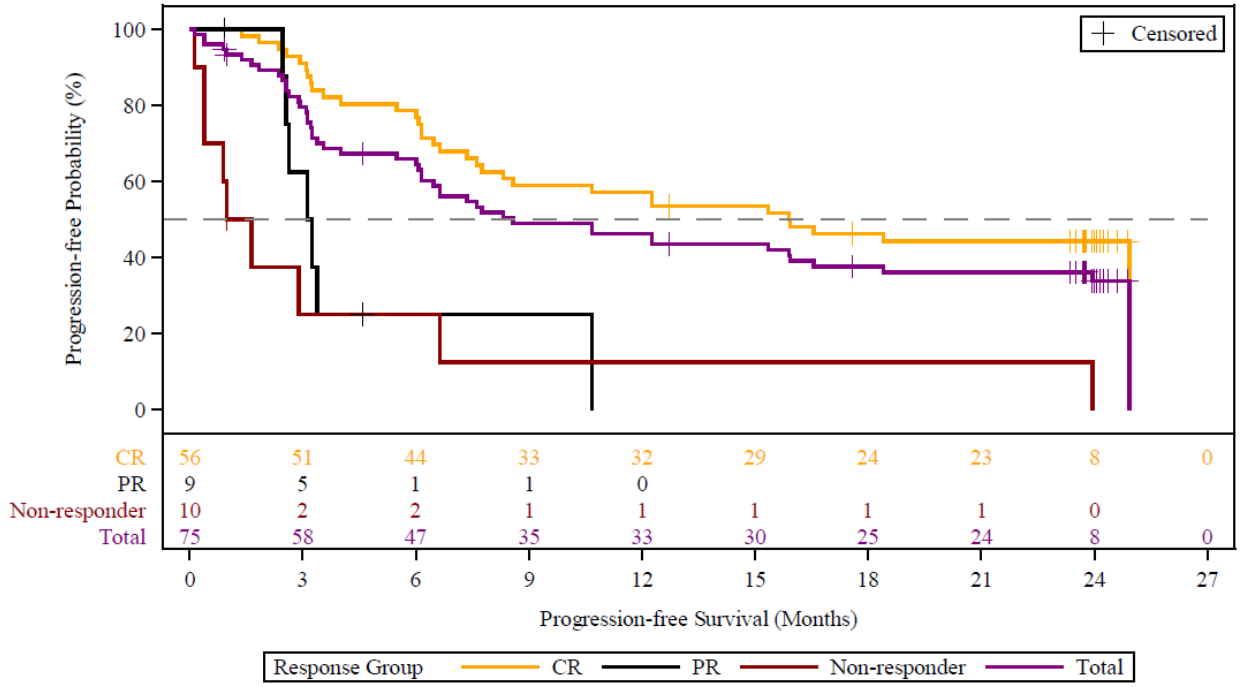
- **At cut-off date 16 May 2024:**

	DL2S **N = 75**
Completed the study	25 (33.3)
Discontinued the study	2 (2.7)
Received liso-cel retreatment	0
PFS (Months)	
Median (95% CI) [a]	8.6, 6.1-16.6
Q1, Q3	3.2, 24.9
Min, Max	0.1, 24.9
Probability of PFS, %	
≥ 6 months	65.8
95% CI [a]	53.8-75.5
≥ 12 months	46.2
95% CI [a]	34.5-57.2
≥ 18 months	37.6
95% CI [a]	26.5-48.7
≥ 24 months	33.9
95% CI [a]	22.9-45.2
Follow-up (Months)	
Median (95% CI) [b]	24.0, 23.7-24.0
Min, Max	0.1, 24.9

[a] KM method is used to obtain 2-sided 95% CIs. [b] Reverse KM method is used to obtain the median follow-up and its 95% CIs. [+] Censored.

Figure 8. Progression-Free Survival - IRC Assessment - EMA Censoring - PAS MCL

- **At cut-off date 16 May 2024:**



In the **Liso-cel-treated Efficacy Analysis Set using EMA censoring rules**, the median IRC-assessed PFS was 10.7 months (95% CI: 6.1, 17.8) for DL2S and 10.7 months (95% CI: 6.1, 16.6) for total.

Sensitivity Analysis of PFS

The results for sensitivity analyses of PFS using EMA censoring rules were:

- Investigator-assessed median PFS in the PAS was 7.8 months (95% CI: 5.3, 15.9)
- IRC-assessed median PFS in the Leukapheresed Set was 9.6 months (95% CI: 7.2, 17.7)

Other secondary endpoints: Overall Survival

Table 30. Overall Survival (OS) - PAS MCL

	DL2S **N = 75**
Death, n (%)	41 (54.7)
Alive, n (%)	34 (45.3)
OS (Months)	
Median, 95% CI [a]	18.4 (13.5, NR)
Q1, Q3	6.7, NR
Min, Max	0.4, 62.1+
Probability of OS, %	

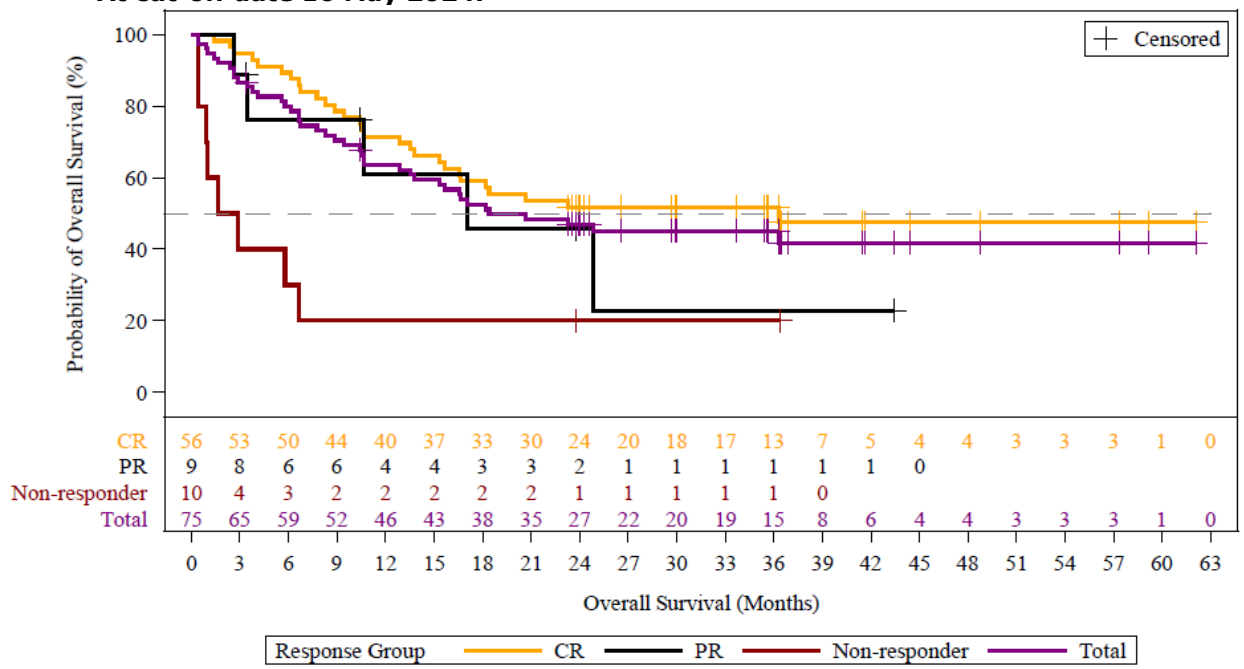
Table 30. Overall Survival (OS) - PAS MCL

	DL2S **N = 75**
≥ 6 months	79.9
95% CI[a]	68.9, 87.4
≥ 12 months	63.6
95% CI[a]	51.5, 73.4
≥ 18 months	52.5
95% CI[a]	40.5, 63.2
≥ 24 months	47.0
95% CI[a]	35.3, 57.9
≥ 30 months	45.0
95% CI[a]	33.2, 56.1
≥ 36 months	45.0
95% CI[a]	33.2, 56.1
≥ 42 months	41.8
95% CI[a]	29.4, 53.7
≥ 48 months	41.8
95% CI[a]	29.4, 53.7
Follow-up (Months)	
Median, 95% CI [b]	35.5 (26.5, 36.4)
Min, Max	0.4, 62.1[+]

The OS analysis includes all available survival information with long-term follow-up data. Data cutoff date: 16-May-2024 for 017001 and 31-Jan-2024 for LTFU. [a] KM method is used to obtain 2-sided 95% CIs. [b] Reverse KM method is used to obtain the median follow-up and its 95% CIs. [+] Alive.

Figure 9. Overall Survival - PAS MCL

- **At cut-off date 16 May 2024:**



In the **Liso-cel-treated Efficacy Analysis Set**, the median OS was 20.7 months (95% CI: 13.5, NR) for DL2S and 18.4 months (95% CI: 12.9, NR) for total.

Sensitivity analysis for OS

Results of a sensitivity analysis of OS in the Leukapheresed Set showed a median OS of 19.6 months (95% CI: 12.5, NR) in the total (DL2S+DL1S) Leukapheresed Set. The median OS follow-up time was 31.5 months (95% CI: 26.7, 37.5) in the total Leukapheresed Set.

Impact of COVID-19 on Efficacy (Sensitivity Analysis)

Among the 7 subjects who died due to COVID 19 in the PAS and the Liso-cel-treated Efficacy Analysis Set, 6 subjects with a CR died in ongoing response within the first year post-liso-cel treatment (Day 72 to 325); these events were censored as discontinued the study and had an impact in the time to event endpoints as follows: for DOR and PFS and alive for OS. The last subject, who died of COVID-19 after experiencing PD, was censored as alive for OS.

DOR, using EMA censoring rules: the median DOR per IRC assessment in the PAS was 15.2 months (95% CI: 6.7, 24.0)

PFS using EMA censoring rules: the median PFS per IRC assessment was 12.3 months (95% CI: 6.1, 24.9)

OS: the median OS was 36.3 months (95% CI: 16.5, NR)

Similar results for the COVID-19 sensitivity analysis were observed in the Liso-cel-treated Efficacy Analysis Set.

Clinical Outcomes Assessments (EORTC QLQ-C30, EQ-5D-5L, EQ-5D-5L VAS)

The PRO/QoL QLQ-C30 and EQ-5D-5L Evaluable Set includes subjects in the MCL Cohort Liso-cel-treated Set who had a baseline and at least one post baseline assessment that was analyzable.

Table 31. Summary of Compliance Rates for HRQoL Questionnaires - PRO/QoL (QLQ-C30) Evaluable Set MCL

- **At cut-off date 19 January 2023:**

Visit	DL2S N = 65 n (%)	DL1S N = 1 n (%)	Total N = 66 n (%)
EORTC QLQ-C30			
Baseline	65/65 (100)	1/1 (100)	66/66 (100)
Post Dose Day 29	49/65 (75.4)	1/1 (100)	50/66 (75.8)
Post Dose Month 2	45/64 (70.3)	1/1 (100)	46/65 (70.8)
Post Dose Month 3	41/62 (66.1)	1/1 (100)	42/63 (66.7)
Post Dose Month 6	36/57 (63.2)	1/1 (100)	37/58 (63.8)
Post Dose Month 9	29/52 (55.8)	1/1 (100)	30/53 (56.6)
Post Dose Month 12	27/45 (60.0)	1/1 (100)	28/46 (60.9)
Post Dose Month 18	16/34 (47.1)	1/1 (100)	17/35 (48.6)
Post Dose Month 24	12/25 (48.0)	1/1 (100)	13/26 (50.0)
EQ-5D Evaluable Set			
Baseline	65/65 (100)	1/1 (100)	66/66 (100)
Post Dose Day 29	48/65 (73.8)	1/1 (100)	49/66 (74.2)
Post Dose Month 2	45/64 (70.3)	1/1 (100)	46/65 (70.8)
Post Dose Month 3	40/62 (64.5)	1/1 (100)	41/63 (65.1)
Post Dose Month 6	36/57 (63.2)	1/1 (100)	37/58 (63.8)
Post Dose Month 9	29/52 (55.8)	1/1 (100)	30/53 (56.6)
Post Dose Month 12	25/45 (55.6)	1/1 (100)	26/46 (56.5)
Post Dose Month 18	16/34 (47.1)	1/1 (100)	17/35 (48.6)
Post Dose Month 24	12/25 (48.0)	1/1 (100)	13/26 (50.0)

A subject is considered as compliant at a visit if at least 15 out of the 30 items in the QLQ-C30 were answered.

A subject is considered as compliant at a visit if at least 1 out of the 5 items in the EQ-5D-5L or VAS were answered.

The denominator for each assessment is the number of subjects in the EQ-5D evaluable population who were still staying in the study at the specified assessment visits.

The denominator for each assessment is the number of subjects in the QLQ-C30 evaluable set who were still staying in the study at the specified assessment visits.

- **At cut-off date 16 May 2024:**

Visit	DL2S N = 68 n (%)	DL1S N = 1 n (%)	Total N = 69 n (%)
EORTC QLQ-C30 Evaluable Set			
Baseline	68/68 (100)	1/1 (100)	69/69 (100)
Post Dose Day 29	51/68 (75.0)	1/1 (100)	52/69 (75.4)
Post Dose Month 2	47/67 (70.1)	1/1 (100)	48/68 (70.6)
Post Dose Month 3	43/65 (66.2)	1/1 (100)	44/66 (66.7)
Post Dose Month 6	39/60 (65.0)	1/1 (100)	40/61 (65.6)
Post Dose Month 9	32/55 (58.2)	1/1 (100)	33/56 (58.9)
Post Dose Month 12	31/47 (66.0)	1/1 (100)	32/48 (66.7)
Post Dose Month 18	21/39 (53.8)	1/1 (100)	22/40 (55.0)
Post Dose Month 24	17/34 (50.0)	1/1 (100)	18/35 (51.4)
EQ-5D Evaluable Set			
Baseline	68/68 (100)	1/1 (100)	69/69 (100)
Post Dose Day 29	50/68 (73.5)	1/1 (100)	51/69 (73.9)
Post Dose Month 2	47/67 (70.1)	1/1 (100)	48/68 (70.6)
Post Dose Month 3	42/65 (64.6)	1/1 (100)	43/66 (65.2)
Post Dose Month 6	39/60 (65.0)	1/1 (100)	40/61 (65.6)
Post Dose Month 9	32/55 (58.2)	1/1 (100)	33/56 (58.9)
Post Dose Month 12	29/47 (61.7)	1/1 (100)	30/48 (62.5)
Post Dose Month 18	21/39 (53.8)	1/1 (100)	22/40 (55.0)
Post Dose Month 24	17/34 (50.0)	1/1 (100)	18/35 (51.4)

A subject is considered as compliant at a visit if at least 15 out of the 30 items in the QLQ-C30 were answered.

A subject is considered as compliant at a visit if at least 1 out of the 5 items in the EQ-5D-5L or VAS were answered.

The denominator for each assessment is the number of subjects in the EQ-5D evaluable population who were still staying in the study at the specified assessment visits.

The denominator for each assessment is the number of subjects in the QLQ-C30 evaluable set who were still staying in the study at the specified assessment visits.

EORTC QLQ-C30

On the **EORTC QLQ-C30**, liso-cel consistently demonstrated improvements over time in evaluations of group-level mean change in the primary domains of **fatigue** (mean change [SD]= -11.9 [27.03] from baseline to Month 6, then stable), **GHS/QoL** (mean change [SD] = 18.1 [22.32] from baseline to Month 6, then stable) and **physical functioning** (mean [SD] change in domain score = 8.0 [23.98] from baseline to month 6). **Pain** was stable until 1 year (mean change [SD] = 1.6 [24.08]) and then showed some worsening at 1.5 and 2 years. The analysis of additional functioning domains showed an improvement also in **emotional functioning** (mean change [SD] = 3.8 [14.49], stable after 6 months), **role functioning** (mean change [SD] in domain score = 20.0 [34.43], stable after 6 months) and **social functioning** (mean change [SD] in domain score = 20.4 [33.01], stable after 6 months). Of the remaining domains, **cognitive functioning, insomnia, financial difficulties, diarrhoea,** and **constipation** did not reach a clinically meaningful change over time.

EQ-5D-5L

Table 32. Summary of Baseline and Change from Baseline for US based EQ-5D-5L Index Score PRO/QoL (EQ-5D) Evaluable Set in MCL Cohort JCAR017-Treated Set

- **At cut-off date 19 January 2023:**

EQ-5D-5L U.S. Based Index Value	DL2S N=65	DL1S N=1	Total N=66
Baseline			
n	65	1	66
Mean (StD)	0.8443 (0.12784)	0.7560 (-)	0.8430 (0.12732)
Median	0.8530	0.7560	0.8530
Q1, Q3	0.7910, 1.0000	0.7560, 0.7560	0.7900, 1.0000
Min, Max	0.540, 1.000	0.756, 0.756	0.540, 1.000

- **At cut-off date 16 May 2024:**

EQ-5D-5L U.S. Based Index Value	DL2S N=68	DL1S N=1	Total N=69
Baseline			
n	68	1	69
Mean (StD)	0.8468 (0.12647)	0.7560 (-)	0.8454 (0.12601)
Median	0.8530	0.7560	0.8530
Q1, Q3	0.7935, 1.0000	0.7560, 0.7560	0.7910, 1.0000
Min, Max	0.540, 1.000	0.756, 0.756	0.540, 1.000

Table 33. Clinically Meaningful Change from Baseline for US based EQ-5D-5L Index Score PRO/QoL (EQ-5D) Evaluable Set in MCL Cohort JCAR017-Treated Set

- **At cut-off date 19 January 2023:**

	DL2S N=65 n (%)	DL1S N=1 n (%)	Total N=66 n (%)
Post Dose Day 29			
n	48	1	49
Improvement[a]	12 (25.0)	1 (100)	13 (26.5)
No Change[a]	24 (50.0)	0	24 (49.0)
Deterioration [a]	12 (25.0)	0	12 (24.5)
Post Dose Month 2			
n	45	1	46
Improvement[a]	16 (35.6)	1 (100)	17 (37.0)
No Change[a]	24 (53.3)	0	24 (52.2)
Deterioration [a]	5 (11.1)	0	5 (10.9)

- **At cut-off date 16 May 2024:**

	DL2S N=68 n (%)	DL1S N=1 n (%)	Total N=69 n (%)
Post Dose Day 29			
n	50	1	51
Improvement[a]	12 (24.0)	1 (100)	13 (25.5)
No Change[a]	26 (52.0)	0	26 (51.0)
Deterioration [a]	12 (24.0)	0	12 (23.5)
Post Dose Month 2			
n	47	1	48
Improvement[a]	16 (34.0)	1 (100)	17 (35.4)
No Change[a]	25 (53.2)	0	25 (52.1)
Deterioration [a]	6 (12.8)	0	6 (12.5)

EQ-5D-5L VAS

Table 34. Summary of Baseline and Change from Baseline for EQ-5D-VAS PRO/QoL (EQ-5D) Evaluable Set in MCL Cohort JCAR017-Treated Set

- **At cut-off date 19 January 2023:**

EQ-5D-5L 5 items & EQ-VAS	DL2S N=65	DL1S N=1	Total N=66
Baseline			
n	65	1	66
Mean (StD)	66.7 (22.26)	75.0 (-)	66.8 (22.11)
Median	65.0	75.0	67.0
Q1, Q3	52.0, 85.0	75.0, 75.0	52.0, 85.0
Min, Max	16, 100	75, 75	16, 100

- **At cut-off date 16 May 2024:**

EQ-5D-5L 5 items & EQ-VAS	DL2S N=68	DL1S N=1	Total N=69
Baseline			
n	68	1	69
Mean (StD)	67.4 (22.22)	75.0 (-)	67.5 (22.07)
Median	67.0	75.0	69.0
Q1, Q3	52.0, 88.5	75.0, 75.0	52.0, 88.0
Min, Max	16, 100	75, 75	16, 100

Table 35. Clinically Meaningful Change from Baseline for EQ-5D VAS PRO/QoL (EQ-5D) Evaluable Set in MCL Cohort JCAR017-Treated Set

- **At cut-off date 19 January 2023:**

	DL2S N=65 n (%)	DL1S N=1 n (%)	Total N=66 n (%)
Post Dose Day 29			
n	48	1	49
Improvement[a]	20 (41.7)	1 (100)	21 (42.9)
No Change[a]	15 (31.3)	0	15 (30.6)
Deterioration [a]	13 (27.1)	0	13 (26.5)
Post Dose Month 2			
n	45	1	46
Improvement[a]	24 (53.3)	1 (100)	25 (54.3)
No Change[a]	13 (28.9)	0	13 (28.3)
Deterioration [a]	8 (17.8)	0	8 (17.4)

- **At cut-off date 16 May 2024:**

	DL2S N=68 n (%)	DL1S N=1 n (%)	Total N=69 n (%)
Post Dose Day 29			
n	50	1	51
Improvement[a]	21 (42.0)	1 (100)	22 (43.1)
No Change[a]	16 (32.0)	0	16 (31.4)
Deterioration [a]	13 (26.0)	0	13 (25.5)
Post Dose Month 2			
n	47	1	48
Improvement[a]	24 (51.1)	1 (100)	25 (52.1)
No Change[a]	15 (31.9)	0	15 (31.3)
Deterioration [a]	8 (17.0)	0	8 (16.7)

- **Efficacy data in section 5.1:**

Efficacy Set for the Proposed Indication (Modified Efficacy Analysis Set or "Efficacy Set")

The efficacy set was defined as all patients treated within the approved dose of Liso-cel (DL1S and DL2S), treated at least 2 prior lines of systemic therapy including a BTKi and analyzed according to EMA censoring rules.

Table 36. Overall Efficacy Summary per IRC Assessment in the Efficacy Set to Support Section 5 of the SmPC

- **At cut-off date 16 May 2024:**

	DL2S+DL1S (N = 81)
ORR, n (%)	
CR+PR	67 (82.7)
95% CI[a]	72.7, 90.2
CR Rate, n (%)	

Table 36. Overall Efficacy Summary per IRC Assessment in the Efficacy Set to Support Section 5 of the SmPC

- **At cut-off date 16 May 2024:**

	DL2S+DL1S (N = 81)
CR	58 (71.6)
95% CI[a]	60.5, 81.1
PR Rate, n (%)	
PR	9 (11.1)
95% CI[a]	5.2, 20.0
DOR, months[b]	
Subjects with CR or PR	
Median (95% CI)[c]	11.5 (6.2, 24.0)
Min, Max	0.0+, 24.0
Median follow-up (95% CI)[d]	22.9 (22.8, 23.0)
Probability of continued response post-initial response, % (95% CI)	
≥ 6 months	63.2 (50.3, 73.6)
≥ 12 months	49.3 (36.7, 60.7)
≥ 18 months	41.2 (29.2, 52.9)
≥ 24 months	41.2 (29.2, 52.9)
Subjects with CR	
Median (95% CI)[c]	15.2 (7.5, 24.0)
Min, Max	0.6, 24.0

Efficacy Set = subjects in the PAS (N=75) and DL1S subjects (N=6) in the EAS.

[a] 2-sided 95% exact Clopper-Pearson CIs.

[b] EMA censoring rules used for DOR. [c] KM method was used to obtain 2-sided 95% CIs. [d] Reverse KM method is used to obtain the median follow-up and its 95% CI. + censored value

All Leukapheresed Set

Table 37. All Leukapheresed: Response rate, duration of response (IRC assessment)

- **At cut-off date 16 May 2024:**

	All Leukapheresed (N=104)
Overall response rate, n (%) [95% CI][a]	73 (70.2) [60.4, 78.8]
Complete response, n (%) [95% CI][a]	64 (61.5) [51.5, 70.9]

	All Leukapheresed (N=104)
Partial response, n (%) [95% CI][a]	9 (8.7) [4.0, 15.8]
Number of responders **Duration of response (DOR) (months)** Median [95% CI][c] Range Rate of continued remission[d], % [95% CI] At 24 months	73 15.2 [7.0, 24.0] 0.0+, 24.0 44.8 (32.9; 55.9)
Median follow-up for DOR (months) Median, [95% CI][d] Range	23.0 [22,8, 23.1] 0.0+, 24.0

[a] 2-sided 95% exact Clopper-Pearson CIs.

[b] EMA censoring rules used for DOR.

[c] KM method was used to obtain 2-sided 95% CIs.

[d] Reverse KM method is used to obtain the median follow-up and its 95% CI. + censored value

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 38. Summary of Efficacy for trial 017001

Title: A Phase 1, Multicenter, Open-Label Study of JCAR017, CD19-targeted Chimeric Antigen Receptor (CAR) T Cells, for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL).		
Study identifier	017001	
Design	This is an open-label, multicenter, multicohort, seamless design, Phase 1 study to determine the safety, antitumor activity, and PK of liso-cel in adult subjects with MCL having received ≥ 2 prior lines of systemic MCL therapy and having been treated with an alkylating agent, a BTKi, and rituximab (or other CD20-targeted agent).	
	Duration of main phase:	- Lymphodepleting chemotherapy (LDC), day 0-day 29 - Single-dose schedule (DL1S or DL2S): liso-cel administration from 2 to 7 day after completion of LDC
	Duration of Run-in phase:	not applicable

	Duration of Extension phase:		- Post-treatment follow-up period: after Day 29, subjects entered the post-treatment follow-up period, and were followed for approximately 2 years - Long-term Follow-up: subjects who received liso-cel were asked to participate in a separate long-term follow-up study (Study GC-LTFU-001) for up to 15 years post-last dose
Hypothesis	Single-arm study		
Treatments groups	Liso-cel, a CD19-directed genetically modified autologous cellular immunotherapy composed of autologous CD4+ and CD8+ T cells that express a CD19-specific CAR, provided as 2 individually formulated CD4+ and CD8+ frozen T-cell suspensions administered in a 1:1 ratio.		Subjects entered the treatment period of the study, which commenced with LDC and ended with the Day 29 evaluation. The treatment cycle included LDC with fludarabine and cyclophosphamide followed by 1 single-dose of liso-cel administered IV.
	Single-dose schedule		Liso-cel administration from 2 to 7 day after completion of LDC.
Endpoints and definitions	Primary endpoint	ORR (CR or PR)	The ORR was defined as the proportion of subjects with a BOR of either CR or PR. The BOR was the best disease response recorded from the time of the liso-cel infusion until disease progression, EOS, the start of another anticancer therapy, or HSCT.

	Secondary endpoints	CR rate DOR PFS PFS ratio OS HRQoL Hospital resource utilization	CR rate was defined as the proportion of subjects with a BOR of CR from the time of the liso-cel infusion until disease progression, end of study, or the start of another anticancer therapy or HSCT. DOR was defined as the interval from the first documentation of CR or PR to the earlier date of disease progression or death due to any cause. PFS was defined as the time from the date of the liso-cel infusion to the earlier date of disease progression or death due to any cause. PFS ratio was defined as the ratio of PFS to the most recent line of therapy (including systemic treatments, radiotherapy, and HSCT prior to liso-cel) to the PFS on liso-cel based on investigator assessment. OS was defined as the interval from the date of the liso-cel infusion to the date of death due to any cause.
	Exploratory endpoints	ATAs to liso-cel B-cell numbers Plasma cytokines and chemokines Liso-cel product characteristics CD19 expression	Immune responses to liso-cel were evaluated with a validated ATA assay to detect the presence of plasma antibodies that bind to the extracellular region of liso-cel. Measurement of B-cell numbers, plasma cytokines and chemokines, changes in tumor and tumor microenvironment factors. Liso-cel product characteristics. Evaluation of tumor biopsies for CD19 expression and attributes of tumor and tumor microenvironment.
Database lock	17-Jul-2024		
Results and Analysis			
Analysis description	**Final Analysis**		

Analysis population and time point description	Leukapheresed Intent to Treat Set: all subjects who signed informed consent, who met all inclusion/exclusion criteria, and underwent leukapheresis. Liso-cel-treated Efficacy Analysis Set: subjects who have PET-positive disease present before liso-cel administration based on IRC assessment. Includes subjects treated with DL1S and DL2S. Primary Analysis Set (PAS): subjects that have PET-positive disease at baseline and have failed at least 2 prior lines of systemic therapy including an alkylating agent, a BTKi, and rituximab (or other CD20-targeted agent), treated at the recommended regimen (DL2S) with conforming product.				
Descriptive statistics and estimate variability	Treatment group	Leukapheresed Set	Efficacy set	Liso-cel-treated Efficacy Analysis Set	Primary Analysis Set (PAS)
	Number of subjects	N=104	N=81	N=83	N=75
	ORR	70.2%	82.7%	83.1%	86.7%
	95% CI	60.4%, 78.8%	72.7%, 90.2%	73.3%, 90.5%	76.8%, 93.4%
	CR rate	61.5%	71.6%	72.3%	74.7%
	95% CI	51.5%, 70.9%	60.5%, 81.1%	61.4%, 81.6%	63.3%, 84.0%
	DOR (Months), Median 95% CI	15.2 7.0, 24.0	11.5 6.2, 24.0	14.5 6.2, 24.0	11.5 5.7, 24.0
	PFS (Months), Median 95% CI	9.6 7.2, 17.7		12.3 6.6, 24.0	12.3 6.5, 24
	OS (Months), Median 95% CI	19.6 12.5, NR		18.4 12.9, NR	18.4 13.5, NR

Analysis performed across trials (pooled analyses and meta-analysis)

Systematic Literature Review of Clinical Efficacy and Safety of Third-Line or Later (3L+) Treatments for Bruton's Tyrosine Kinase Inhibitor (BTKi)-Exposed Adults with Relapsed or Refractory (R/R) Mantle Cell Lymphoma (MCL)

Aim of the study

The aim of this study was to conduct a systematic literature review (SLR) to identify evidence on the clinical efficacy and safety of 3L+ treatment options for adult R/R MCL patients who have been previously exposed to a BTKi. As a secondary objective, the feasibility of conducting meta-analyses (MAs) of reported key efficacy outcomes (ie, overall response rate [ORR], OS, and progression-free survival [PFS]) was considered using the studies identified in the SLR.

Methodology

Searches in databases (Ovid MEDLINE®, Embase, and the Cochrane Central Register of Controlled Trials using the Ovid interface) were restricted to randomized controlled trials (RCTs), single-arm studies, and non-randomized studies (including real-world evidence [RWE], registries, retrospective cohort, cross-sectional, and case-control) published from database inception, with the most recent searches conducted on 7-Aug-2024. Study eligibility criteria were assessed according to pre-specified Population, Intervention, Comparator, Outcome, and Study design (PICOS) criteria, which included BTKi-exposed adult R/R MCL patients in the 3L+ setting who received systemic treatments recommended by NCCN/ESMO guidelines and/or treatments deemed relevant to current clinical practice for MCL. All identified articles were screened by 2 independent reviewers; any discrepancies were resolved through discussion or a third (independent) reviewer. Conference abstracts published from 2020 onwards were included only if considered relevant by two reviewers.

Eligible studies (ie, those with full text publications) underwent quality assessment using checklists recommended by the National Institute for Health and Care Excellence (NICE) to assess the potential risk of bias.

Statistical considerations

Meta-analysis feasibility assessments were conducted for included studies that reported ORR, CR rate, OS, and/or PFS outcomes and was determined based on a qualitative assessment of heterogeneity in study characteristics and clinically significant patient baseline characteristics.

Results

Nineteen studies were included: 5 (26%) interventional studies and 14 (74%) observational studies.

Ten studies (53%) investigated non-CAR T-cell therapies, including pirtobrutinib and 9 (47%) examined CAR T-cell therapies, including brexu-cel and liso-cel.

Table 39. Summary of efficacy outcomes across treatments in 3L+ BTKi-exposed MCL patients

Treatment	Response outcome ranges across studies				Survival outcome ranges across studies	
	ORR	CR	PR	Median DOR (months)	Median OS (months)	Median PFS (months)
Non-CAR T-cell therapies (n = 10 studies)						
Rituximab-bendamustine combination regimens (n = 3 studies)						
BR (n = 1 study[a])	53% (median follow-up: NR)	40% (median follow-up: NR)	13% (median follow-up: NR)	NR	NR	NR
R-BAC (n = 2 studies)	83% (median follow-up: 18 months) (n = 1 study)	60% (median follow-up: 18 months) (n = 1 study)	NR	NR	12.5 (median follow-up: NR) to 14 (median follow-up: 23 months) (n = 2 studies)	10.1 (median follow-up: NR) (n = 1 study)
Lenalidomide-based regimens (n = 1 study)						
Lenalidomide + rituximab (n = 1 study)	27% (median follow-up: NR)	9.1% (median follow-up: NR)	18.2% (median follow-up: NR)	4.6 (median follow-up: NR)	NR	NR
Mixed treatment basket (n = 5 studies)						
Various treatments (n = 5 studies)	NR	NR	NR	NR	3.6 (median follow-up: NR) to 13.2 (median follow-up: NR) (n = 5 studies)	NR
BTKi therapies (n = 2 studies)						
Pirtobrutinib (n = 2 studies)	52%, 49.3%, 62.9% (median follow-up: 6 months, 24.2 months, NR, respectively) (n = 2 studies)	25%, 15.8%, 11.4% (median follow-up: 6 months, 24.2 months, NR, respectively) (n = 2 studies)	27%, 33.6%, 51.4% (median follow-up: 6 months, 24.2 months, NR, respectively) (n = 2 studies)	21.6 (median follow-up: 24.2 months) (n = 1 study)[b]	15.5 (median follow-up: 12.3 months)[c] to 23.5 (median follow-up: 24.2 months) (n = 2 studies)	5.6 (median follow-up: 15.9 months) to 9.4 (median follow-up: 7.4 months)[c] (n = 2 studies)
CAR T-cell therapies (n = 9 studies)						
Brexu-cel (n = 8 studies)	**ZUMA-2:** 93% and 91% (median follow-up: 12.3 and 35.6 months, respectively) (n = 1 study)	**ZUMA-2:** 67%, 68%, 67.6% (median follow-up: 12.3 months, 35.6 months, 47.5 months, respectively) (n = 1 study)	**ZUMA-2:** 27%, 24%, 23.5% (median follow-up: 12.3 months, 35.6 months, 47.5 months, respectively) (n = 1 study)	**ZUMA-2:** 28.2 (median follow-up: 35.6 months) (n = 1 study)[d]	**ZUMA-2:** 46.6 (median follow-up: 35.6 months) (n = 1 study)[e]	**ZUMA-2:** 25.8 (median follow-up: 35.6 months) (n = 1 study)[f]
	Observational: 81% (median follow-up: 14.3 months) to 100% (median follow-up: 11.7 months) (n = 7 studies)	**Observational:** 47% (median follow-up: 14.3 months) to 94% (median follow-up: 11.7 months) (n = 7 studies)	**Observational:** 6% (median follow-up: 11.7 and 13.3 months) to 17.6% (median follow-up: 24.5 months) (n = 3 studies)	**Observational:** 5.3 (median follow-up: 3.3 months) to 19 (median follow-up: 24.5 months) (n = 2 studies)[d]	**Observational:** 14.7 (median follow-up: 14.3 months) to 23.3 (median follow-up: 12.2 months) (n = 3 studies)[e]	**Observational:** 6.3 (median follow-up: NR) to 21 (median follow-up: 13.3 months) (n = 4 studies)[f]
Liso-cel (n = 1 study)	86.5% (median follow-up: 16.1 months)[g]	74.3% (median follow-up: 16.1 months)[g]	10.8% (median follow-up: 16.1 months)[g]	11.3 (median follow-up: 16.1 months)[g]	18.2 (median follow-up: 23.8 months)	12.3 (median follow-up: 23.5 months)

[a] Based on the long-term follow-up of RAY (MCL3001), a subgroup of patients went on to receive subsequent treatment with BR.
[b] Median DOR was reported in 2 pirtobrutinib studies; 1 study reported median DOR as not reached (median follow-up was not reported).
[c] Reported for patients with central histologically confirmed non-blastoid MCL, measurable disease, and prior BTKi exposure in the J2N-MC-JZNJ study (ie, not reported for all patients with MCL and prior BTKi exposure in the study).

Matching-adjusted indirect comparisons (MAICs) for lisocabtagene maraleucel in the treatment of third-line or later (3L+) relapsed/refractory (R/R) mantle cell lymphoma (MCL)

Aim of the study

The primary objective was to estimate the comparative efficacy and safety of lisocabtagene maraleucel (liso-cel) versus brexucabtagene autoleucel (brexu-cel), and pirtobrutinib in patients with third-line or later (3L+) relapsed or refractory (R/R) mantle cell lymphoma (MCL).

Methodology

An unanchored matching-adjusted indirect comparisons (MAICs) were used to estimate population-adjusted relative treatment effects associated with liso-cel in the MCL cohort in TRANSCEND-NHL-001 trial compared to brexu-cel (CD19-directed genetically modified autologous T cell immunotherapy; ZUMA-2 trial) and pirtobrutinib (noncovalent, reversible, Bruton's tyrosine kinase inhibitor [BTKi]; BRUIN trial). For comparison versus brexu-cel, the outcomes included both efficacy and safety outcomes, while with pirtobrutinib comparison was feasible only for efficacy endpoints because of the

presence of substantial differences in the safety profile and differences in the monitoring periods for AESIs.

Diagnosis and main criteria for inclusion in the study

All participants were required to meet the inclusion/exclusion criteria specified in their respective trials (i.e.,TRANSCEND-NHL-001, ZUMA-2, and BRUIN). Furthermore, in conducting the MAICs, patients from the liso-cel trial who did not satisfy the inclusion/exclusion criteria of the comparator trials were excluded (to the best extent possible) prior to commencing the analysis.

Criteria for evaluation and statistical considerations

Primary Endpoint: The outcomes of interest included efficacy outcomes (ORR, CRR, DOR, PFS, and OS) and safety outcomes (CRS, NT, corticosteroid, tocilizumab and/or vasopressor use for the management of CRS and NT, infections, any prolonged cytopenia, any prolonged thrombocytopenia, any prolonged neutropenia).

Secondary Endpoints: Not applicable

Individual patient data (IPD) from the TRANSCEND-NHL-001 trial were adjusted to match the marginal distribution (e.g., proportions) of clinical factors among patients from the ZUMA-2 and BRUIN trials. Patients from TRANSCEND-NHL-001 were excluded from the IPD set if they did not meet the eligibility criteria specified in ZUMA-2 and BRUIN, particularly if they were identified as important effect modifiers or prognostic variables by clinical experts. IPD for patients who remained in the TRANSCEND-NHL-001 data set were weighted using a method-of-moments propensity score model.

Results

Table 40. Primary endpoint results

	Estimate (95% CI)		Estimate (95% CI)	
	Naïve (unadjusted)	Primary MAIC scenario	Naïve (unadjusted)	Primary MAIC scenario
Overall response rate	OR: 0.477 (0.173, 1.317)	OR: 0.791 (0.194, 3.220)	**OR: 2.418 (1.427, 4.095)**	**OR: 2.756 (1.456, 5.218)**
Complete response rate	OR: 1.248 (0.620, 2.511)	OR: 1.389 (0.537, 3.596)	**OR: 8.533 (4.738, 15.368)**	**OR: 8.220 (4.222, 16.004)**
Duration of response	HR: 1.617 (0.974, 2.687)	HR: 1.576 (0.825, 3.009)	HR: 1.157 (0.712, 1.881)	HR: 1.170 (0.687, 2.021)
Progression-free survival	HR: 1.536 (0.963, 2.449)	HR: 1.425 (0.776, 2.620)	**HR: 0.689 (0.489, 0.970)**	**HR: 0.642 (0.426, 0.966)**
Overall Survival	HR: 1.436 (0.920, 2.240)	HR: 0.793 (0.403, 1.562)	HR: 1.180 (0.824, 1.689)	HR: 1.231 (0.814, 1.862)

OR > 1 and HR <1 indicates favorable results for liso-cel vs brexu-cel/pirtobrutinib. Statistically significant results are **bolded**.

CI: confidence interval; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OR: odds ratio

Table 41. Safety results

	Liso-cel vs Brexu-cel OR (95% CI)	
	Naïve (unadjusted)	Primary MAIC scenario
CRS, any grade	**0.154 (0.060, 0.394)**	**0.123 (0.041, 0.367)**
CRS, Grade≥3	**0.067 (0.008, 0.535)**	0.045 (0.001, 2.541)
Corticosteroid use for CRS management	**0.403 (0.164, 0.987)**	**0.161 (0.027, 0.973)**
Tocilizumab use for CRS management	**0.248 (0.126, 0.488)**	**0.122 (0.041, 0.363)**
Vasopressor use for CRS management	**0.121 (0.026, 0.564)**	0.081 (0.005, 1.470)
iiNT, any grade	**0.257 (0.132, 0.503)**	**0.221 (0.088, 0.556)**
iiNT, Grade≥3	**0.224 (0.092, 0.545)**	**0.134 (0.027, 0.659)**
Corticosteroid use for iiNT management	**0.306 (0.144, 0.648)**	**0.167 (0.046, 0.607)**
Tocilizumab use for iiNT management	**0.032 (0.004, 0.246)**	**0.033 (0.001, 0.869)**
Infections, any grade	**0.429 (0.225, 0.821)**	**0.333 (0.135, 0.818)**
Infections, Grade≥3	**0.339 (0.156, 0.735)**	**0.245 (0.073, 0.826)**
Any prolonged cytopenia	**0.517 (0.281, 0.951)**	**0.212 (0.077, 0.582)**
Any prolonged thrombocytopenia	**0.423 (0.227, 0.790)**	**0.160 (0.052, 0.497)**
Any prolonged neutropenia	**0.346 (0.180, 0.665)**	**0.142 (0.041, 0.496)**

OR < 1 indicates favorable results for liso-cel vs brexu-cel. Statistically significant results are **bolded**.

CI: confidence interval; CRS: Cytokine release syndrome; iiNT: investigator-identified neurologic toxicity; MAIC: matching-adjusted indirect comparison; NA: not available; OR: odds ratio

2.5.3. Discussion on clinical efficacy

Rationale for dose selection

The main efficacy analysis came from the MCL cohort of the pivotal study 017001, in which data from patients treated with the dose level 1 (DL1S, 50 × 10^6 CAR+ T cells [25 × 10^6 CD8+ CAR+ T cells and 25 × 10^6 CD4+ CAR+ T cells in a single dose regimen] and the dose level 2 (DL2S, 100 × 10^6 CAR+ T cells [50 × 10^6 CD8+ CAR+ T cells and 50 × 10^6 CD4+ CAR+ T cells] in a single-dose regimen) were considered appropriate for supporting the proposed therapeutic dose of 100 × 10^6 CAR+ viable T cells (consisting of a target 1:1 ratio of CD4+ and CD8+ T cell components)). In fact, consistently with the experience in R/R LBCLs (see procedure EMEA/H/C/004731/0000), the DL2S (i.e. 100 × 10^6) was eventually chosen by the steering committee as the recommended dose also for the MCL Cohort.

The ORR by IRC in the DL1S subgroup (N=6) of the liso-cel treated MCL efficacy analysis set was lower (33.3%) compared to the ORR in the DL2S subgroup (N=77, ORR 87.0%), hence uncertainties remain on the possibility that lower liso-cel doses might result in reduced efficacy. Dose-response data in the MCL cohort of study 017001 were, however, confounded by the fact that subjects in the DL1S group were more likely to present with prognostic factors associated with poor outcome (e.g. higher incidence of blastoid morphology, higher median number of previous lines of therapy and refractoriness status) compared with

subjects in the DL2S cohort. Further, long-lasting remissions and a positive B/R balance could be observed across the whole dose range recommended in Section 4.2 of the SmPC. Finally, as specified by the MAH, post marketing data in the EU showed that Breyanzi has been manufactured so far to a target dose of 100 x 10^6 CAR+ viable T cells in ~99% of patients. The very limited number of patients expected to receive liso-cel at doses lower than the target dose makes further requests to collect additional dose-response data in the post-approval setting unfeasible.

In conclusion, based on cumulative safety and efficacy data, the choice of 100 × 10^6 CAR+ T cells as target dose is considered appropriate. The dose regimen proposed for this extension of indication is in line with the current posology recommendations in section 4.2 of the SmPC for the approved indications of Breyanzi (i.e. target dose 100 x 10^6 CAR-positive viable T cells within an acceptance range of 44 to 120 x 10^6 CAR-positive viable T cells).

Design and conduct of clinical studies

The trial design of Study 017001 is in line with other registrational CAR-T trials (i.e. three distinct phases: pre-treatment, treatment and post-treatment, follow-up and possibility to participate in a LTFU study), with study schedules and duration of follow-up consistent with the purpose of the trial.

The single arm nature of study 017001 presents intrinsic limitations, mostly related to the absence of an active control arm, which brings uncertainties to efficacy assessments and results contextualisation. The absence of a standard of care when the trial was designed is acknowledged and the absence of control acceptable, considering the high unmet medical need in the claimed indication when the trial began.

ORR by IRC according to the 2014 Lugano criteria was the primary endpoint, which is acceptable considering the design features of study 017001. ORR is a direct measure of the anti-tumour activity of liso-cel, yet its clinical relevance is limited, since the value of partial responses in the context of rapidly progressing malignancies is uncertain. Therefore, clinical benefit is better captured by the key secondary endpoint of CRR, since achieving complete remission is a pre-requisite to experience prolonged disease control. Duration of response (DOR), the other key secondary endpoint, is also considered a key measure to inform clinical benefit evaluations since, in the advanced setting targeted by the MAH, achieving long-lasting remission with conventional treatments is unlikely. DOR evaluation needs, however, to be supported by a proper duration of follow-up: in respect to that, the first efficacy analysis (cut-off date 19-Jan-2023) corresponded to at least 6 months of follow-up from first objective response in all subjects, while the final analysis (cut-off date 16-May-2024) provided at least 24 months of follow-up, with all patients who either completed or discontinued the study.

No substantial differences were noted between the results obtained in the first and the final analysis and, although it cannot be considered exhaustive, the provided follow-up time can be considered sufficient to weight the efficacy of liso-cel, especially considering the aggressive behaviour of MCL in the R/R setting. Study 017001 was not originally developed using the estimand framework, as the original protocol was released in May-2015, prior to the publication of the draft version of the ICH E9(R1) addendum in Nov-2019. The estimands for the primary and secondary endpoints were retrospectively described and were in line with EMA guidelines; for DOR, in the primary analysis the estimand framework was reported following the FDA censoring rule, yet a sensitivity analysis performed according to EMA requests was submitted.

PFS and OS data, which are usually considered the most relevant endpoints to inform clinical benefit evaluations in non-Hodgkin lymphomas, are only considered supportive for weighting the clinical benefit of liso-cel in MCL. In the absence of a randomised reference, in fact, disentangling the effect of the intervention from the possible impact of underlying tumour/patient characteristics (e.g. differences in

tumour growth rates) on survival times is not possible, hampering reliable interpretations of the results. Similar considerations can also be applied to the evaluation of HRQoL and Hospital Resource Utilization.

Primary efficacy analysis in study 017001 was performed on subjects from the MCL cohort who had PET-positive disease before liso-cel administration, received liso-cel at the recommended dose regimen and had at least one post-infusion response assessment; this is acceptable to control possible confounding factors unrelated to liso-cel activity. However, results from all leukapheresed subjects, irrespectively on whether they actually received liso-cel, are considered more in line with the ITT principle and with real world clinical practice.

Sample size calculation for the primary analysis was based on the assumed thresholds for efficacy (i.e. ORR 40%, CRR 18%): this approach can be considered acceptable in the context of the exploratory nature of the study and the available treatment options at the time of study was designed, when the alternatives for BTKi exposed patients were limited. Notably, the statistical hypothesis for the definition of the primary endpoint was set on literature data about the efficacy of lenalidomide (alone or combination with rituximab) [Witzig 2017, Andorsky 2016, Wang 2015], bortezomib+ rituximab [Chiappella 2009, 2015], obinutuzumab [Morschhauser 2013], or post-ibrutinib [Martin 2016]. To note, the validity of the assumptions can be maintained even considering that the target population (BTKi and anti-CD20 exposed after at least 2 lines of therapy) was introduced in 2019 (with Amendment 7), although it is not completely adherent to the current therapeutic panorama, especially when the anti-CD19 CART brexucabtagene autoleucel is taken into account. It is highlighted, however, that MCL is a heterogeneous condition with respect to clinical and biological features and, when the limits of a SAT design are taken into consideration (see e.g. the EMA guidance EMA/CHMP/458061/2024), a more conservative approach in the selection of the efficacy thresholds (e.g. considering the upper limit of the 95%CI for the ORR and CRR meta-analysis estimates) would have been preferred. It is acknowledged, however, that the high response rates eventually observed in the MCL cohort of study 017001 left no remaining concerns about clinical relevance. Further, as specified by the MAH, the initial sample size calculations (N=50) were subsequently increased based on feedback from health authorities to a minimum of N=70 evaluable subjects.

Two hypotheses (ORR ≤40% vs. ORR > 40% and CRR ≤18% vs. >18%) were sequentially tested at an overall 1-sided 0.025 level of significance. The overall Type-1 error was controlled using a Hierarchical Testing strategy, and only if the null hypothesis was rejected in the first hypothesis test, the second hypothesis testing could be performed. This is acceptable. Sensitivity analyses were performed to better define the robustness of results obtained with the primary analysis. Four sensitivity analyses were performed: 1. using the Leukapheresed (ITT) set (n = 104), 2. based on responses adjudicated by Investigator, 3. using the Liso-cel- treated Efficacy Analysis Set (defined as all patients having received at least one dose of conforming liso-cel product and have baseline PET-positive disease present before liso-cel administration and have PET/CT assessment repeated after bridging therapy before liso-cel administration; n = 83) and 4. assessing the impact of COVID-19 (as a post hoc analysis to evaluate the impact of COVID-19 pandemic on the study). In addition, a post-hoc modified efficacy analysis set ("efficacy set") was also defined as all patients from the Liso-cel- treated Efficacy Analysis Set who have received prior treatment with at least 2 prior lines of systemic therapy including a BTKi and analyzed according to EMA censoring rules (n = 81), which is the dataset that is used for the presentation of efficacy outcomes in the SmPC. All the sensitivity analyses were deemed supportive for the initial purpose. In respect to the principal analysis, subjects in the Leukapheresed (ITT) Set who did not receive the cell product was considered not evaluable (i.e., non-responder); moreover, for PFS and OS evaluation, the date of the first leukapheresis served as the reference date instead of the date of the first liso-cel infusion. The pre-specified subgroups analyses, based on demographic (e.g. age categories, ethnic groups, gender) and prognostic/biological features (e.g. TP53 and KI67 status, chemo-

responsiveness, prior HSCT, CNS involvement) were deemed informative and in line with the clinical and biological features of R/R MCL.

At the time of the final analysis (data cut-off: 16-May-2024), with a longer on-study follow-up (median of 19.53 months), no formal hypothesis was tested.

Overall, the planned statistical methods used for the analyses of time-to-event and binary endpoints analyses were standard and acceptable and, despite the above mentioned limits, the current base of evidence is still in line with what has been previously considered adequate by the CAT/CHMP to conclude for a positive B/R with other CARTs in the clinical setting defined by the claimed indication.

Extent of exposure and patient flow

All subjects in study 017001 were screened at 14 sites in the US: although the substantial uniformity in terms of guidelines and approved treatments between US and EU at the time study 017001 was conducted is acknowledged, due to possible differences in treatment access or positioning (e.g. with respect to ASCT/alloHSCT) uncertainties on results generalizability to the EU setting cannot be excluded. The MAH agreed on amending the ongoing PASS JCAR017-BCM-005 study to include the collection of data on EU subjects with R/R MCL treated with liso-cel.

In general, the disposition of patients is considered justified by the clinical/management complexity of cellular therapies like CAR-Ts in a rapidly evolving disease setting and disease characterised by poor response with conventional treatments: in particular, the observed high rate of study discontinuation due to death of participants (50%) is expected in an aggressive disease like MCL.

As a general principle, major changes in the study protocol of an ongoing registrational trial are considered of potential regulatory concern: especially when involving the eligibility criteria, the definition of the primary analysis set and the SAP. However, it is also noted that the statistical hypotheses for rejecting the null hypothesis were not affected, as well as the estimated sample size and the total number of subjects enrolled in the Primary Analysis Set (N=75), which already exceeded the number of 50 patients estimated in the SAP. Further, the changes in the study population introduced are believed to not have had a significant impact on the integrity of the trial.

Most of the subjects in the Liso-cel-treated Analysis Set received treatment during the COVID-19 pandemic, with 75% of the subjects treated from Jan-2020 to May-2022. The impact of the pandemic on study conduct was, apparently, negligible, since no major COVID-19-related protocol deviation was reported. The clinical impact of the pandemic was investigated in a dedicated sensitivity analysis.

Major protocol deviations were collected in 6/88 subjects (6.8%), the most frequent being study treatment deviations (4 subjects, 4.5%). In general, the rate of deviations is considered low and without critical impact on the study conduction.

Number analysed and baseline data

The wording of indication proposed by the MAH is considered adherent to the patients included in the Primary Analysis Set (PAS) used for the primary hypothesis testing. Overall, at the time of final analysis (data cut date of 16-MAY-2024), in the PAS a total of 75 patients were included, corresponding to 72% of the Leukapheresed Set (ITT). Compared to the primary analysis (data cut date of 19-JAN-2023), 1 additional subject was identified meeting the PAS criteria.

The demographic and baseline characteristics of all subjects in the PAS as reported in the sections above were representative of an R/R MCL population with moderate comorbidities and in line with the known epidemiology of MCL.

Most subjects had at least one high risk feature and secondary CNS lymphoma involvement was not rare (active CNS disease at liso-cel infusion was present in 9.3% of patients). Overall, 65.3% of subjects were refractory to their most recent prior treatment and all (100%) received prior BTKi, with 54.7% being refractory to BTKi (40% refractory to ibrutinib); 22.7% of subjects were also refractory to venetoclax.

As per the data presented in the sections above, all (100%) subjects received at least one prior alkylating agent and the median number of previous lines of therapy was 3 (2-11). The global number of patients who had received a prior ASCT was 29.3% and it is considered in line with the median age of subjects enrolled in the study; as expected, the global number of patients with a prior allogeneic SCT was low (5.3%). The median time from diagnosis to first liso-cel infusion for all subjects was 63.75 months (range 3.9 to 299.5 months) and it is considered in line with the disease-history of MCL. The high variability observed in terms of number of prior lines of therapy and time from diagnosis to liso-cel administration further highlights the significant clinical heterogeneity of MCL.

In general, demographics and baseline characteristics were similar between the PAS, the Liso-cel-treated Analysis Set, and the Leukapheresed Set.

The administration of a bridging therapy between leukapheresis and LDC administration was required in most subjects (65.3%). In principle, the need for bridging therapy in most patients reflects the aggressive behavior of MCL, given the disease's tendency to present systemic recurrences in the advanced stages.

Overall, the manufacturing of liso-cel did not present critical issues able to affect the protocol's results. It is noted, however, that in some cases remarkable delays were collected (80 days for product availability), whose impact on treatment compliance and effectiveness is not completely characterised. While the occurrence of intercurrent clinical events could explain the longer time intervals between product availability and administration, the reasons behind the delays in product availability are less clear. Nevertheless, considering the low number of patients experiencing such delay this does not represent an issue for the final assessment of the data provided

The exposure to the liso-cel was in line with the intended use in terms of median total dose (99.6×10^6 range: 62 to 103 CAR+ viable T cells), median CD8 and CD4 component doses (49.8×10^6, range: 22 to 56 and 49.4×10^6, range: 35 to 52 CAR+ viable T cells, respectively) and median CD4:CD8 ratio (1.00, range: 0.8 to 1.8).

Efficacy data and additional analyses

Outcomes and estimation

The primary analysis was performed at a median follow up of 16.10 months for the MCL PAS Cohort (data cut date 19 Jan 2023). The primary endpoint of ORR was met in the PAS (ORR: 86.5% [95% CI: 76.5, 93.3] p value < 0.0001), allowing to reject the cohort null hypothesis of ORR ≤ 40%. The final analysis (data cut date 16 May-2024) reported a similar ORR of 86.7% [95% CI: 76.8, 93.4]. Most of the responses were represented by Complete Response (see Key secondary endpoint); Stable Disease (SD) was reported in 5 cases (6.7%) and Progression in 1 (1.3%). Notably, in 4 cases the Response was reported as Not Evaluable (5.3%) as no post liso-cel infusion scans were performed for these patients

Sensitivity analyses were applied to the primary endpoint in order to evaluate the robustness of the primary analysis, and showed consistent results (data cut date 16 May-2024):

- In the **Liso-cel treated Efficacy Analysis Set**, the overall ORR was 83.1% (95% CI 73.3-90.5), with a total CR rate of 72.3% (95% CI 61.4-81.6). To note, in this analysis set were included subjects treated with two different levels of dose (DL1S: 50 x 10^6 CAR-positive viable

T cells and DL2S: 100 x 10^6 CAR-positive viable T cells, i.e. the recommended regimen) and reflects the range of acceptability (44-120 x 10^6 CAR-positive cell) reported in the SmPC of liso-cel. To note, the ORR reported for the DL2S recommended regimen was far higher (ORR: 87.0%, 95% CI: 77.4, 93.6) than that reported for DL1S (ORR: 33.3%, 95% CI 4.4-77.7). This inconsistency could result from the reduced sample size in the DL1S cohort (DL1S: N=6) and the higher frequency of adverse prognostic factors like blastoid morphology, higher median number of previous lines and refractoriness status in comparison with the DL2S cohort, although a dose-response effect on response could not be definitively excluded. Overall, the results for DL1S should be interpreted with caution due to the small sample size of DL1S.

- **Investigator-assessed** ORR in the PAS was 85.3% (95% CI: 75.3, 92.4) and was consistent with the IRC assessment; in general, this analysis is considered reliable, given the high rate of concordance (98.6%) between the IRC and Investigator assessments for BOR.

IRC-assessed ORR in the **Leukapheresed Set** was 70.2% (95% CI: 60.4, 78.8), lower than the IRC-assessed ORR in the PAS. This is an expected finding, since the Leukapheresed Set included all subjects who underwent leukapheresis, including those subjects who did not receive liso-cel (12 subjects) and those who received nonconforming product (4 subjects).

In the **post-hoc defined modified Efficacy Analysis Set ("Efficacy Set")**, which is used to present data in the SmPC, response rates were consistent: ORR of 82.7% (95% CI: 72.7, 90.2) and CRR of 71.6% (95% CI: 60.5, 81.1).

The subgroup analysis for the primary endpoint showed a consistent efficacy of liso-cel; ORR rates slightly below 80% but still clinically relevant were observed in patients with adverse prognostic factors such as prior HSCT, refractoriness to last therapy, mutated TP53 or general chemo-refractoriness and blastoid morphology, in absence of a clear trend of lack of efficacy in any of them. In general, a lower performance is expected in patients with adverse clinical/biological prognostic factors; however, in most of these cases, the small number of enrolled patients impaired the overall evaluation of the reported subgroup analysis. This is particularly evident for some categories of subjects like patients aged < 65 years (N=15), Non-White (N=5), presence of CNS disease (N=6), KI67 <30% (N=9). A trend towards reduced efficacy in subjects with high disease burden have been previously shown with immunotherapy, yet due to limited numbers in the post-hoc "high-disease burden subgroup" (LDH > 500 U/L: N=7; SPD > 50 cm^2: N=4, bulky disease N=2) no definitive conclusion could be drawn for liso-cel in the targeted indication.

The study also met its key secondary efficacy endpoint, rejecting the null hypothesis of CR rate ≤ 18% ($p<0.0001$) in the MCL Cohort PAS; the **IRC-assessed CR rate** at the time of the primary analysis (data cut date 19 Jan 2023) was 74.3% (95% CI: 62.8, 83.8). The final analysis (data cut date 16 May-2024) reported a similar CRR of 74.7% (95% CI: 63.3, 84.0). Similar results were also obtained in the sensitivity analyses applied to the secondary endpoint (Investigator assessment: 72.3%, 95% CI 61.4-81.6; Leukapheresed Set: 61.5%, 95% CI 51.5-70.9).

The subgroup analysis for CRR showed a trend similar to that reported for the ORR and this finding was expected, given that most of the response to Liso-cel were CR. In general, all the considerations made the primary endpoint in terms of sensitivity and subgroup analyses can be extended also to the secondary endpoint of CRR.

Given the single-arm design and the aim of pivotal trial 017001, the **Duration of Response** per IRC assumes a critical value to weight the clinical relevance of the antitumoral effect of liso-cel. In the PAS, the DOR was calculated for the 65 responders; the median IRC-assessed DOR at the time of the final analysis (data cut date 16 May-2024) was 11.3 months (95% CI: 5.7, 24.0). The KM plots for DOR showed how the majority of events occurred within the first 12 months after liso-cel infusion; the event

rate seemed to slow down in the tails of the curves (although no clear plateau phase could be identified), likely reflecting the clinical and prognostic heterogeneity in MCL, yet late events could still be observed and heavy censoring after 21 months hampered the assessment of long-term benefit. Although the probability of continued response decreased from 62% (48.9-72.7) after 6 months to 39.4% (27.4-51.2) at 24 months, a subgroup of patients was still able to achieve durable remission with liso-cel despite the advanced setting of relapse. Most DoR events can be attributed to progression of disease (43.1%) or death (16.9%), with 2 patients censored because of start of a new anticancer therapy. Achieving CR was associated with a longer duration of response, with a median IRC-assessed DOR of 14.5 months (95% CI: 7.0, 24.0) in subjects in CR compared to 2.2 months (95% CI: 1.5, 2.4) in subjects with a BOR of PR. Responses were also rapidly achieved, with a median Time to Response of 0.95 months (range: 0.7 to 3.0). DOR results in the Efficacy Analysis Set were similar to those reported in the PAS, with a median value reached at 13.3 months (95% CI: 6.7-24), which was not unexpected considering that all but 6 subjects in this analysis came from the DL2S cohort. Similar results were also reported in the other sensitivity analyses (investigator-assessed median DOR in the PAS: 11.3 months, 95% CI: 5.7, 23.3; IRC-assessed median DOR in the Leukapheresed Set: 15.2 months (95% CI: 7.0, 24.0). Finally, the median DOR in most subgroups was consistent with that observed in the overall PAS responder population, although these results should be interpreted with caution, given the small sample size in some subgroups. No substantial difference was noted when DoR was calculated according to the FDA or EMA censoring rules.

The results of the other time-to-event endpoints of PFS and OS should be considered as descriptive, since the absence of a control arm reduce their strength in terms of contextualization of the efficacy of the drug. The sensitivity analyses for PFS were consistent with the primary analysis.

Similarly, for what reported for DOR and PFS, the achievement of a BOR of CR correlated with a numerically longer median OS compared to subjects with a BOR of PR. Data reported in the EAS and in the Leukapheresed Set were consistent with the results in the primary analysis.

The majority (75%) of subjects in the MCL cohort of study 017001 received treatment during the COVID-19 pandemic. Seven subjects died due to COVID 19: 6 subjects who achieved CR died in ongoing response within the first year post-liso-cel infusion (Day 72 to 325). Since these events impacted on the analysis of time to event endpoints, a sensitivity analysis where COVID 19-related events were censored as discontinued from study for DOR and PFS and as alive for OS was provided. These results can be considered similar to those in the PAS, with a median DOR of 15.2 months (95% CI: 6.7, 24.0), a median PFS of 12.3 months (95% CI: 6.1, 24.9) and a median OS of 36.3 months (95% CI: 16.5, NR). Based on the provided analyses, although COVID 19 influenced time to event endpoints, its impact is not considered critical for the interpretation of the trial's results.

The evaluation of Patient's Reported Outcome included subjects in the MCL Cohort Liso-cel-treated Set who had a baseline and at least one post baseline assessment that was analysable; the EORTC QLQ-C30, EQ-5D-5L, EQ-5D-5L VAS questionaries were used for the assessment. The compliance rate for all questionnaires decreased over time; to note, as reported by the MAH, noncompliance was mostly due to administrative and logistical delays around the implementation of the PROs in the study rather than to an explicit refusal of patients. The EORTC QLQ-C30, liso-cel consistently demonstrated improvements over time in evaluations of group-level mean change in the several primary domains. The **EQ-5D-5L Index Score** group-level mean remained consistent over the course of the study (from baseline to Month 24 post dose) for all subjects (total [DL1S+DL2S]) in the PRO/QoL (EQ 5D) Evaluable Set. With respect to the **EQ-5D-5L VAS**, liso-cel demonstrated clinically meaningful improvement for all subjects (total [DL1S+DL2S]) as the **HRQoL** measured by the EQ-5D-5L VAS improved from baseline to Month 2 (mean change [SD[in VAS = 10.5 [22.31]), and the improvement remained consistent until Month 18. In general, despite the improvement in symptoms and QoL reported in questionnaires, the overall level of the evidence from the PROs was considered low, primarily because of the limits related to lack

of controls and blinding. The supportive role of the provided PROs analysis for the global definition of the clinical benefit with liso-cel is, therefore, limited.

Supportive Studies

To contextualize the results of the pivotal single arm trial, the MAH reported the results of 2 supportive studies a systematic literature review and an unanchored MAIC.

The aim of the systematic literature review (SLR) was to identify evidence on the clinical efficacy and safety of 3L+ treatment options for adult R/R MCL patients previously exposed to a BTKi.

Overall, the results from this SLR confirmed the presence of an unmet medical need for additional options in BTKi-pretreated R/R MCL patients in their third or subsequent line of therapy. The analysis of efficacy of the non-CAR-T therapies showed that the rate of ORR/CR was variable and largely influenced by the intensity (e.g. better results could be observed with the R-BAC regimen) and type of treatment (novel drugs like pirtobrutinib were associated with better outcomes). As expected, the efficacy outcomes, especially in terms of depth and duration of responses were consistently better with brexu-cel compared to standard therapies, although data from real life experience showed increased variability compared to clinical trials, further highlighting the heterogeneity in the targeted condition.

The MAH also provided unanchored MAIC exercises to better contextualise the extent of benefit with liso-cel: liso-cel compared favourably with pirtobrutinib in terms of ORR, CRR and PFS, yet no substantial differences were noted in terms of DOR and OS. Compared to brexu-cel, the point estimations were favourable to liso-cel only in terms of CRR and OS (it should be noted, however, that no comparison between liso-cel and brexu-cel was statistically significant. The intrinsic methodological limitations (e.g. the assumption that all variables with prognostic value should be accounted for in the model) and the limited sample size limited the reliability of the provided comparisons, especially when the significant clinical and biological heterogeneity of R/R MCL is taken into account.

Overall, although the results of the provided indirect comparison exercises provided some information to contextualise the extent of benefit observed with liso-cel in the uncontrolled study 017001, their role to support B/R evaluations is necessarily limited. The intrinsic methodological limitations (e.g. the assumption that all variables with prognostic value should be accounted for in the model) and the limited sample size limited the reliability of the provided comparisons, especially when the significant clinical and biological heterogeneity of R/R MCL is taken into account.

Furthermore, the applicant commits to collect further information on the mantle cell lymphoma patients which will be included in the ongoing post-authorization safety study (PASS) JCAR017-BCM-005 through the necessary adaptation of the protocol (in the RMP) to be submitted for assessment to the Agency within 2 months from receiving the commission decision on the current extension of indication.

2.5.4. Conclusions on the clinical efficacy

Efficacy data from the MCL cohort of pivotal study 017001 showed that treatment with liso-cel resulted in a clinically relevant rate of deep and durable responses in an advanced setting of relapse of MCL. In particular, a trend towards long-lasting disease control could be observed in a subgroup of patients who were able to achieve CR with liso-cel.

2.6. Clinical safety

Introduction

For this proposed indication, the safety evaluation is primarily based on the safety data from **Study 017001** (TRANSCEND NHL-001) as of data cutoff date of 16-May-2024, to support the use of

lisocabtagene maraleucel (Breyanzi®; JCAR017;) for the treatment of adult patients with R/R MCL after at least 2 lines of systemic therapy, including a BTKi.

Safety data for liso-cel from the MCL Cohort (3L+ MCL; referred to as the R/R MCL Treated Set) of Study 017001 (n = 88 [DL1S + DL2S]) are presented side-by-side and pooled (n= 826) with safety data for liso-cel in 2L/3L+ LBCL and 2L+ FL.

For a comparison of the safety profile of liso-cel in the R/R MCL population to the known safety profile in the R/R LBCL population in the current SmPC, the supporting liso-cel monotherapy R/R LBCL studies from which 2L LBCL and 3L+ LBCL safety data were pooled and include:

- **3 studies for 2L R/R LBCL**:

- Study JCAR017-BCM-003 Arm B (hereafter referred to as "Study BCM-003")
- Study 017006
- Study JCAR017-BCM-001 (hereafter referred to as "Study BCM-001") Cohort 2

- **4 studies for 3L+ R/R LBCL:**

- Study BCM-001 Cohorts 1, 3, and 7
- Study 017001 DLBCL Cohort
- Study 017007
- Study JCAR017-BCM-002 (hereafter referred to as "Study BCM-002")

Data from each of the respective studies are summarized as:

- R/R MCL Treated Set: 3L+ MCL (017001 MCL Cohort)
- R/R FL Treated Set: 2L+ FL
- R/R LBCL Treated Set: 2L/3L+ LBCL

Study 017001 in R/R MCL

The MCL Cohort initially included subjects with R/R MCL after at least 1 prior line of MCL therapy. Following Study 017001 Protocol Amendment 07, subjects in the MCL Cohort were required to have received ≥ 2 prior lines of systemic MCL therapy and to have been previously treated with an alkylating agent, a BTKi and rituximab (or other CD20-targeted agents).

Patient exposure

In Study 017001, in the MCL Cohort a total of 105 subjects were screened, 104 underwent leukapheresis, 93 received LDC, and 92 received CAR+ T cells drug product. Among the 92 who received CAR+ T cells drug product, 88 subjects received liso-cel which comprised the Liso-cel Treated Analysis Set (i.e., R/R MCL Treated Set). Four subjects received nonconforming products.

As of the 16-May-2024 data cutoff date, the R/R MCL Treated Set had a longer **median on-study follow-up time of 19.53 months**, compared to 12.39 months in the R/R LBCL Treated Set. More subjects had completed the study in the R/R MCL Treated Set compared to the R/R LBCL Treated Set (45.5% vs 25.3%, respectively). In addition, a higher proportion of subjects enrolled in the LTFU study from the R/R MCL Treated Set compared to the R/R LBCL Treated Set (33% vs 18.3%). The most common reason for study discontinuation among both treated sets was death (Table 42).

Table 42. Subject Disposition - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
STUDY STATUS					
ONGOING	0	110 (84.6)	151 (24.8)	151 (21.7)	261 (31.6)
COMPLETED STUDY	40 (45.5)	1 (0.8)	154 (25.3)	194 (27.9)	195 (23.6)
DISCONTINUED FROM STUDY	48 (54.5)	19 (14.6)	303 (49.8)	351 (50.4)	370 (44.8)
ADVERSE EVENT	0	1 (0.8)	0	0	1 (0.1)
DEATH	44 (50.0)	7 (5.4)	237 (39.0)	281 (40.4)	288 (34.9)
LOST TO FOLLOW-UP	0	1 (0.8)	5 (0.8)	5 (0.7)	6 (0.7)
OTHER (A)	0	3 (2.3)	23 (3.8)	23 (3.3)	26 (3.1)
STUDY TERMINATION BY SPONSOR	0	0	0	0	0
SUBJECT WITHDREW CONSENT	4 (4.5)	7 (5.4)	38 (6.3)	42 (6.0)	49 (5.9)
CONSENTED TO THE LONG-TERM FOLLOW UP STUDY	29 (33.0)	2 (1.5)	111 (18.3)	140 (20.1)	142 (17.2)
SUBJECTS RECEIVED RETREATMENT	2 (2.3)	0	19 (3.1)	21 (3.0)	21 (2.5)

Demographic and baseline characteristics

Demographics and baseline disease characteristics in the R/R MCL Treated Set were representative of a R/R high risk MCL population.

The median time from diagnosis to first liso-cel infusion for all R/R MCL subjects was 63.75 months (range: 3.9 to 299.5 months).

The median number of prior therapies in R/R MCL Treated Set was 3 (range: 1-11), reflecting a heavily pretreated population with advanced disease. Two subjects had received only 1 prior line of therapy for MCL, as allowed by the study protocol prior to Protocol Amendment 07.

In the R/R MCL Treated Set, 29 subjects (33.0%) had prior HSCT, where 26 (29.5%) subjects received prior autologous HSCT and 6 (6.8%) subjects received prior allogeneic HSCT.

Baseline characteristics of the R/R MCL population were reflective of MCL epidemiology. The majority (72.7%) of subjects in the R/R MCL Treated Set were ≥ 65 years old compared to 50.8% in the R/R LBCL Treated Set. 20.5% of R/R MCL subjects were ≥ 75 years old compared to 14.5% of subjects in the R/R LBCL Treated Set. There was no clinically meaningful difference in pre-LDC LDH or pre-LDC SPD between R/R MCL Treated Set and the R/R LBCL Treated Set.

For additional details on demographic and baseline characteristics of Study 017001 MCL Cohort Population, please refer to Clinical Efficacy part.

The proportion of subjects who received anticancer therapy for disease control (i.e., bridging therapy) in the R/R MCL Treated Set was similar to that in the R/R LBCL Treated Set (65.9% vs 60.9%, respectively), reflective of a population with high disease burden and rapidly progressing disease.

In the R/R MCL Treated Set, the median time from last lymphodepleting chemotherapy (LDC) to liso-cel treatment was 4.0 days (range: 3 to 13 days), which was consistent with the protocol guidelines. The majority of subjects in the R/R MCL (71.6%) and R/R LBCL (82.9%) Treated Sets received the full specified dose of fludarabine and cyclophosphamide at the planned time with no missing doses; 25 (28.4%) subjects in the R/R MCL Treated Set received a reduced dose of fludarabine or cyclophosphamide that was mostly related to reduced CrCl.

Liso-cel Dose

Subjects in the R/R MCL Treated Set received a median total liso-cel administered dose of 99.5×10^6 CAR+ viable T cells; the median CD8+ and CD4+ component doses were 49.7×10^6 and 49.4×10^6 CAR+ viable T cells, respectively, which was similar to the R/R LBCL Treated Set. All subjects in the R/R

MCL Treated Set were dosed without delay or interruption, with the exception of 1 subject in which dosing was delayed beyond the specified window of 7 days after the completion of LDC due to an AE of hyperbilirubinemia (Grade 2) which was resolved at the time of liso-cel infusion.

Adverse events

Overall Safety Summary

The safety events were consistent with previously reported safety findings with liso-cel in R/R LBCL and in 2L+ FL (Table 43).

Table 43. Overview of Treatment-emergent Adverse Events - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
DURATION OF PERIOD (DAYS), MEDIAN (RANGE)	90.0 (5-90)	90.0 (29-90)	90.0 (7-218)	90.0 (5-218)	90.0 (5-218)
SUBJECTS WITH ANY TEAE	88 (100.0)	129 (99.2)	602 (99.0)	690 (99.1)	819 (99.2)
SUBJECTS WITH ANY GRADE 3-4 TEAE	72 (81.8)	99 (76.2)	482 (79.3)	554 (79.6)	653 (79.1)
SUBJECTS WITH ANY GRADE 3-5 TEAE	76 (86.4)	100 (76.9)	497 (81.7)	573 (82.3)	673 (81.5)
SUBJECTS WITH ANY GRADE 5 TEAE	4 (4.5)	1 (0.8)	15 (2.5)	19 (2.7)	20 (2.4)
SUBJECTS WITH ANY SERIOUS TEAE	47 (53.4)	31 (23.8)	260 (42.8)	307 (44.1)	338 (40.9)
SUBJECTS WITH ANY LDC-RELATED TEAE	74 (84.1)	98 (75.4)	498 (81.9)	572 (82.2)	670 (81.1)
SUBJECTS WITH ANY LDC-RELATED GRADE 3-4 TEAE	57 (64.8)	81 (62.3)	419 (68.9)	476 (68.4)	557 (67.4)
SUBJECTS WITH ANY LDC-RELATED GRADE 3-5 TEAE	59 (67.0)	81 (62.3)	427 (70.2)	486 (69.8)	567 (68.6)
SUBJECTS WITH ANY LDC-RELATED GRADE 5 TEAE	2 (2.3)	0	8 (1.3)	10 (1.4)	10 (1.2)
SUBJECTS WITH ANY LDC-RELATED SERIOUS TEAE	13 (14.8)	8 (6.2)	67 (11.0)	80 (11.5)	88 (10.7)
SUBJECTS WITH ANY JCAR017-RELATED TEAE	77 (87.5)	115 (88.5)	486 (79.9)	563 (80.9)	678 (82.1)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 3-4 TEAE	40 (45.5)	80 (61.5)	277 (45.6)	317 (45.5)	397 (48.1)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 3-5 TEAE	43 (48.9)	81 (62.3)	285 (46.9)	328 (47.1)	409 (49.5)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 5 TEAE	3 (3.4)	1 (0.8)	8 (1.3)	11 (1.6)	12 (1.5)
SUBJECTS WITH ANY JCAR017-RELATED SERIOUS TEAE	34 (38.6)	24 (18.5)	181 (29.8)	215 (30.9)	239 (28.9)

Treatment Emergent Adverse Events (TEAEs)

In the R/R MCL Treated Set, the most frequently occurring TEAEs by SOC are reported in the Table 44.

Table 44.Treatment-emergent Adverse Events by System Organ Class and Preferred Term Reported in ≥ 10% of MCL or LBCL Subjects - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ MCL N = 88 n (%)	2L+ FL N = 130 n (%)	2L/3L+ LBCL Total N = 608 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 696 n (%)	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826 n (%)
SUBJECTS WITH ANY TEAE	88 (100.0)	129 (99.2)	602 (99.0)	690 (99.1)	819 (99.2)
Blood and lymphatic system disorders	68 (77.3)	100 (76.9)	494 (81.3)	562 (80.7)	662 (80.1)
Neutropenia	52 (59.1)	88 (67.7)	409 (67.3)	461 (66.2)	549 (66.5)
Anaemia	39 (44.3)	52 (40.0)	275 (45.2)	314 (45.1)	366 (44.3)
Thrombocytopenia	26 (29.5)	38 (29.2)	228 (37.5)	254 (36.5)	292 (35.4)
Leukopenia	6 (6.8)	18 (13.8)	140 (23.0)	146 (21.0)	164 (19.9)
Lymphopenia	6 (6.8)	19 (14.6)	69 (11.3)	75 (10.8)	94 (11.4)
General disorders and administration site conditions	59 (67.0)	58 (44.6)	386 (63.5)	445 (63.9)	503 (60.9)
Fatigue	31 (35.2)	20 (15.4)	205 (33.7)	236 (33.9)	256 (31.0)
Pyrexia	15 (17.0)	21 (16.2)	120 (19.7)	135 (19.4)	156 (18.9)
Oedema peripheral	15 (17.0)	6 (4.6)	76 (12.5)	91 (13.1)	97 (11.7)
Chills	10 (11.4)	4 (3.1)	44 (7.2)	54 (7.8)	58 (7.0)
Gastrointestinal disorders	46 (52.3)	61 (46.9)	378 (62.2)	424 (60.9)	485 (58.7)
Nausea	16 (18.2)	12 (9.2)	164 (27.0)	180 (25.9)	192 (23.2)
Diarrhoea	15 (17.0)	22 (16.9)	127 (20.9)	142 (20.4)	164 (19.9)
Constipation	12 (13.6)	27 (20.8)	121 (19.9)	133 (19.1)	160 (19.4)
Vomiting	5 (5.7)	5 (3.8)	88 (14.5)	93 (13.4)	98 (11.9)
Abdominal pain	7 (8.0)	9 (6.9)	70 (11.5)	77 (11.1)	86 (10.4)

System Organ Class Preferred Term	3L+ MCL N = 88 n (%)	2L+ FL N = 130 n (%)	2L/3L+ LBCL Total N = 608 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 696 n (%)	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826 n (%)
Nervous system disorders	42 (47.7)	56 (43.1)	352 (57.9)	394 (56.6)	450 (54.5)
Headache	20 (22.7)	38 (29.2)	154 (25.3)	174 (25.0)	212 (25.7)
Dizziness	6 (6.8)	6 (4.6)	101 (16.6)	107 (15.4)	113 (13.7)
Tremor	10 (11.4)	19 (14.6)	82 (13.5)	92 (13.2)	111 (13.4)
Metabolism and nutrition disorders	56 (63.6)	32 (24.6)	292 (48.0)	348 (50.0)	380 (46.0)
Decreased appetite	18 (20.5)	7 (5.4)	124 (20.4)	142 (20.4)	149 (18.0)
Hypokalaemia	21 (23.9)	9 (6.9)	100 (16.4)	121 (17.4)	130 (15.7)
Hypomagnesaemia	13 (14.8)	4 (3.1)	86 (14.1)	99 (14.2)	103 (12.5)
Hypophosphataemia	15 (17.0)	2 (1.5)	57 (9.4)	72 (10.3)	74 (9.0)
Hyponatraemia	9 (10.2)	4 (3.1)	32 (5.3)	41 (5.9)	45 (5.4)
Hypocalcaemia	11 (12.5)	2 (1.5)	13 (2.1)	24 (3.4)	26 (3.1)
Immune system disorders	56 (63.6)	77 (59.2)	283 (46.5)	339 (48.7)	416 (50.4)
Cytokine release syndrome	54 (61.4)	75 (57.7)	254 (41.8)	308 (44.3)	383 (46.4)
Hypogammaglobulinaemia	6 (6.8)	3 (2.3)	61 (10.0)	67 (9.6)	70 (8.5)
Musculoskeletal and connective tissue disorders	39 (44.3)	40 (30.8)	244 (40.1)	283 (40.7)	323 (39.1)
Arthralgia	10 (11.4)	11 (8.5)	66 (10.9)	76 (10.9)	87 (10.5)
Back pain	13 (14.8)	9 (6.9)	65 (10.7)	78 (11.2)	87 (10.5)
Pain in extremity	9 (10.2)	3 (2.3)	41 (6.7)	50 (7.2)	53 (6.4)
Respiratory, thoracic and mediastinal disorders	26 (29.5)	21 (16.2)	233 (38.3)	259 (37.2)	280 (33.9)
Cough	9 (10.2)	9 (6.9)	91 (15.0)	100 (14.4)	109 (13.2)
Vascular disorders	27 (30.7)	22 (16.9)	184 (30.3)	211 (30.3)	233 (28.2)
Hypotension	11 (12.5)	10 (7.7)	97 (16.0)	108 (15.5)	118 (14.3)
Hypertension	9 (10.2)	6 (4.6)	58 (9.5)	67 (9.6)	73 (8.8)
Psychiatric disorders	27 (30.7)	19 (14.6)	187 (30.8)	214 (30.7)	233 (28.2)
Insomnia	11 (12.5)	7 (5.4)	67 (11.0)	78 (11.2)	85 (10.3)
Confusional state	14 (15.9)	3 (2.3)	66 (10.9)	80 (11.5)	83 (10.0)
Anxiety	11 (12.5)	2 (1.5)	40 (6.6)	51 (7.3)	53 (6.4)

Table was sorted by SOC and PT in descending order of incidence in the Overall Total column.
A subject was counted only once for multiple events within a PT/SOC.

Grade 3 and Higher TEAEs

Overall, the types and frequency of the most common Grade ≥ 3 TEAEs reported in ≥ 2% of subjects were similar between the R/R MCL and the R/R LBCL Treated Sets. In the R/R MCL Treated Set, the most frequently occurring Grade ≥ 3 TEAEs by SOC are reported in the Table 45.

Table 45. Grade 3 or Higher Treatment-emergent Adverse Events by System Organ Class and Preferred Term Reported in ≥ 2% of MCL or LBCL Subjects - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ MCL N = 88 n (%)	2L+ FL N = 130 n (%)	2L/3L+ LBCL Total N = 608 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 696 n (%)	3L+ MCL, 2L/3L+ LBCL and 2L+ FL Total N = 826 n (%)
SUBJECTS WITH ANY GRADE 3 OR HIGHER TEAE	76 (86.4)	100 (76.9)	497 (81.7)	573 (82.3)	673 (81.5)
Blood and lymphatic system disorders	64 (72.7)	91 (70.0)	460 (75.7)	524 (75.3)	615 (74.5)
Neutropenia	49 (55.7)	79 (60.8)	388 (63.8)	437 (62.8)	516 (62.5)
Anaemia	33 (37.5)	13 (10.0)	203 (33.4)	236 (33.9)	249 (30.1)
Thrombocytopenia	22 (25.0)	15 (11.5)	177 (29.1)	199 (28.6)	214 (25.9)
Leukopenia	6 (6.8)	15 (11.5)	127 (20.9)	133 (19.1)	148 (17.9)
Lymphopenia	5 (5.7)	16 (12.3)	63 (10.4)	68 (9.8)	84 (10.2)
Febrile neutropenia	4 (4.5)	7 (5.4)	46 (7.6)	50 (7.2)	57 (6.9)
Metabolism and nutrition disorders	21 (23.9)	2 (1.5)	80 (13.2)	101 (14.5)	103 (12.5)
Hypophosphataemia	8 (9.1)	0	27 (4.4)	35 (5.0)	35 (4.2)
Hypokalaemia	7 (8.0)	0	15 (2.5)	22 (3.2)	22 (2.7)
Hyponatraemia	3 (3.4)	0	16 (2.6)	19 (2.7)	19 (2.3)
Decreased appetite	4 (4.5)	0	12 (2.0)	16 (2.3)	16 (1.9)
Hyperglycaemia	2 (2.3)	1 (0.8)	5 (0.8)	7 (1.0)	8 (1.0)
Hypocalcaemia	3 (3.4)	0	4 (0.7)	7 (1.0)	7 (0.8)
Tumour lysis syndrome	2 (2.3)	0	2 (0.3)	4 (0.6)	4 (0.5)
Hyperuricaemia	2 (2.3)	0	0	2 (0.3)	2 (0.2)
Infections and infestations	13 (14.8)	7 (5.4)	73 (12.0)	86 (12.4)	93 (11.3)
Pneumonia	0	1 (0.8)	17 (2.8)	17 (2.4)	18 (2.2)
Urinary tract infection	3 (3.4)	0	6 (1.0)	9 (1.3)	9 (1.1)
Upper respiratory tract infection	2 (2.3)	0	2 (0.3)	4 (0.6)	4 (0.5)
Staphylococcal bacteraemia	2 (2.3)	0	1 (0.2)	3 (0.4)	3 (0.4)

System Organ Class Preferred Term	3L+ MCL N = 88 n (%)	2L+ FL N = 130 n (%)	2L/3L+ LBCL Total N = 608 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 696 n (%)	3L+ MCL, 2L/3L+ LBCL and 2L+ FL Total N = 826 n (%)
Nervous system disorders	7 (8.0)	5 (3.8)	62 (10.2)	69 (9.9)	74 (9.0)
Encephalopathy	3 (3.4)	1 (0.8)	18 (3.0)	21 (3.0)	22 (2.7)
Syncope	2 (2.3)	2 (1.5)	12 (2.0)	14 (2.0)	16 (1.9)
Somnolence	2 (2.3)	0	4 (0.7)	6 (0.9)	6 (0.7)
Gastrointestinal disorders	5 (5.7)	2 (1.5)	45 (7.4)	50 (7.2)	52 (6.3)
Abdominal pain	2 (2.3)	1 (0.8)	8 (1.3)	10 (1.4)	11 (1.3)
Nausea	2 (2.3)	0	6 (1.0)	8 (1.1)	8 (1.0)
Vascular disorders	4 (4.5)	4 (3.1)	42 (6.9)	46 (6.6)	50 (6.1)
Hypertension	3 (3.4)	2 (1.5)	21 (3.5)	24 (3.4)	26 (3.1)
Hypotension	0	0	16 (2.6)	16 (2.3)	16 (1.9)
Psychiatric disorders	5 (5.7)	3 (2.3)	32 (5.3)	37 (5.3)	40 (4.8)
Confusional state	2 (2.3)	1 (0.8)	10 (1.6)	12 (1.7)	13 (1.6)
Delirium	2 (2.3)	0	4 (0.7)	6 (0.9)	6 (0.7)
Respiratory, thoracic and mediastinal disorders	2 (2.3)	1 (0.8)	27 (4.4)	29 (4.2)	30 (3.6)
Hypoxia	2 (2.3)	1 (0.8)	6 (1.0)	8 (1.1)	9 (1.1)
General disorders and administration site conditions	3 (3.4)	1 (0.8)	22 (3.6)	25 (3.6)	26 (3.1)
Fatigue	2 (2.3)	0	6 (1.0)	8 (1.1)	8 (1.0)
Cardiac disorders	6 (6.8)	2 (1.5)	14 (2.3)	20 (2.9)	22 (2.7)
Atrial fibrillation	2 (2.3)	0	4 (0.7)	6 (0.9)	6 (0.7)

Table was sorted by SOC and PT in descending order of incidence in the Overall Total column.
A subject was counted only once for multiple events within a PT/SOC.

TEAEs Related to Liso-cel

Overall, the type and frequency of the most commonly reported **liso-cel-related TEAEs** reported in ≥ 10% of subjects were similar between the R/R MCL and the R/R LBCL Treated Sets. In the R/R MCL Treated Set, the most frequently occurring liso-cel-related TEAEs by SOC are reported in the Table 46.

Table 46. Liso-cel Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term Reported in ≥ 10% of MCL or LBCL Subjects - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ MCL N = 88 n (%)	2L+ FL N = 130 n (%)	2L/3L+ LBCL Total N = 608 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 696 n (%)	3L+ MCL, 2L/3L+ LBCL and 2L+ FL Total N = 826 n (%)
SUBJECTS WITH ANY LISO-CEL RELATED TEAE	77 (87.5)	115 (88.5)	486 (79.9)	563 (80.9)	678 (82.1)
Immune system disorders	56 (63.6)	77 (59.2)	274 (45.1)	330 (47.4)	407 (49.3)
Cytokine release syndrome	54 (61.4)	75 (57.7)	254 (41.8)	308 (44.3)	383 (46.4)
Blood and lymphatic system disorders	38 (43.2)	80 (61.5)	264 (43.4)	302 (43.4)	382 (46.2)
Neutropenia	31 (35.2)	70 (53.8)	193 (31.7)	224 (32.2)	294 (35.6)
Anaemia	11 (12.5)	38 (29.2)	124 (20.4)	135 (19.4)	173 (20.9)
Thrombocytopenia	10 (11.4)	27 (20.8)	122 (20.1)	132 (19.0)	159 (19.2)
Leukopenia	2 (2.3)	11 (8.5)	68 (11.2)	70 (10.1)	81 (9.8)
Nervous system disorders	28 (31.8)	29 (22.3)	197 (32.4)	225 (32.3)	254 (30.8)
Headache	14 (15.9)	13 (10.0)	64 (10.5)	78 (11.2)	91 (11.0)
General disorders and administration site conditions	32 (36.4)	41 (31.5)	198 (32.6)	230 (33.0)	271 (32.8)
Fatigue	18 (20.5)	17 (13.1)	96 (15.8)	114 (16.4)	131 (15.9)
Pyrexia	11 (12.5)	17 (13.1)	76 (12.5)	87 (12.5)	104 (12.6)
Psychiatric disorders	17 (19.3)	10 (7.7)	84 (13.8)	101 (14.5)	111 (13.4)
Confusional state	14 (15.9)	2 (1.5)	53 (8.7)	67 (9.6)	69 (8.4)

Table was sorted by SOC and PT in descending order of incidence in the Overall Total column.
A subject was counted only once for multiple events within a PT/SOC.

The overall types and frequency of the most commonly reported **liso-cel-related Grade ≥ 3 TEAEs** reported in ≥ 2% of subjects were similar between the R/R MCL and the R/R LBCL Treated Sets (Table 47).

Table 47. Liso-cel Related Grade 3 or Higher Treatment-emergent Adverse Events by System Organ Class and Preferred Term Reported in ≥ 2% of MCL or LBCL Subjects - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ MCL N = 88 n (%)	2L+ FL N = 130 n (%)	2L/3L+ LBCL Total N = 608 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 696 n (%)	3L+ MCL, 2L/3L+ LBCL and 2L+ FL Total N = 826 n (%)
SUBJECTS WITH ANY LISO-CEL RELATED GRADE 3 OR HIGHER TEAE	43 (48.9)	81 (62.3)	285 (46.9)	328 (47.1)	409(49.5)
Blood and lymphatic system disorders	32 (36.4)	73 (56.2)	240 (39.5)	272 (39.1)	345 (41.8)
Neutropenia	27 (30.7)	62 (47.7)	181 (29.8)	208 (29.9)	270 (32.7)
Thrombocytopenia	9 (10.2)	10 (7.7)	96 (15.8)	105 (15.1)	115 (13.9)
Anaemia	9 (10.2)	10 (7.7)	87 (14.3)	96 (13.8)	106 (12.8)
Leukopenia	2 (2.3)	7 (5.4)	56 (9.2)	58 (8.3)	65 (7.9)
Lymphopenia	1 (1.1)	15 (11.5)	35 (5.8)	36 (5.2)	51 (6.2)
Febrile neutropenia	1 (1.1)	6 (4.6)	28 (4.6)	29 (4.2)	35 (4.2)
Nervous system disorders	6 (6.8)	3 (2.3)	41 (6.7)	47 (6.8)	50 (6.1)
Encephalopathy	3 (3.4)	1 (0.8)	16 (2.6)	19 (2.7)	20 (2.4)
Somnolence	2 (2.3)	0	4 (0.7)	6 (0.9)	6 (0.7)
Psychiatric disorders	4 (4.5)	3 (2.3)	24 (3.9)	28 (4.0)	31 (3.8)
Confusional state	2 (2.3)	1 (0.8)	9 (1.5)	11 (1.6)	12 (1.5)
Delirium	2 (2.3)	0	4 (0.7)	6 (0.9)	6 (0.7)
Metabolism and nutrition disorders	7 (8.0)	0	11 (1.8)	18 (2.6)	18 (2.2)
Decreased appetite	2 (2.3)	0	2 (0.3)	4 (0.6)	4 (0.5)
Tumour lysis syndrome	2 (2.3)	0	1 (0.2)	3 (0.4)	3 (0.4)

Table was sorted by SOC and PT in descending order of incidence in the Overall Total column.
A subject was counted only once for multiple events within a PT/SOC.

Post-treatment-emergent Period Adverse Events

AEs in the post-treatment emergent period (≥ 91 days after liso-cel infusion) were numerically higher in R/R MCL Treated Set Compared to R/R LBCL Treated Set (54.9% vs 45.4%, respectively) (Table 48).

Table 48. Overview of Adverse Events - Post-treatment-emergent Period - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

	3L+ MCL N = 82	2L+ FL N = 129	2L/3L+ LBCL Total N = 559	3L+ MCL and 2L/3L+ LBCL Total N = 641	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 770
DURATION OF PERIOD (DAYS), MEDIAN (RANGE)	620.0 (3-686)	739.0 (25-1042)	359.0 (2-1287)	388.0 (2-1287)	469.5 (2-1287)
SUBJECTS WITH ANY AE	45 (54.9)	46 (35.7)	254 (45.4)	299 (46.6)	345 (44.8)
SUBJECTS WITH ANY GRADE 3-4 AE	20 (24.4)	22 (17.1)	124 (22.2)	144 (22.5)	166 (21.6)
SUBJECTS WITH ANY GRADE 3-5 AE	25 (30.5)	25 (19.4)	143 (25.6)	168 (26.2)	193 (25.1)
SUBJECTS WITH ANY GRADE 5 AE	5 (6.1)	3 (2.3)	19 (3.4)	24 (3.7)	27 (3.5)
SUBJECTS WITH ANY SERIOUS AE	23 (28.0)	21 (16.3)	85 (15.2)	108 (16.8)	129 (16.8)
SUBJECTS WITH ANY LDC-RELATED AE	17 (20.7)	11 (8.5)	89 (15.9)	106 (16.5)	117 (15.2)
SUBJECTS WITH ANY LDC-RELATED GRADE 3-4 AE	9 (11.0)	4 (3.1)	51 (9.1)	60 (9.4)	64 (8.3)
SUBJECTS WITH ANY LDC-RELATED GRADE 3-5 AE	10 (12.2)	5 (3.9)	56 (10.0)	66 (10.3)	71 (9.2)
SUBJECTS WITH ANY LDC-RELATED GRADE 5 AE	1 (1.2)	1 (0.8)	5 (0.9)	6 (0.9)	7 (0.9)
SUBJECTS WITH ANY LDC-RELATED SERIOUS AE	5 (6.1)	3 (2.3)	25 (4.5)	30 (4.7)	33 (4.3)

	3L+ MCL N = 82	2L+ FL N = 129	2L/3L+ LBCL Total N = 559	3L+ MCL and 2L/3L+ LBCL Total N = 641	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 770
SUBJECTS WITH ANY JCAR017-RELATED AE	16 (19.5)	31 (24.0)	111 (19.9)	127 (19.8)	158 (20.5)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 3-4 AE	7 (8.5)	15 (11.6)	56 (10.0)	63 (9.8)	78 (10.1)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 3-5 AE	8 (9.8)	16 (12.4)	60 (10.7)	68 (10.6)	84 (10.9)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 5 AE	1 (1.2)	1 (0.8)	4 (0.7)	5 (0.8)	6 (0.8)
SUBJECTS WITH ANY JCAR017-RELATED SERIOUS AE	5 (6.1)	10 (7.8)	22 (3.9)	27 (4.2)	37 (4.8)

The most severe grade was used for AEs that occurred more than once in an individual subject during the period.
Post-treatment-emergent period started from 91 days post final liso-cel infusion or initiation of subsequent anticancer therapy/product retreatment if subject initiated subsequent anticancer therapy/product retreatment prior to Study Day 91.

In the R/R MCL Treated Set, the most frequently occurring **post-treatment-emergent period AEs** by SOC were Blood and lymphatic system disorders as well as Neoplasms benign, malignant and unspecified (17.1% each), and Infections and infestations (13.4%). The most frequently occurring post-treatment-emergent period AEs by PT were thrombocytopenia (7.3%) and neutropenia and anaemia (6.1% each) (Table 49).

Table 49. Adverse Events by System Organ Class and Preferred Term Reported in ≥ 5% of MCL or LBCL Subjects - Post-treatment-emergent Period - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ MCL N = 82 n (%)	2L+ FL N = 129 n (%)	2L/3L+ LBCL Total N = 559 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 641 n (%)	3L+ MCL, 2L/3L+ LBCL and 2L+ FL Total N = 770 n (%)
SUBJECTS WITH ANY AE POST-TREATMENT-EMERGENT PERIOD	45 (54.9)	46 (35.7)	254 (45.4)	299 (46.6)	345 (44.8)

System Organ Class Preferred Term	3L+ MCL N = 82 n (%)	2L+ FL N = 129 n (%)	2L/3L+ LBCL Total N = 559 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 641 n (%)	3L+ MCL, 2L/3L+ LBCL and 2L+ FL Total N = 770 n (%)
Blood and lymphatic system disorders	14 (17.1)	18 (14.0)	133 (23.8)	147 (22.9)	165 (21.4)
Neutropenia	5 (6.1)	13 (10.1)	66 (11.8)	71 (11.1)	84 (10.9)
Thrombocytopenia	6 (7.3)	3 (2.3)	54 (9.7)	60 (9.4)	63 (8.2)
Anaemia	5 (6.1)	1 (0.8)	55 (9.8)	60 (9.4)	61 (7.9)
General disorders and administration site conditions	4 (4.9)	3 (2.3)	49 (8.8)	53 (8.3)	56 (7.3)
Fatigue	0	1 (0.8)	29 (5.2)	29 (4.5)	30 (3.9)

Post-treatment-emergent period started from 91 days post final liso-cel infusion or initiation of subsequent anticancer therapy/product retreatment if subject initiated subsequent anticancer therapy/product retreatment prior to Study Day 91.

Table was sorted by SOC and PT in descending order of incidence in the Overall Total column.

A subject was counted only once for multiple events within a PT/SOC.

Overall, the frequency of the most commonly reported Grade ≥ 3 post-treatment-emergent period AEs was similar between the R/R MCL and the R/R LBCL Treated Sets (30.5% vs 25.6%, respectively) (Table 50).

Table 50. Grade 3 or Higher Adverse Events by System Organ Class and Preferred Term Reported in ≥ 2% of MCL or LBCL Subjects - Post-treatment-emergent Period - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ MCL N = 82 n (%)	2L+ FL N = 129 n (%)	2L/3L+ LBCL Total N = 559 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 641 n (%)	3L+ MCL, 2L/3L+ LBCL and 2L+ FL Total N = 770 n (%)
SUBJECTS WITH ANY GRADE 3 OR HIGHER AE POST TREATMENT-EMERGENT PERIOD	25 (30.5)	25 (19.4)	143 (25.6)	168 (26.2)	193 (25.1)
Blood and lymphatic system disorders	10 (12.2)	10 (7.8)	97 (17.4)	107 (16.7)	117 (15.2)
Neutropenia	4 (4.9)	10 (7.8)	51 (9.1)	55 (8.6)	65 (8.4)
Anaemia	2 (2.4)	1 (0.8)	41 (7.3)	43 (6.7)	44 (5.7)
Thrombocytopenia	4 (4.9)	2 (1.6)	35 (6.3)	39 (6.1)	41 (5.3)
Febrile neutropenia	1 (1.2)	0	15 (2.7)	16 (2.5)	16 (2.1)
Leukopenia	0	0	14 (2.5)	14 (2.2)	14 (1.8)
Lymphopenia	2 (2.4)	0	11 (2.0)	13 (2.0)	13 (1.7)
Infections and infestations	6 (7.3)	6 (4.7)	28 (5.0)	34 (5.3)	40 (5.2)
COVID-19	4 (4.9)	2 (1.6)	3 (0.5)	7 (1.1)	9 (1.2)
COVID-19 pneumonia	2 (2.4)	2 (1.6)	2 (0.4)	4 (0.6)	6 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (9.8)	7 (5.4)	19 (3.4)	27 (4.2)	34 (4.4)
Myelodysplastic syndrome	2 (2.4)	1 (0.8)	10 (1.8)	12 (1.9)	13 (1.7)
Metabolism and nutrition disorders	2 (2.4)	0	13 (2.3)	15 (2.3)	15 (1.9)
Hypokalaemia	2 (2.4)	0	2 (0.4)	4 (0.6)	4 (0.5)

Post-treatment-emergent period started from 91 days post final liso-cel infusion or initiation of subsequent anticancer therapy/product retreatment if subject initiated subsequent anticancer therapy/product retreatment prior to Study Day 91.

Table was sorted by SOC and PT in descending order of incidence in the Overall Total column.

A subject was counted only once for multiple events within a PT/SOC.

COVID-19 Infections

The majority of the subjects in the MCL Cohort (75%) were treated during the COVID-19 pandemic. In the R/R MCL Treated Set, treatment-emergent COVID-19 infections occurred in 2 (2.3%) subjects, of which 1 was a fatal COVID-19 pneumonia. In the 2L/3L+ LBCL population, treatment-emergent COVID-19 infections occurred in 8 (1.3%) subjects, of which 2 were fatal.

In the post-treatment-emergent period, the overall incidence of SOC Infections and infestations was 13.4% in the R/R MCL Treated Set and 10.9% in the R/R LBCL Treated Set, while the frequency of Grade ≥ 3 post-treatment-emergent period infection and infestation AEs was 7.3% and 5.0%, respectively. Notably, in the R/R MCL Treated Set, all of the Grade ≥ 3 post-treatment infections and infestations AEs reported were COVID-19 related AEs (6 of 6), as opposed to 5 out of 28 subjects with COVID-19 related AEs in the 2L/3L+ LBCL population.

Serious adverse event/deaths/other significant events

Deaths

In the R/R MCL Liso-cel-treated Analysis Set (n= 88), 46 (52.3%) subjects died any time after the first liso-cel infusion. Of these subjects, most (29 [33.0%]) died due to disease progression, with 22 (25.0%) deaths occurring after 90 days post liso-cel infusion (Table 51).

Table 51. Summary of Deaths - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
DEATHS OCCURRED AFTER FIRST LISO-CEL INFUSION	46 (52.3)	13 (10.0)	258 (42.4)	304 (43.7)	317 (38.4)
PRIMARY CAUSE OF DEATH					
DISEASE PROGRESSION	29 (33.0)	7 (5.4)	206 (33.9)	235 (33.8)	242 (29.3)
ADVERSE EVENT	5 (5.7)	3 (2.3)	23 (3.8)	28 (4.0)	31 (3.8)
COVID-19	7 (8.0)	2 (1.5)	9 (1.5)	16 (2.3)	18 (2.2)
UNKNOWN	1 (1.1)	0	6 (1.0)	7 (1.0)	7 (0.8)
OTHER (A)	4 (4.5)	1 (0.8)	14 (2.3)	18 (2.6)	19 (2.3)
DEATHS OCCURRED AFTER FIRST LISO-CEL INFUSION AND WITHIN 30 DAYS POST LISO-CEL INFUSION	4 (4.5)	1 (0.8)	12 (2.0)	16 (2.3)	17 (2.1)
PRIMARY CAUSE OF DEATH					
DISEASE PROGRESSION	3 (3.4)	0	7 (1.2)	10 (1.4)	10 (1.2)
ADVERSE EVENT	1 (1.1)	1 (0.8)	5 (0.8)	6 (0.9)	7 (0.8)
COVID-19	0	0	0	0	0
UNKNOWN	0	0	0	0	0
OTHER (A)	0	0	0	0	0
DEATHS OCCURRED BETWEEN 31 AND 90 DAYS POST LISO-CEL INFUSION	8 (9.1)	0	45 (7.4)	53 (7.6)	53 (6.4)
PRIMARY CAUSE OF DEATH					
DISEASE PROGRESSION	4 (4.5)	0	31 (5.1)	35 (5.0)	35 (4.2)
ADVERSE EVENT	3 (3.4)	0	9 (1.5)	12 (1.7)	12 (1.5)
COVID-19	1 (1.1)	0	2 (0.3)	3 (0.4)	3 (0.4)
UNKNOWN	0	0	2 (0.3)	2 (0.3)	2 (0.2)
OTHER (A)	0	0	1 (0.2)	1 (0.1)	1 (0.1)
DEATHS OCCURRED FROM 91 DAYS POST LISO-CEL INFUSION UNTIL THE END OF STUDY	34 (38.6)	12 (9.2)	201 (33.1)	235 (33.8)	247 (29.9)
PRIMARY CAUSE OF DEATH					
DISEASE PROGRESSION	22 (25.0)	7 (5.4)	168 (27.6)	190 (27.3)	197 (23.8)
ADVERSE EVENT	1 (1.1)	2 (1.5)	9 (1.5)	10 (1.4)	12 (1.5)
COVID-19	6 (6.8)	2 (1.5)	7 (1.2)	13 (1.9)	15 (1.8)
UNKNOWN	1 (1.1)	0	4 (0.7)	5 (0.7)	5 (0.6)
OTHER (A)	4 (4.5)	1 (0.8)	13 (2.1)	17 (2.4)	18 (2.2)

(A) Events listed as Other for the MCL Cohort include GVHD, respiratory failure of unknown origin, motor vehicle accident, complications from lung cancer and failure to thrive. Refer to Listing 2.7.5 in Appendix 2 for details.

As of the data cutoff date (Ref Table 1.1-1)

In the R/R MCL Treated Set, of the 5 subjects died due to AE, 4 (4.5%) died due to Grade 5 TEAEs (compared with 2.5% of subjects in the R/R LBCL Treated Set (Table 52). Grade 5 TEAEs in the R/R MCL Treated Set in R/R MCL Treated Set included COVID-19 pneumonia, cryptococcal meningoencephalitis, cardio-respiratory arrest, and tumor lysis syndrome. Of all 4 cases, 3 seems related to the liso-cel treatment and only one death case caused by cardio-respiratory arrest is reported to be unrelated to liso-cel treatment.

Table 52. Grade 5 TEAEs by System Organ Class and Preferred Term - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+LBCL

System Organ Class Preferred Term	3L+ MCL N = 88 n (%)	2L+ FL N = 130 n (%)	2L/3L+ LBCL Total N = 608 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 696 n (%)	3L+ MCL, 2L/3L+ LBCL and 2L+ FL Total N = 826 n (%)
SUBJECTS WITH ANY GRADE 5 TEAE	4 (4.5)	1 (0.8)	15 (2.5)	19 (2.7)	20 (2.4)
Infections and infestations	2 (2.3)	0	7 (1.2)	9 (1.3)	9 (1.1)
COVID-19 pneumonia	1 (1.1)	0	1 (0.2)	2 (0.3)	2 (0.2)
COVID-19	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Candida sepsis	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Cryptococcal meningoencephalitis	1 (1.1)	0	0	1 (0.1)	1 (0.1)
Pneumonia	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Progressive multifocal leukoencephalopathy	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Septic shock	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Staphylococcal sepsis	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	0	3 (0.5)	3 (0.4)	3 (0.4)
Diffuse alveolar damage	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Pulmonary haemorrhage	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Respiratory failure	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Cardiac disorders	1 (1.1)	0	1 (0.2)	2 (0.3)	2 (0.2)
Cardio-respiratory arrest	1 (1.1)	0	0	1 (0.1)	1 (0.1)
Cardiomyopathy	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Immune system disorders	0	1 (0.8)	1 (0.2)	1 (0.1)	2 (0.2)
Haemophagocytic lymphohistiocytosis	0	1 (0.8)	1 (0.2)	1 (0.1)	2 (0.2)
Metabolism and nutrition disorders	1 (1.1)	0	1 (0.2)	2 (0.3)	2 (0.2)
Failure to thrive	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Tumour lysis syndrome	1 (1.1)	0	0	1 (0.1)	1 (0.1)
General disorders and administration site conditions	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Multiple organ dysfunction syndrome	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Nervous system disorders	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Leukoencephalopathy	0	0	1 (0.2)	1 (0.1)	1 (0.1)

Table was sorted by SOC and PT in descending order of incidence in the Overall Total column.
A subject was counted only once for multiple events within a PT/SOC.

Treatment-emergent Serious Adverse Events

The overall types and frequency of treatment-emergent SAEs were similar between the R/R MCL and the R/R LBCL Treated Sets (Table 53).

Table 53. Treatment-emergent SAEs by System Organ Class and Preferred Term Reported in ≥ 2% of MCL or LBCL Subjects- Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ MCL N = 88 n (%)	2L+ FL N = 130 n (%)	2L/3L+ LBCL Total N = 608 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 696 n (%)	3L+ MCL, 2L/3L+ LBCL and 2L+ FL Total N = 826 n (%)
SUBJECTS WITH ANY SERIOUS TEAE	47 (53.4)	31 (23.8)	260 (42.8)	307 (44.1)	338 (40.9)
Immune system disorders	21 (23.9)	13 (10.0)	101 (16.6)	122 (17.5)	135 (16.3)
Cytokine release syndrome	21 (23.9)	12 (9.2)	100 (16.4)	121 (17.4)	133 (16.1)
Nervous system disorders	8 (9.1)	7 (5.4)	78 (12.8)	86 (12.4)	93 (11.3)
Aphasia	1 (1.1)	5 (3.8)	17 (2.8)	18 (2.6)	23 (2.8)
Encephalopathy	2 (2.3)	0	20 (3.3)	22 (3.2)	22 (2.7)
Tremor	0	3 (2.3)	14 (2.3)	14 (2.0)	17 (2.1)
Infections and infestations	9 (10.2)	7 (5.4)	61 (10.0)	70 (10.1)	77 (9.3)
Pneumonia	0	1 (0.8)	13 (2.1)	13 (1.9)	14 (1.7)
Upper respiratory tract infection	2 (2.3)	0	2 (0.3)	4 (0.6)	4 (0.5)
Blood and lymphatic system disorders	2 (2.3)	5 (3.8)	48 (7.9)	50 (7.2)	55 (6.7)
Febrile neutropenia	1 (1.1)	4 (3.1)	22 (3.6)	23 (3.3)	27 (3.3)
Neutropenia	0	1 (0.8)	19 (3.1)	19 (2.7)	20 (2.4)
Thrombocytopenia	1 (1.1)	0	17 (2.8)	18 (2.6)	18 (2.2)

System Organ Class Preferred Term	3L+ MCL N = 88 n (%)	2L+ FL N = 130 n (%)	2L/3L+ LBCL Total N = 608 n (%)	3L+ MCL and 2L/3L+ LBCL Total N = 696 n (%)	3L+ MCL, 2L/3L+ LBCL and 2L+ FL Total N = 826 n (%)
Psychiatric disorders	7 (8.0)	5 (3.8)	39 (6.4)	46 (6.6)	51 (6.2)
Confusional state	5 (5.7)	2 (1.5)	19 (3.1)	24 (3.4)	26 (3.1)
Mental status changes	2 (2.3)	0	9 (1.5)	11 (1.6)	11 (1.3)
General disorders and administration site conditions	4 (4.5)	4 (3.1)	29 (4.8)	33 (4.7)	37 (4.5)
Pyrexia	3 (3.4)	3 (2.3)	21 (3.5)	24 (3.4)	27 (3.3)
Respiratory, thoracic and mediastinal disorders	2 (2.3)	1 (0.8)	19 (3.1)	21 (3.0)	22 (2.7)
Pleural effusion	2 (2.3)	0	2 (0.3)	4 (0.6)	4 (0.5)
Metabolism and nutrition disorders	4 (4.5)	0	12 (2.0)	16 (2.3)	16 (1.9)
Decreased appetite	2 (2.3)	0	2 (0.3)	4 (0.6)	4 (0.5)

Table was sorted by SOC and PT in descending order of incidence in the Overall Total column.
A subject was counted only once for multiple events within a PT/SOC.

Other Significant Adverse Events of Special Interest

The profile of reported AESIs in the R/R MCL Liso-cel-treated Analysis Set was consistent with the known profile for R/R LBCL.

Table 54. Treatment-emergent AESIs by Grade - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
CRS	54 (61.4)	75 (57.7)	254 (41.8)	308 (44.3)	383 (46.4)
GRADE 1-2	53 (60.2)	74 (56.9)	244 (40.1)	297 (42.7)	371 (44.9)
GRADE 3-4	1 (1.1)	1 (0.8)	10 (1.6)	11 (1.6)	12 (1.5)
GRADE 5	0	0	0	0	0
SAE	21 (23.9)	12 (9.2)	100 (16.4)	121 (17.4)	133 (16.1)
NT	27 (30.7)	21 (16.2)	151 (24.8)	178 (25.6)	199 (24.1)
GRADE 1-2	19 (21.6)	17 (13.1)	100 (16.4)	119 (17.1)	136 (16.5)
GRADE 3-4	8 (9.1)	4 (3.1)	51 (8.4)	59 (8.5)	63 (7.6)
GRADE 5	0	0	0	0	0
SAE	11 (12.5)	7 (5.4)	76 (12.5)	87 (12.5)	94 (11.4)
INFUSION RELATED REACTION	2 (2.3)	0	6 (1.0)	8 (1.1)	8 (1.0)
GRADE 1-2	2 (2.3)	0	6 (1.0)	8 (1.1)	8 (1.0)
GRADE 3-4	0	0	0	0	0
GRADE 5	0	0	0	0	0
SAE	1 (1.1)	0	0	1 (0.1)	1 (0.1)
MACROPHAGE ACTIVATION SYNDROME	0	1 (0.8)	4 (0.7)	4 (0.6)	5 (0.6)
GRADE 1-2	0	0	1 (0.2)	1 (0.1)	1 (0.1)
GRADE 3-4	0	0	2 (0.3)	2 (0.3)	2 (0.2)
GRADE 5	0	1 (0.8)	1 (0.2)	1 (0.1)	2 (0.2)
SAE	0	1 (0.8)	3 (0.5)	3 (0.4)	4 (0.5)
TUMOR LYSIS SYNDROME	2 (2.3)	0	2 (0.3)	4 (0.6)	4 (0.5)
GRADE 1-2	0	0	0	0	0
GRADE 3-4	1 (1.1)	0	2 (0.3)	3 (0.4)	3 (0.4)
GRADE 5	1 (1.1)	0	0	1 (0.1)	1 (0.1)
SAE	1 (1.1)	0	0	1 (0.1)	1 (0.1)
GRADE>= 3 INFECTIONS	13 (14.8)	7 (5.4)	73 (12.0)	86 (12.4)	93 (11.3)
GRADE 3-4	11 (12.5)	7 (5.4)	66 (10.9)	77 (11.1)	84 (10.2)
GRADE 5	2 (2.3)	0	7 (1.2)	9 (1.3)	9 (1.1)
GRADE >= 3 BACTERIAL INFECTIONS	4 (4.5)	2 (1.5)	25 (4.1)	29 (4.2)	31 (3.8)
GRADE 3-4	4 (4.5)	2 (1.5)	24 (3.9)	28 (4.0)	30 (3.6)
GRADE 5	0	0	1 (0.2)	1 (0.1)	1 (0.1)
GRADE >= 3 FUNGAL INFECTIONS	1 (1.1)	0	5 (0.8)	6 (0.9)	6 (0.7)
GRADE 3-4	0	0	4 (0.7)	4 (0.6)	4 (0.5)
GRADE 5	1 (1.1)	0	1 (0.2)	2 (0.3)	2 (0.2)

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
GRADE >= 3 VIRAL INFECTIONS	4 (4.5)	1 (0.8)	10 (1.6)	14 (2.0)	15 (1.8)
GRADE 3-4	3 (3.4)	1 (0.8)	7 (1.2)	10 (1.4)	11 (1.3)
GRADE 5	1 (1.1)	0	3 (0.5)	4 (0.6)	4 (0.5)
GRADE >= 3 INFECTIONS -PATHOGEN UNSPECIFIED	5 (5.7)	5 (3.8)	43 (7.1)	48 (6.9)	53 (6.4)
GRADE 3-4	5 (5.7)	5 (3.8)	41 (6.7)	46 (6.6)	51 (6.2)
GRADE 5	0	0	2 (0.3)	2 (0.3)	2 (0.2)
GRADE >= 3 CYTOPENIA (A) FROM DAY 1 THROUGH DAY 29 OR 35 (B)	75 (85.2)	103 (79.2)	545 (89.6)	620 (89.1)	723 (87.5)
GRADE >= 3 AT DAY 29 OR 35	35 (39.8)	29 (22.3)	217 (35.7)	252 (36.2)	281 (34.0)
GRADE <= 2 AT DAY 29 OR 35	32 (36.4)	64 (49.2)	273 (44.9)	305 (43.8)	369 (44.7)
UNKNOWN AT DAY 29 OR 35	8 (9.1)	10 (7.7)	55 (9.0)	63 (9.1)	73 (8.8)

(A) Prolonged cytopenia was defined as Grade ≥3 laboratory results of decreased hemoglobin, decreased neutrophil count, or decreased platelet count.

(B) Visit considered at Day 35 (+/- 6 days) after liso-cel infusion for BCM-003, and at Day 29 (+/- 2 days) after liso-cel infusion in other studies.

A subject was counted only once for multiple events within a PT/SOC.

Infection included grade 3 or higher TEAEs from Infections and infestations SOC, by AE HLGT.

The most severe grade was used for AEs that occur more than once in an individual subject during the period.

If multiple test results are available in the window, the maximum grade is selected.

Results after the initiation of subsequent anticancer therapy or product retreatment are excluded.

Table 55. Second Primary Malignancies, Hypogammaglobulinemia, and Autoimmune Disorders in the Treatment-emergent and Post-treatment-emergent Periods - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

TREATMENT-EMERGENT PERIOD	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
SUBJECTS WITH AESI (ANY GRADE)					
SECOND PRIMARY MALIGNANCY (A)	3 (3.4)	2 (1.5)	8 (1.3)	11 (1.6)	13 (1.6)
HYPOGAMMAGLOBULINAEMIA	6 (6.8)	5 (3.8)	65 (10.7)	71 (10.2)	76 (9.2)
AUTOIMMUNE DISORDERS (A)	0	0	0	0	0
SUBJECTS WITH AESI (GRADE >= 3)					
SECOND PRIMARY MALIGNANCY (A)	2 (2.3)	2 (1.5)	4 (0.7)	6 (0.9)	8 (1.0)
HYPOGAMMAGLOBULINAEMIA	0	0	1 (0.2)	1 (0.1)	1 (0.1)
AUTOIMMUNE DISORDERS (A)	0	0	0	0	0

Post-TREATMENT-EMERGENT PERIOD	3L+ MCL N = 82	2L+ FL N = 129	2L/3L+ LBCL Total N = 559	3L+ MCL and 2L/3L+ LBCL Total N = 641	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 770
SUBJECTS WITH AESI (ANY GRADE)					
SECOND PRIMARY MALIGNANCY (A)	14 (17.1)	8 (6.2)	29 (5.2)	43 (6.7)	51 (6.6)
HYPOGAMMAGLOBULINAEMIA	4 (4.9)	3 (2.3)	27 (4.8)	31 (4.8)	34 (4.4)
AUTOIMMUNE DISORDERS (A)	0	0	0	0	0
SUBJECTS WITH AESI (GRADE >= 3)					
SECOND PRIMARY MALIGNANCY (A)	8 (9.8)	5 (3.9)	19 (3.4)	27 (4.2)	32 (4.2)
HYPOGAMMAGLOBULINAEMIA	0	1 (0.8)	0	0	1 (0.1)
AUTOIMMUNE DISORDERS (A)	0	0	0	0	0

(A) Based on adjudicated results.

Post-treatment-emergent period started from 91 days post final liso-cel infusion or initiation of subsequent anticancer therapy/product retreatment if subject initiated subsequent anticancer therapy/product retreatment prior to Study Day 91.

Cytokine Release Syndrome

Table 56. Treatment-emergent CRS Symptoms by Grade in ≥ 10% of Subjects - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
SUBJECTS WITH TREATMENT-EMERGENT CRS SYMPTOMS (ANY GRADE)	54 (61.4)	75 (57.7)	254 (41.8)	308 (44.3)	383 (46.4)
SUBJECTS WITH TREATMENT-EMERGENT CRS SYMPTOMS (GRADE >= 3)	7 (8.0)	2 (1.5)	42 (6.9)	49 (7.0)	51 (6.2)
FEVER	53 (60.2)	74 (56.9)	243 (40.0)	296 (42.5)	370 (44.8)
GRADE 1-2	53 (60.2)	74 (56.9)	231 (38.0)	284 (40.8)	358 (43.3)
GRADE 3-4	0	0	12 (2.0)	12 (1.7)	12 (1.5)
GRADE 5	0	0	0	0	0
HYPOTENSION	19 (21.6)	18 (13.8)	98 (16.1)	117 (16.8)	135 (16.3)
GRADE 1-2	16 (18.2)	16 (12.3)	84 (13.8)	100 (14.4)	116 (14.0)
GRADE 3-4	3 (3.4)	2 (1.5)	14 (2.3)	17 (2.4)	19 (2.3)
GRADE 5	0	0	0	0	0
TACHYCARDIA	9 (10.2)	1 (0.8)	65 (10.7)	74 (10.6)	75 (9.1)
GRADE 1-2	9 (10.2)	1 (0.8)	64 (10.5)	73 (10.5)	74 (9.0)
GRADE 3-4	0	0	1 (0.2)	1 (0.1)	1 (0.1)
GRADE 5	0	0	0	0	0
HYPOXIA	10 (11.4)	3 (2.3)	44 (7.2)	54 (7.8)	57 (6.9)
GRADE 1-2	7 (8.0)	3 (2.3)	28 (4.6)	35 (5.0)	38 (4.6)
GRADE 3-4	3 (3.4)	0	16 (2.6)	19 (2.7)	19 (2.3)
GRADE 5	0	0	0	0	0

A CRS symptom that started from start of product infusion through and including 90 days post product infusion was considered treatment-emergent.
Grouped term Fever includes PTs Pyrexia; grouped term Hypotension includes PTs Hypotension and Orthostatic hypotension.
A subject was counted only once for multiple events within a preferred term or grouped term.
The table summarizes data collected on the CRS Symptom eCRF.
The most severe grade was used for AEs that occurred more than once in an individual subject during the period.

Table 57. Time to Onset and Time to Resolution of Treatment-emergent CRS - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
TIME TO ONSET OF FIRST CRS (DAYS) (A)					
N	54	75	254	308	383
MEAN	4.7	5.7	5.2	5.1	5.2
STANDARD DEVIATION	2.44	2.77	4.65	4.35	4.09
MEDIAN	4.0	6.0	4.0	4.0	5.0
Q1 , Q3	3.0 , 7.0	4.0 , 7.0	3.0 , 7.0	3.0 , 7.0	3.0 , 7.0
MIN , MAX	1 , 10	1 , 17	1 , 63	1 , 63	1 , 63
TIME TO RESOLUTION OF FIRST CRS (DAYS) (B)					
N	53	75	250	303	378
MEAN	4.7	3.8	5.2	5.1	4.9
STANDARD DEVIATION	2.55	2.18	3.47	3.33	3.18
MEDIAN	4.0	3.0	5.0	4.0	4.0
Q1 , Q3	3.0 , 6.0	2.0 , 5.0	2.0 , 7.0	3.0 , 7.0	2.0 , 6.0
MIN , MAX	1 , 14	1 , 10	1 , 17	1 , 17	1 , 17
TIME TO ONSET OF FIRST GRADE >= 3 CRS (DAYS) (A)					
N	1	1	10	11	12
MEAN	11.0	5.0	6.8	7.2	7.0
STANDARD DEVIATION	N.A.	N.A.	2.74	2.89	2.83
MEDIAN	11.0	5.0	6.5	7.0	6.5
Q1 , Q3	11.0 , 11.0	5.0 , 5.0	5.0 , 9.0	5.0 , 9.0	5.0 , 9.0
MIN , MAX	11 , 11	5 , 5	3 , 12	3 , 12	3 , 12
TIME TO RESOLUTION OF FIRST GRADE >= 3 CRS (DAYS) (B)					
N	0	1	8	8	9
MEAN		2.0	6.6	6.6	6.1
STANDARD DEVIATION		N.A.	3.96	3.96	4.01
MEDIAN		2.0	5.5	5.5	5.0
Q1 , Q3		2.0 , 2.0	4.5 , 8.0	4.5 , 8.0	4.0 , 7.0
MIN , MAX		2 , 2	2 , 15	2 , 15	2 , 15

(A) Time to onset was calculated from the latest liso-cel infusion date to the first onset of a CRS event.
(B) Any CRS events stop/start within 7 days (start date-stop date <= 7) were considered in a single episode.
Time to resolution of CRS was defined as the number of days from onset to when the last CRS event of the first episode ends.
Subjects with an unresolved event in the episode were excluded from the summary.

The most common manifestations of CRS included pyrexia (60%), hypotension (22%), hypoxia (11%) tachycardia (10%), chills (8%), headache (8%), nausea (3%), and dyspnoea (2%).

In the TRANSCEND-MCL Cohort, 24 of 88 (27%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. 15 (17%) patients received tocilizumab only, 8 (9%) received tocilizumab and a corticosteroid and 1 (1%) patient received corticosteroids only

Neurological Toxicity

In the R/R MCL Treated Set, iiNT occurred in 30.7% of subjects (vs 24.8% in the R/R LBCL Treated Set) and the majority of events were Grade 1-2 (21.6% vs 16.4%), with no Grade 5 events. SAEs of iiNT were similar between the R/R MCL and the R/R LBCL Treated Sets (12.5% in each). The most common (≥ 5%) iiNTs by NESI Group Term and the median time to onset are reported in the Table 58.

Table 58. Treatment-emergent Investigator-identified Neurological Toxicity by NESI Group Term, Preferred Term and Grade in ≥ 5% of Subjects - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
Encephalopathy -ANY EVENT	23 (26.1)	6 (4.6)	103 (16.9)	126 (18.1)	132 (16.0)
GRADE 1-2	15 (17.0)	3 (2.3)	71 (11.7)	86 (12.4)	89 (10.8)
GRADE 3-4	8 (9.1)	3 (2.3)	32 (5.3)	40 (5.7)	43 (5.2)
GRADE 5	0	0	0	0	0
SAE	9 (10.2)	4 (3.1)	49 (8.1)	58 (8.3)	62 (7.5)
Confusional state	14 (15.9)	2 (1.5)	52 (8.6)	66 (9.5)	68 (8.2)
GRADE 1-2	12 (13.6)	1 (0.8)	43 (7.1)	55 (7.9)	56 (6.8)
GRADE 3-4	2 (2.3)	1 (0.8)	9 (1.5)	11 (1.6)	12 (1.5)
GRADE 5	0	0	0	0	0
SAE	5 (5.7)	2 (1.5)	18 (3.0)	23 (3.3)	25 (3.0)
Encephalopathy	5 (5.7)	1 (0.8)	29 (4.8)	34 (4.9)	35 (4.2)
GRADE 1-2	2 (2.3)	0	13 (2.1)	15 (2.2)	15 (1.8)
GRADE 3-4	3 (3.4)	1 (0.8)	16 (2.6)	19 (2.7)	20 (2.4)
GRADE 5	0	0	0	0	0
SAE	2 (2.3)	0	17 (2.8)	19 (2.7)	19 (2.3)
Tremor -ANY EVENT	6 (6.8)	10 (7.7)	53 (8.7)	59 (8.5)	69 (8.4)
GRADE 1-2	6 (6.8)	10 (7.7)	49 (8.1)	55 (7.9)	65 (7.9)
GRADE 3-4	0	0	4 (0.7)	4 (0.6)	4 (0.5)
GRADE 5	0	0	0	0	0
SAE	0	3 (2.3)	15 (2.5)	15 (2.2)	18 (2.2)
Tremor	6 (6.8)	10 (7.7)	52 (8.6)	58 (8.3)	68 (8.2)
GRADE 1-2	6 (6.8)	10 (7.7)	48 (7.9)	54 (7.8)	64 (7.7)
GRADE 3-4	0	0	4 (0.7)	4 (0.6)	4 (0.5)
GRADE 5	0	0	0	0	0
SAE	0	3 (2.3)	14 (2.3)	14 (2.0)	17 (2.1)
Aphasia -ANY EVENT	5 (5.7)	10 (7.7)	44 (7.2)	49 (7.0)	59 (7.1)
GRADE 1-2	5 (5.7)	8 (6.2)	31 (5.1)	36 (5.2)	44 (5.3)
GRADE 3-4	0	2 (1.5)	13 (2.1)	13 (1.9)	15 (1.8)
GRADE 5	0	0	0	0	0
SAE	1 (1.1)	6 (4.6)	18 (3.0)	19 (2.7)	25 (3.0)
Aphasia	3 (3.4)	9 (6.9)	36 (5.9)	39 (5.6)	48 (5.8)
GRADE 1-2	3 (3.4)	8 (6.2)	25 (4.1)	28 (4.0)	36 (4.4)
GRADE 3-4	0	1 (0.8)	11 (1.8)	11 (1.6)	12 (1.5)
GRADE 5	0	0	0	0	0
SAE	1 (1.1)	5 (3.8)	17 (2.8)	18 (2.6)	23 (2.8)

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
Delirium -ANY EVENT	5 (5.7)	5 (3.8)	29 (4.8)	34 (4.9)	39 (4.7)
GRADE 1-2	3 (3.4)	3 (2.3)	19 (3.1)	22 (3.2)	25 (3.0)
GRADE 3-4	2 (2.3)	2 (1.5)	10 (1.6)	12 (1.7)	14 (1.7)
GRADE 5	0	0	0	0	0
SAE	2 (2.3)	3 (2.3)	13 (2.1)	15 (2.2)	18 (2.2)

NESI group terms were ordered by (1) 8 main NESI groups (Encephalopathy, Delirium, Aphasia, Tremor, Dizziness, Headache, Anxiety, Insomnia), and (2) all the other groups. Within (1) and (2), table was sorted by group term and preferred term in descending order of incidence in the 'Overall Total' column.
A subject was counted only once for multiple events within a preferred term/system organ class.

Table 59. Time to Onset and Time to Resolution of Treatment-emergent iiNT - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
TIME TO ONSET OF FIRST NT (DAYS) (A)					
N	27	21	151	178	199
MEAN	8.4	8.6	10.6	10.2	10.1
STANDARD DEVIATION	5.34	2.56	9.15	8.70	8.28
MEDIAN	8.0	8.0	8.0	8.0	8.0
Q1 , Q3	5.0 , 11.0	7.0 , 9.0	6.0 , 12.0	6.0 , 12.0	6.0 , 11.0
MIN , MAX	1 , 25	4 , 16	1 , 66	1 , 66	1 , 66
TIME TO RESOLUTION OF FIRST NT (DAYS) (B)					
N	26	21	142	168	189
MEAN	11.0	4.5	14.4	13.8	12.8
STANDARD DEVIATION	11.89	3.80	16.98	16.31	15.70
MEDIAN	5.0	3.0	8.0	7.5	7.0
Q1 , Q3	2.0 , 16.0	2.0 , 5.0	4.0 , 17.0	3.0 , 17.0	3.0 , 16.0
MIN , MAX	1 , 45	1 , 17	1 , 89	1 , 89	1 , 89

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL 2L/3L+ LBCL and 2L+ FL Total N = 826
TIME TO ONSET OF FIRST GRADE >= 3 NT (DAYS) (A)					
N	8	4	51	59	63
MEAN	10.0	10.3	11.4	11.2	11.1
STANDARD DEVIATION	7.48	2.22	8.02	7.90	7.66
MEDIAN	8.5	10.0	9.0	9.0	9.0
Q1 , Q3	6.5 , 10.5	8.5, 12.0	7.0 , 14.0	7.0 , 14.0	7.0 , 13.0
MIN , MAX	2 , 27	8 , 13	2 , 44	2 , 44	2 , 44
TIME TO RESOLUTION OF FIRST GRADE >= 3 NT (DAYS) (B)					
N	8	4	44	52	56
MEAN	11.3	5.5	18.2	17.1	16.3
STANDARD DEVIATION	11.74	7.68	18.80	17.98	17.66
MEDIAN	5.5	2.0	10.5	10.0	9.5
Q1 , Q3	2.5 , 19.0	1.5 , 9.5	5.0 , 23.5	5.0 , 21.5	4.0 , 21.0
MIN , MAX	2 , 34	1 , 17	3 , 83	2 , 83	1 , 83

(A) Time to onset was calculated from the liso-cel infusion date to the first onset of a NT event.
(B) Any NT events stop/start within 7 days (start date-stop date <= 7) were considered in a single episode.
Time to resolution of NT was defined as the number of days from onset to when the last NT event of the first episode ends. Subjects with an unresolved event in the episode were excluded from the summary.

The most common neurologic toxicities included encephalopathy (26%), tremor (7%), delirium (6%), aphasia (6%), headache (5%), and dizziness (3%). Seizures (1%) have occurred in patients treated with Breyanzi.

Macrophage Activation Syndrome

There were no MAS events reported in the R/R MCL Treated Set and 4 (0.7%) reported in the R/R LBCL Treated Set.

Infusion Related Reaction (IRR)

The frequency of IRR was similar between the R/R MCL Treated Set (2.3%) and the R/R LBCL Treated Set (1.0%), and all IRR events were mild to moderate (Grade 1-2). There were no Grade ≥3 events reported. There was 1 SAE of IRR reported in the R/R MCL Treated Set, and none in the R/R LBCL Treated Set (see Table 54).

Infections (Grade 3 and Higher)

The rate of Grade ≥ 3 infections and infestations was similar between the R/R MCL and the R/R LBCL Treated Sets, 14.8% vs 12.0%, respectively (see Table 54). The most common Grade ≥ 3 infections and infestations in the R/R MCL Treated Set by HLGT were unspecified pathogen (5.7%) and bacterial and viral (4.5%, each), similar to the R/R LBCL Treated Set. The frequency of Grade 5 infections and infestations was low in both R/R MCL and the R/R LBCL Treated Sets (2.3% vs 1.2%); in the R/R MCL Treated Set, 1 subject died due to COVID-19 pneumonia and 1 due to cryptococcal meningoencephalitis.

The frequency of Grade ≥ 3 post-treatment-emergent period infection and infestation AEs was 7.3% and 5.0% in the R/R MCL and the R/R LBCL Treated Sets, respectively.

Prolonged Cytopenia

The rate of prolonged cytopenia (defined as Grade ≥ 3 cytopenias not resolved by Study Day 29 visit, or Day 35 for BCM-003, based on laboratory results of low hemoglobin, absolute neutrophil count decreased and platelet count decreased) was similar between the R/R MCL and the R/R LBCL Treated Sets (39.8% and 35.7%, respectively). In the R/R MCL Treated Set, the majority of subjects with Grade ≥ 3 decreased hemoglobin, decreased absolute neutrophil count, or decreased platelet count at Day 29 visits (±2 days) had recovered to Grade ≤ 2 by Month 2 (Table 60).

Table 60. Recovery of Prolonged Cytopenia - Liso-cel 3L+ MCL, 2L+ FL, and 2L/3L+ LBCL

	3L+ MCL N = 88	2L+ FL N = 130	2L/3L+ LBCL Total N = 608	3L+ MCL and 2L/3L+ LBCL Total N = 696	3L+ MCL, 2L/3L+ LBCL and 2L+ FL Total N = 826
GRADE >= 3 DECREASED HEMOGLOBIN AT MONTH 1 (A)	4 (4.5)	6 (4.6)	43 (7.1)	47 (6.8)	53 (6.4)
HAD HEMOGLOBIN LAB RESULTS POST MONTH 1 (A)	4 (4.5)	6 (4.6)	34 (5.6)	38 (5.5)	44 (5.3)
RECOVERED TO GRADE <= 2 BY MONTH 2 (B)	4 (4.5)	4 (3.1)	25 (4.1)	29 (4.2)	33 (4.0)
RECOVERED TO GRADE <= 2 BY MONTH 3 (C)	4 (4.5)	6 (4.6)	30 (4.9)	34 (4.9)	40 (4.8)
RECOVERED TO GRADE <= 2 BY EOS	4 (4.5)	6 (4.6)	32 (5.3)	36 (5.2)	42 (5.1)
GRADE >= 3 DECREASED ABSOLUTE NEUTROPHIL COUNT AT MONTH 1 (A)	21 (23.9)	20 (15.4)	131 (21.5)	152 (21.8)	172 (20.8)
HAD ABSOLUTE NEUTROPHIL COUNT LAB RESULTS POST MONTH 1 (A)	21 (23.9)	20 (15.4)	110 (18.1)	131 (18.8)	151 (18.3)
RECOVERED TO GRADE <= 2 BY MONTH 2 (B)	15 (17.0)	17 (13.1)	68 (11.2)	83 (11.9)	100 (12.1)
RECOVERED TO GRADE <= 2 BY MONTH 3 (C)	18 (20.5)	18 (13.8)	95 (15.6)	113 (16.2)	131 (15.9)
RECOVERED TO GRADE <= 2 BY EOS	19 (21.6)	19 (14.6)	105 (17.3)	124 (17.8)	143 (17.3)
GRADE >= 3 DECREASED PLATELET COUNT AT MONTH 1 (A)	28 (31.8)	19 (14.6)	175 (28.8)	203 (29.2)	222 (26.9)
HAD PLATELET LAB RESULTS POST MONTH 1 (A)	27 (30.7)	19 (14.6)	135 (22.2)	162 (23.3)	181 (21.9)
RECOVERED TO GRADE <= 2 BY MONTH 2 (B)	20 (22.7)	10 (7.7)	64 (10.5)	84 (12.1)	94 (11.4)
RECOVERED TO GRADE <= 2 BY MONTH 3 (C)	22 (25.0)	12 (9.2)	95 (15.6)	117 (16.8)	129 (15.6)
RECOVERED TO GRADE <= 2 BY EOS	25 (28.4)	17 (13.1)	110 (18.1)	135 (19.4)	152 (18.4)

Prolonged cytopenia is defined as any grade ≥ 3 lab results of decreased hemoglobin, decreased neutrophil count or decreased platelets at Month 1 Visit.
(A) Month 1 Visit is at Day 35 (+/- 6 days) after liso-cel infusion for BCM-003 and at Day 29 (+/- 2 days) after liso-cel infusion in other studies. Results after the initiation of subsequent anticancer therapy or product retreatment are excluded.
(B) Include subjects who recovered to grade <= 2 after Month 1 through Month 2 (Day 62 (+6) for Study BCM-003 Arm B, and Day 60 [+14] for other studies).
(C) Include subjects who recovered to grade <= 2 after Month 1 through Month 3 (Day 98 (+7) for Study BCM-003 Arm B, and Day 90 [+14] for other studies).

Tumor Lysis Syndrome

The frequency of TLS was similar between the R/R MCL and the R/R LBCL Treated Sets (2.3% vs 0.3%, respectively) (see Table 54). In the R/R MCL Treated Set, TLS occurred in 2 subjects: 1 subject had a Grade 3 event (related to liso-cel/LDC) which was ongoing at time of death from disease progression. Another subject with high tumor burden before infusion (SPD per IRC at 52.02 cm^2) experienced a Grade 5 SAE of TLS (related to liso-cel). After infusion, on Day 10, the subject developed Grade 4 TLS, Grade 4 shock (related to liso-cel), and Grade 2 CRS which later worsened to Grade 4 (related to liso-cel). The subject died on Day 12, due to TLS (Grade 5).

Second Primary Malignancy

Overall, the frequency of SPMs during the treatment-emergent period was 3.4% vs 1.3% in R/R MCL and the R/R LBCL Treated Sets, respectively (see Table 55).

In the treatment-emergent period, 3 out of 88 (3.4%) subjects had ≥ 1 SPM one each of Grade 3 squamous cell carcinoma, Grade 3 acinar cell carcinoma of the pancreas, and Grade 2 basal cell carcinoma. None of them were of hematopoietic origin.

In the post-treatment-emergent period, 14 out of 82 (17.1%) subjects had ≥ 1 SPM. Among those, 2 subjects developed new a hematopoietic malignancy (myelodysplastic syndrome) which was considered related to LDC. The other 12 subjects developed solid tumors, the majority were non-melanomatous

skin cancer. Submitted samples of neoplastic tissue from subjects with SPMs in Study 017001 MCL Cohort were tested for the presence of liso-cel transge. In total, 12 tumor samples from 11 subjects, were submitted for transgene testing by ISH and 8 results were negative for the detection of transgene, 4 were indeterminate due to insufficient RNA quality or no tumor present.

Autoimmune Disorders

There were no incidences of autoimmune disorders in the R/R MCL Treated Set.

Hypogammaglobulinemia

The frequency of hypogammaglobulinemia was similar between the R/R MCL and the R/R LBCL Treated Sets during the treatment-emergent period (6.8% vs 10.7%, respectively) and post-treatment-emergent period (4.9% vs 4.8%, respectively) (see Table 55). All events were low grade (Grade 1-2).

Other 017001 Study specific Adverse Events

GVHD in Subjects with Prior Allogeneic HSCT. In the R/R MCL Treated set, 29 subjects (33.0%) had prior HSCT, where 26 (29.5%) subjects received prior autologous HSCT, and 6 (6.8%) subjects received prior allogeneic HSCT. No AEs of GVHD were reported in the R/R MCL Treated Set in subjects with prior allogeneic HSCT, either in the treatment-emergent period, or in the post-treatment-emergent period.

Subjects with CNS Lymphoma Involvement. In the R/R MCL Treated Set, 7 subjects had secondary CNS lymphoma involvement at baseline and 4 of them received bridging therapy. Any grade iiNT occurred in 3 subjects (42.9%) and Grade 3 iiNT in 1 subject (14.3%, PT confusion) while in subjects with no secondary CNS disease any grade iiNT occurred in 24 subjects (29.6%) and Grade ≥3 in 7 subjects (8.6%).

Cardiac Events. In the R/R MCL Treated Set, any grade TEAE within the SOC of Cardiac disorders occurred in 21 of 88 subjects (23.9%), and Grade ≥ 3 in 6/88 (6.8%). Similarly, in the R/R LBCL Treated Set, any grade cardiac TEAEs occurred in 21.2% of subjects and Grade ≥ 3 in 2.3%.

Overall, in the R/R MCL Treated Set, cardiac TEAEs were mostly low grade (Grade 1-2) rhythm abnormalities, as in the R/R LBCL Treated Set. The majority of cardiac events in R/R MCL resolved within 7 days. Grade ≥ 3 cardiac TEAEs occurred in 2 subjects with no CRS, in 2 subjects before or during CRS, or ≤ 7 days from CRS resolution, and in 2 subjects >7 days after CRS resolution.

A description of the R/R MCL subjects who experienced cardiac TEAEs and their temporal relationship to CRS is provided:

- Five of 21 subjects experienced at least one cardiac TEAE (any grade) without experiencing CRS. Among these, one subject experienced Grade 5 cardio-respiratory arrest in the context of treatment for a pancreatic carcinoma.
- Twelve of 21 subjects developed at least one any grade cardiac TEAE before or during CRS, or ≤ 7 days from CRS resolution. Among these, 2 subjects had Grade ≥ 3 events;
- Four of 21 subjects developed at least one any grade cardiac TEAE with onset date >7 days after CRS resolution. Among these, 2 subjects had Grade ≥ 3 events.

In the post-treatment-emergent period, in the R/R MCL Treated set, any grade AEs in the Cardiac Disorders SOC were experienced by 2 of 82 subjects (2.4%), and Grade ≥ 3 in 2/82 (2.4%).

Extra-nodal disease. A total of 46 of 88 subjects (52.3%) were identified with extra-nodal disease in the Liso-cel Treated Analysis Set. In R/R MCL with extra-nodal disease, the frequency of subjects with Grade 3 or higher TEAEs was 87.0%, versus 86.4% in the R/R MCL Liso-cel Treated Set. The most frequently occurring Grade ≥ 3 TEAEs by SOC were Blood and lymphatic disorders (69.6%), Metabolism

and nutrition disorders (21.7%) and Infection and Infestations (19.6%). The most frequently occurring Grade ≥ 3 TEAEs by PT were neutropenia (47.8%), anemia (39.1%), and thrombocytopenia (21.7%). The most common AESIs in R/R MCL subjects with extra-nodal disease were CRS (67.4%), iiNT (30.4%) and Grade ≥3 infections (19.6%).

Laboratory findings

Haematology

In the R/R MCL Treated Set, changes in hematology laboratory results were consistent with the receipt of anticancer therapy for disease control and LDC prior to liso-cel treatment, followed by the expected recovery. The most common new or worsening haematological abnormalities (all grade) in the R/R MCL Treated set were neutrophil count decreased (77.3%), anemia (55.7%) and white blood cell decreased (53.4%) which were similar to the R/R LBCL Treated Set (79.4%, 51.5%, 59.5%, respectively).

Clinical Chemistry

In the R/R MCL Treated Set, most chemistry parameters remained stable over time. The most frequent Grade 3-4 new or worsening chemistry laboratory abnormality was hyperuricemia in 10.2%, hyponatremia in 8.0%, and hypophosphatemia in 8.0% of subjects. In the R/R LBCL Treated Set the incidence of the same Grade 3-4 new or worsening chemistry laboratory abnormality were 2.0%, 5.3% and 10.4%, respectively.

Coagulation

The overall proportions of subjects with Grade 3-4 new or worsening abnormalities in fibrinogen (decreased) was generally similar between the R/R MCL and the R/R LBCL Treated Set, 2.3% and 7.9%, respectively.

Safety in special populations

Intrinsic Factors

There were no major differences in the frequency of TEAEs and Grade ≥ 3 TEAEs across subgroups (age, sex, ethnicity, race, anticancer treatment of disease control status [yes vs no], and region) in the R/R MCL Treated Set. However, some variability was observed due to the small size of some subgroups (Table 61).

Table 61. Summary of Intrinsic Factors in R/R MCL subjects in Study 017001

Intrinsic Factor	Results
Age	Age (< 65 vs ≥ 65 and < 75 years vs ≥ 75 years): No clear differences (defined as difference of ≥ 20% between subgroups) were observed between subgroups in overall rates of subjects with any TEAEs, Grade ≥ 3 TEAEs, or AESIs. The 3 most frequently reported TEAEs were consistent between the subgroups.
Sex	Sex (male vs female): No clear differences were observed between subgroups in overall rates of subjects with any TEAEs, Grade ≥ 3 TEAEs, or AESIs.
Race	Race (white vs other races vs unknown or missing): No clear differences in rates of overall TEAEs, Grade ≥ 3 TEAEs, or AESIs were observed between subgroups. Because the subgroups other than white were small (for other races and unknown or missing n < 10) differences by PT may have been due to small sample size instead of actual differences between groups.
Ethnicity	The difference between the number of Hispanic (n = 4) and non-Hispanic (n = 81) subjects limits the interpretability of potential differences in safety by ethnicity.
Pre-LDC LDH	Liso-cel related G3-5 TEAEs had higher frequency (> 20%) in LDH ≥ ULN group compared to LDH < ULN group, 61.0% vs 38.3%, respectively. TEAEs, G3-4 TEAEs, G5 TEAEs, and SAEs rates were generally similar.
Pre-LDC SPD	The difference between the number of pre-LDC SPD < 50 cm^2 (n = 73) and pre-LDC SPD ≥ 50 cm^2 (n = 7) subjects limits the interpretability of potential differences in safety by pre-LDC SPD.
Baseline CRP	Overall TEAE, Grade 3-5 TEAE, and SAE rates were generally similar by baseline CRP.
Screening ECOG	Overall TEAE, SAE, Grade 3-4 TEAE, and AESI rates were generally similar by Screening ECOG of 0 and 1.
CrCl	Overall TEAE, SAE, Grade 3-4 TEAE, and AESI rates were generally similar between subjects with CrCL < 60 mL/min and CrCl ≥ 60 mL/min although the limited sample size for the < 60 mL/min subgroup (n = 19) limits the interpretability of differences in safety.
Screening LVEF	The small sample size for the Screening LVEF < 50% subgroup (n = 5) limits the interpretability of differences in safety.
Refractory Status	Overall TEAE, SAE, Grade 3-4 TEAE, and AESI rates were generally similar by Refractory Status.
Systemic Bridging Therapy	Overall TEAE, SAE, Grade 3-4 TEAE, and AESI rates were generally similar in the subgroup that received systemic bridging therapy.
Region	Overall TEAE, SAE, Grade 3-4 TEAE, and AESI rates from North American MCL subjects were generally similar in the LBCL by Region.

Safety to support the Product Information

The approved dose range of liso-cel in the SmPC is 44 to 120 × 10^6 CAR+ T cells. Thus, pooled safety analyses were performed for 779 subjects receiving liso-cel dose in the range of 44 to 120×10^6 CAR+ T cells. These analyses included subjects with R/R MCL (n= 88 from 017001 [MCL cohort], i.e. Liso-cel Treated Analysis Set), 2L LBCL (n= 177), 3L+ LBCL (n= 384) and 2L+ FL (n= 130). ADRs represent all reported TEAEs across all indications and are not restricted to AEs deemed related by the investigator. ADRs from time of infusion in subjects with R/R MCL from Study 017001, who received a dose of liso-cel within the dose range of 44 to 120×10^6 CAR+ T cells, were integrated with data from the approved

SmPC (n= 779). The results of this assessment do not impact heavily on the list of ADRs with, as included changes, a rearrangement of *Hypophosphatemia* and *tumour lysis syndrome* under a new SOC of *Metabolism and nutrition disorder* and the increase in frequency from common to very common for Rush (see final SmPC).

Safety related to drug-drug interactions and other interactions

Liso-cel is a cellular product that is generally administered as a one-time infusion. Being a cellular product, liso-cel is not cleared by the usual mechanisms that apply to small molecules or antibodies. No controlled clinical studies have been performed to directly address drug interactions with liso-cel.

Discontinuation due to adverse events

Given that liso-cel was administered as a single dose for all subjects in Study 017001 and follow-up continued for subjects regardless of AEs, this analysis is not applicable.

Post marketing experience

Liso-cel was approved in the EU for the treatment of adult patients with 3L+ R/R LBCL on 04-Apr-2022. A Type II variation for extension of indication to include 2L LBCL was approved on 28-Apr-2023. Additionally, a Type II variation for extension of indication to include 3L+ FL was approved on 12-Mar-2025. Review of available post-marketing data presented in the Periodic Benefit-Risk Evaluation Report (reporting period 05-Feb-2024 through 04-Aug-2024) did not reveal any significant safety/efficacy concerns that changed the existing benefit-risk profile of liso-cel.

Indirect Comparison with Brexu-cel (Study CA0821138)

Study CA0821138 was a non-interventional MAIC study using indirect treatment comparison methods to estimate the comparative efficacy and safety of liso-cel vs brexu-cel and comparative efficacy of liso-cel vs pirtobrutinib in patients with 3L+ R/R MCL. Population-adjusted relative treatment effects associated with liso-cel in Study 017001 MCL Cohort compared to brexu-cel (ZUMA-2 study) and pirtobrutinib (BRUIN study) were estimated. For the safety outcomes, matching adjusted comparisons between liso-cel and pirtobrutinib were not conducted due to differences in the type of the majority of the AESIs reported for the two medicinal products and differences in the monitoring periods for AESIs. When compared to brexu-cel, the results favored liso-cel over brexu-cel for most safety outcomes, both before and after the adjustment (Table 62).

Table 62. Naive and MAIC-adjusted Relative Treatment Effect Estimates - Safety Outcomes

	Liso-cel vs Brexu-cel OR (95% CI)	
	Naïve (unadjusted)	**MAIC-adjusted**
CRS, any grade	**0.154 (0.060, 0.394)**	**0.123 (0.041, 0.367)**
CRS, Grade ≥ 3	**0.067 (0.008, 0.535)**	0.045 (0.001, 2.541)
Corticosteroid use for CRS management	**0.403 (0.164, 0.987)**	**0.161 (0.027, 0.973)**
Tocilizumab use for CRS management	**0.248 (0.126, 0.488)**	**0.122 (0.041, 0.363)**
Vasopressor use for CRS management	**0.121 (0.026, 0.564)**	0.081 (0.005, 1.470)
iiNT, any grade	**0.257 (0.132, 0.503)**	**0.221 (0.088, 0.556)**
iiNT, Grade ≥ 3	**0.224 (0.092, 0.545)**	**0.134 (0.027, 0.659)**
Corticosteroid use for iiNT management	**0.306 (0.144, 0.648)**	**0.167 (0.046, 0.607)**
Tocilizumab use for iiNT management	**0.032 (0.004, 0.246)**	**0.033 (0.001, 0.869)**
Infections, any grade	**0.429 (0.225, 0.821)**	**0.333 (0.135, 0.818)**
Infections, Grade ≥ 3	**0.339 (0.156, 0.735)**	**0.245 (0.073, 0.826)**
Any prolonged cytopenia	**0.517 (0.281, 0.951)**	**0.212 (0.077, 0.582)**
Any prolonged thrombocytopenia	**0.423 (0.227, 0.790)**	**0.160 (0.052, 0.497)**
Any prolonged neutropenia	**0.346 (0.180, 0.665)**	**0.142 (0.041, 0.496)**

OR < 1 indicates favorable results for liso-cel vs brexu-cel. Statistically significant results are **bolded**.

2.6.1. Discussion on clinical safety

Safety data for liso-cel from the MCL Cohort (3L+ MCL; referred to as the R/R MCL Treated Set) of Study 017001 (n= 88 [DL1S + DL2S]) were presented side-by-side and pooled (n= 826) with safety data for liso-cel in 2L/3L+ LBCL and 2L+ FL. This allowed comparison of the safety profile of liso-cel in R/R MCL population (proposed indication) to the established safety profile of liso-cel in the approved SmPC.

Four subjects received nonconforming products. Although the efficacy and safety data in these 4 subjects are overall in line with those from patients receiving liso-cel (ORR of 50%, CRR of 50%, median DOR and PFS not reached), considering the small sample size, no definite conclusion is possible.

The proportion of subjects who received anticancer therapy for disease control (i.e., bridging therapy) in the R/R MCL Treated Set was similar to that in the R/R LBCL Treated Set (65.9% vs 60.9%, respectively), reflecting a population with high disease burden and rapid disease progression.

The exposure to liso-cel was adequate and in line with EU SmPC recommendations (i.e., 44 to 120 × 10^6 CAR+ T cells). All subjects in the R/R MCL Treated Set were dosed without delay or interruption, except 1 subject where dosing was delayed beyond the specified window of 7 days after the completion of LDC due to an AE of hyperbilirubinemia (Grade 2), which was resolved at the time of liso-cel infusion.

As of the data cut-off (16-May-2024)**, with a median on-study follow-up time of 19.53 months (min, max: 0.4, 72.0) months**, no new safety concerns with liso-cel were identified in subjects with R/R MCL.

In the R/R MCL Treated Set (n= 88), **TEAEs of any grade** occurred in 88 (100%) of subjects. Overall, the types and frequency of the most common TEAEs in ≥ 10% of subjects were consistent between the R/R MCL Liso-cel-treated Analysis Set and the R/R LBCL Treated Set.

Liso-cel-related TEAEs occurred in 77 (87.5%) subjects overall. In the R/R MCL Treated Set, the most frequently occurring liso-cel-related TEAEs were consistent with the R/R LBCL Treated Sets.

Deaths were mainly due to disease progression. 5 (5.7%) subjects died from AEs, versus 23 (3.8%) in the R/R LBCL Treated Set.

Treatment-emergent Grade 5 AEs were reported in 4 (4.5%) subjects with single cases of COVID-19 pneumonia, cryptococcal meningoencephalitis (both assessed as related to liso-cel/LDC), TLS (assessed as related to liso-cel only), and cardio-respiratory arrest (assessed as not related to liso-cel/LDC).

In the R/R MCL Treated Set, 7 (8%) subjects died due to **COVID-19** (1 in the treatment-emergent period and 6 in the post-treatment-emergent period) compared with 9 subjects (1.5%) in the R/R LBCL Treated Set.

COVID-19 could have had an impact on clinical safety/death in the immunocompromised R/R MCL patient population. Nevetheless, considering the limited and heterogeneous evidence available in the literature, differences in follow-up durations across published studies, and the variable timing of data collection relative to the pandemic phases, the number of COVID-19-related deaths reported in the MCL Cohort (7 subjects) as of the data cut-off date (16 May 2024) is consistent with findings in comparable MCL populations (*Leuva et al., Seminars in Oncology, 2022; Tilch et al., HemaSphere, 2022; Vijenthira et al., Blood, 2020*).

The profile of reported **AESIs** in the R/R MCL Liso-cel-treated Analysis Set was consistent with the known profile for R/R LBCL.

Most AESIs were mild to moderate in severity (Grade 1-2), considered to be liso-cel-related by the investigator, and manageable with protocol-specified guidelines and/or local standard of care. No subjects had AESIs of MAS or autoimmune disorders.

The frequency of all-grade **CRS** was higher in the R/R MCL Liso-cel-treated Analysis Set (61.4%) compared to the R/R LBCL Treated Set (41.8%), attributed primarily to disease biology of MCL (*Yang et al. Blood 2024; Lionel et al. Blood Adv. 2024; Hay et al. Blood 2017*). This difference was largely due to the higher incidence of Grade 1-2 events (60.2%) within the R/R MCL population compared to the R/R LBCL population (40.1%), with no difference in Grade 3-4 events (1.1% vs. 1.6%, respectively). The increased incidence of Grade 1 CRS in the R/R MCL Treated Set - for which only supportive care (e.g., paracetamol) is typically required - may account for the similar rates of tocilizumab and corticosteroid use observed between the R/R MCL and R/R LBCL Treated Sets, as these treatments are primarily used for managing higher-grade CRS.

Neurological Toxicity (iiNT) occurred in 27 (30.7%) subjects with R/R MCL (vs 24.8% in the R/R LBCL Treated Set). The percentage of subjects who received tocilizumab and/or corticosteroids for iiNT was similar in the R/R MCL Treated Set and the R/R LBCL Treated Set. ICANS-specific assessments were not implemented in the MCL Cohort of Study 017001. Nevertheless, the SmPC already includes relevant information on ICANS as an adverse drug reaction (ADR), including ICANS grading and the Immune Effector Cell-Associated Encephalopathy (ICE) score, which is considered sufficient for the characterization and management of this risk.

Infections (Grade 3 and higher). The rate of Grade ≥ 3 infections and infestations was similar between the R/R MCL and the R/R LBCL Treated Sets, 14.8% vs 12.0%, respectively. The frequency of Grade 5 infections and infestations was low (2.3%). The frequency of Grade ≥ 3 post-treatment-emergent period infection and infestation AEs was 7.3% and 5.0% in the R/R MCL and the R/R LBCL Treated Sets, respectively. The

findings observed in the MCL Cohort are consistent with the established infectious risk profile of patients who have received multiple prior lines of therapy, including Bruton tyrosine kinase inhibitors (BTKi) such as ibrutinib. These data are also aligned with the findings reported by Varughese et al. (*Clin Infect Dis. 2018*), in which 11.4% of patients with lymphoid malignancies treated with ibrutinib experienced serious infections - defined as those requiring hospitalization or parenteral antimicrobial therapy from the initiation of ibrutinib treatment until 30 days post-discontinuation - including 4.2% who developed invasive fungal infections (IFIs).

Infections are an important identified risk associated with liso-cel. Section 4.4 of the current SmPC already provides guidance on prophylaxis, monitoring, and management of infections. Furthermore, infections will continue to be closely monitored through ongoing pharmacovigilance activities.

Prolonged Cytopenia. The rate of prolonged cytopenia, defined as Grade ≥ 3 cytopenia at the Day 29 (± 2 days) visit based on local laboratory assessments of neutropenia, thrombocytopenia, or anaemia, was similar between the R/R MCL and the R/R LBCL Treated Sets (39.8% and 35.7%, respectively). Of the 88 total patients treated in the MCL Cohort, Grade 3-4 thrombocytopenia (n= 28, 31.8%), Grade 3-4 neutropenia (n= 21, 23.9%) or Grade 3-4 anaemia (n= 4, 4.5%) had recovered to Grade ≤ 2 by Month 2.

The frequency of **hypogammaglobulinemia** was similar between the R/R MCL and the R/R LBCL Treated Sets during the treatment-emergent period (6.8% vs 10.7%, respectively) and post-treatment-emergent period (4.9% vs 4.8%, respectively).

Similar rates of **Second Primary Malignancies (SPM**) were observed in the treatment-emergent period between the R/R MCL Liso-cel-treated Analysis Set and R/R LBCL Treated Set (3.4% and 1.3%, respectively). In the R/R MCL Liso-cel-treated Analysis Set, 3 SPMs were reported in 3 subjects. None of these SPMs were considered related to liso-cel.

During the post-treatment-emergent period, the frequency of SPMs was higher in the R/R MCL Liso-cel-treated Analysis Set compared with the R/R LBCL Treated Set (17.1% vs 5.2%). In the R/R MCL Liso-cel-treated Analysis Set, 14 SPMs were reported in 14 subjects. None of the SPMs were considered related to liso-cel. MCL subjects have an increased risk of SPMs, particularly if treated with R-bendamustine, immunosuppressants or BTKi (i.e., skin cancers) (*Starace et al. Cancers 2024*). The intensive treatments needed for long-term remissions are a concern (*Abalo et al. Eur J Cancer. 2023),* and many studies highlight the growing recognition of SPMs in MCL, reinforcing the necessity for continuous vigilance in these patients (*Barista et al. Ann Oncol 2002*; *Shah et al, Anticancer Res. 2015; Rock et al. Advances in Radiation Oncology 2022; Bhanushali et al. Blood 2024; Zanelli et al. Cancers 2023*).

It is considered that comprehensive clinical and diagnostic evaluations already enable early assessment of patients' eligibility for treatment with Breyanzi. While current clinical practice tends to prioritize timely transplant or CAR-T cell therapy procedures, adjustments may be required to account for infections or other unresolved serious adverse events that, in the judgement of the treating physician, may increase patient risk. This consideration is reflected in section 4.4 of the SmPC.

Additionally, section 4.4 of the current SmPC recommends long-term, lifelong monitoring for secondary malignancies following treatment with Breyanzi. Further characterisation and monitoring SPMs in patients with MCL will continue through the ongoing GC-LTFU-001 long-term follow-up study and the BCM-005 post-authorisation safety study (PASS).

Cardiac Events. In the R/R MCL Treated Set, any grade TEAE within the SOC of Cardiac disorders occurred in 21 of 88 subjects (23.9%), and Grade ≥ 3 in 6/88 (6.8%). Similarly, in the R/R LBCL Treated Set, any grade cardiac TEAEs occurred in 21.2% of subjects and Grade ≥ 3 in 2.3%. Overall, cardiac TEAEs were mostly low grade (Grade 1-2), rhythm abnormalities as in the R/R LBCL Treated Set, and the majority of cardiac events resolved within 7 days. In the post-treatment-emergent period, any grade AEs

in the Cardiac Disorders SOC were experienced by 2 of 82 MCL subjects (2.4%), and Grade ≥ 3 in 2/82 (2.4%). Cardiovascular complications, likely associated with cytokine release syndrome (CRS) and systemic inflammation, have been reported to occur with CAR-T (*Camilli et al. Cardio-Oncology 2024; Gill J. Current Cardiology Reviews, 2023*). It is noteworthy that all subjects in the MCL Cohort had received prior therapies with known or potential cardiotoxicity, including Bruton tyrosine kinase (BTK) inhibitors. Furthermore, section 4.4 of the current SmPC (*Special warnings and precautions for use*) already advises that patients who develop CRS should be closely monitored for cardiac and other organ function until resolution of symptoms. Nevertheless, the MAH acknowledges the clinical importance of a potential association between CRS and cardiac events and remains committed to continuous pharmacovigilance. Post-marketing data on cardiac events in patients with R/R MCL treated with liso-cel will continue to be monitored and will be included in forthcoming Periodic Safety Update Reports (PSURs).

In general, safety results in the extra-nodal disease subgroup were consistent with those of the overall population, but a definitive conclusion cannot be drawn considering the limitations in the adjudication of extra-nodal disease.

No major differences were observed in the frequency of TEAEs and Grade ≥ 3 TEAEs across other subgroups (age, sex, ethnicity, race, anticancer treatment of disease control status [yes vs no], and region). Some variability was noted, which may be attributed to the small sample size of some subgroups. No clear age-related differences in the frequency of TEAEs or AESIs were observed.

Moreover, considering that surface expression of EGFRt could serve as a target for selective depletion of chimeric antigen receptor (CAR) T cells using anti-EGFR medical products such as cetuximab as a strategy to mitigate severe adverse events associated with CAR T cells, an update of the clinical experience so far has been provided. To date, no subjects have received treatment with an anti-EGFR antibody for any of the currently approved indications in the European Union (EU), either in the parent studies or in the GC-LTFU-001 long-term follow-up study.

Product Information. Pooled safety analyses were performed for 779 subjects receiving liso-cel dose in the range of 44 to 120 × 10^6 CAR+ T cells. These analyses included subjects with R/R MCL (n= 88 from 017001 [MCL cohort], i.e. Liso-cel Treated Analysis Set), 2L LBCL (n= 177), 3L+ LBCL (n= 384) and 2L+ FL (n= 130). ADRs represent all reported TEAEs across all indications and are not restricted to AEs deemed related by the investigator. Given the consistency between the safety profiles of R/R MCL and 2L/3L+ LBCL, the inclusion of the R/R MCL dataset in the Product Information is justified. This approach aligns with practices for other CAR-T products and supports a more comprehensive safety overview.

Furthermore, the MAH commits to collect safety information on the mantle cell lymphoma patients which will be included in the ongoing post-authorization safety study (PASS) JCAR017-BCM-005 through the necessary adaptation of the protocol (in the RMP) to be submitted for assessment to the Agency within 2 months from receiving the commission decision on the current extension of indication.

2.6.2. Conclusions on clinical safety

Safety data for the R/R MCL Liso-cel-treated Analysis Set from Study 017001 were consistent with the known liso-cel safety profile for R/R LBCL Treated Set. With a median follow up of 19.53 months (min, max: 0.4, 72.0) months, no new safety concerns or new types of clinically important events with liso-cel were identified in subjects with R/R MCL. However, while this period is enough to identify the earlier and immediate AEs, there are potential risks for which conclusive data could not be obtained due to the limited sample size and a limited follow-up time, especially in terms of long-term safety. Long-term safety data for liso-cel in the mantle cell lymphoma (MCL) indication are being collected in Study GC-LTFU-001 and the ongoing post-authorization safety study (PASS) JCAR017-BCM-005. Safety concerns remain unchanged.

2.6.3. 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.

2.7. Risk management plan

The MAH submitted an updated RMP version (v 9.1) with this application.

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

The PRAC considered that the risk management plan version 9.1 is acceptable.

The CAT-CHMP endorsed the Risk Management Plan version 9.1 with the following content:

Safety concerns

Important identified risks	Cytokine release syndrome
	Neurologic toxicity including ICANS
	Infections
	Hypogammaglobulinaemia
	Macrophage activation syndrome/haemophagocytic lymphohistiocytosis
	Tumour lysis syndrome
	Cytopenia, including bone marrow failure
	Secondary malignancy of T-cell origin
Important potential risks	Autoimmune disorders
	Aggravation of graft versus host disease
	Secondary malignancies (except secondary malignancy of T-cell origin)
	Generation of replication competent lentivirus
	Immunogenicity
	Transmission of infectious agents
	Reduced viability of liso-cel due to inappropriate product handling
Missing information	Impact on pregnancy and lactation
	Long-term safety
	Safety in patients < 18 years old
	Safety in patients ≥ 75 years

Pharmacovigilance plan

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
PASS (JCAR017-BCM-005) / Ongoing	Primary Objective: To characterise the incidence and severity of selected ADRs, as outlined in the SmPC, in patients treated with liso-cel in the postmarketing setting, and to monitor for potential clinically important AEs that have not yet been identified as part of the liso-cel safety profile. Secondary Objectives: To assess long-term effectiveness in patients treated with liso-cel in the postmarketing setting. To assess the liso-cel safety and effectiveness profile in certain subgroups including but not limited to: 1) By large B-cell lymphoma subtypes (eg, FL3B, PMBCL, DLBCL not otherwise specified, high grade B-cell lymphoma). 2) According to geographical regions (eg, Europe). 3) Subjects aged ≥ 75 years. 4) Subjects with comorbid conditions (eg, renal impairment, reduced cardiac function). 5) Subjects with secondary CNS involvement. 6) Subjects with ECOG performance score ≥ 2. 7) By possible prognostic factors (eg, high-risk IPI). 8) Subjects previously exposed to anti-CD19 therapy. 9) Subjects with low pre-leukapheresis absolute lymphocyte count (< 0.3×10^9/L).	CRS/MAS[a]/HLH[a] NT including ICANS[b] Infections Hypogammaglobulinaemia TLS Cytopenia, including bone marrow failure Secondary malignancy of T-cell origin Secondary malignancies (except secondary malignancy of T-cell origin) Impact on pregnancy and lactation (for pregnancy events) Long-term safety Aggravation of GvHD[a] Safety in patients ≥ 75 years	Protocol Submission to EMA Date of protocol approval by PRAC Start of data collection[c] Safety reports[d] Interim reports[e] Date of Study Completion[f] Date of Final Study Report Submission to EMA	14-Apr-2022 01-Dec-2022 Q1 2023 Safety reports every 6 months (eg, aligned with the reporting period of the PSURs); additional reports every 3 months if a new safety concern is identified At Year 5, 10, and 15 or when last patient is out of the registry-based study Q4 2042 Q4 2043

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
	10) Subjects treated with out-of-specification product.			
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
LTFU study (GC-LTFU-001)/ Ongoing	Long-term follow-up of safety and efficacy for all paediatric and adult subjects exposed do a GM T-cell therapy in Bristol-Myers Squibb sponsored, or Bristol-Myers Squibb alliance partner sponsored, clinical trials in accordance with Health Authorities' guidance for long-term (up to 15 years) follow-up of subjects treated with gene therapy products.	Infections Cytopenia, including bone marrow failure Autoimmune disorders Secondary malignancy of T-cell origin Secondary malignancies (except secondary malignancy of T-cell origin) Impact on pregnancy and lactation Long-term safety Safety in patients < 18 years old Generation of replication competent lentivirus	Subjects to be followed up for 15 years. Interim reports (5 and 10 years from FSFV [Jul 2018]). LSLV Final database lock Final report of GC-LTFU-001 follow-up of 3L+ large B-cell lymphoma liso-cel treated subjects Safety data will be reported in PSURs.	 Q3 2023 and Q3 2028 Estimated Q3 2038 Q3 2038 Q3 2039 Submitted in accordance with the EURD list
Non-interventional cohort study of patients treated with liso-cel (lisocabtagene maraleucel) for relapsed/refractory follicular lymphoma in the postmarketing setting (CA082-1175) / Ongoing	To characterize the incidence and severity of selected AEs, including secondary malignancy, and to assess the long-term effectiveness in patients receiving liso-cel to treat R/R FL.	CRS/MAS[a]/HLH[a] NT including ICANS[b] Infections Hypogammaglobulinaemia TLS Cytopenia, including bone marrow failure Secondary malignancy of T-cell origin Secondary malignancies (except secondary	Start of data collection Progress updates Interim reports	31-Aug-2024 corresponds to the date from which data extraction starts. Aligned with the reporting period of the PSURs At Year 5 and 10

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
		malignancy of T-cell origin) Impact on pregnancy and lactation (for pregnancy events) Long-term safety Aggravation of GvHD[a] Safety in patients ≥ 75 years	Date of Study Completion	End of Q1 2044 (Study completion 15 years after reaching the defined patient number, no further data will be included in the study analyses.)
			Date of Final Study Report Submission to EMA	Q4 2045
Transgene assay service testing of secondary malignancies with insertion site analysis as applicable	Tumour tissue sample testing from patients that develop a secondary malignancy	Secondary malignancy of T-cell origin Secondary malignancies (except secondary malignancy of T-cell origin)[g]	Safety data will be reported in PSURs.	Submitted in accordance with the EURD list.
			European Commission decision + 5 years	Q2 2026
			European Commission decision + 10 years	Q2 2031
			European Commission decision + 15 years	Q2 2036

[a] Included under the category of Other AEs considered related to liso-cel treatment in Study BCM-005.

[b] NT is a primary endpoint in Study BCM-005, which comprises symptoms of NT, including cerebral oedema.

[c] Based on the European Commission decision and protocol approval timeline. As the data collection in the EBMT Registry is independent of this study (secondary use of data), the start of data collection corresponds to the date from which data extraction starts. First data extraction for Study BCM-005 will take place 3 months after protocol approved by EMA.

[d] 6-month safety reports will be provided with the PSUR submission (PSUR single assessment [PSUSA]) as determined by the EURD list.

[e] Interim reports will be prepared at year 5, 10, and 15 after EC decision date or when last patient is out of the registry-based study.

[f] Fifteen years after reaching the defined patient number, no further data will be included in the study analyses.

[g] Only reported secondary malignancies where insertional oncogenesis is suspected and a sample is available

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Cytokine release syndrome	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4, PL Sections 2 and 3 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** 11) Educational programme for HCPs and patients 12) Controlled Distribution Programme	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)
Neurologic toxicity including ICANS	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 and 4.7, PL Sections 2 and 3 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** 13) Educational programme for HCPs and patients 14) Controlled Distribution Programme	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)
Infections	**Routine risk minimisation measures:** SmPC Section 4.4, PL Section 2 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175) LTFU study (GC-LTFU-001)
Hypogammaglobulinaemia	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		US registry study (CA082-1175)
Macrophage activation syndrome/haemophagocytic lymphohistiocytosis	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management discussed SmPC Section 4.8 - histiocytosis haematophagic listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175), considered as part of the spectrum of CRS.
Tumour lysis syndrome	**Routine risk minimisation measures:** SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)
Cytopenia, including bone marrow failure	**Routine risk minimisation measures:** SmPC Section 4.4, PL Section 2 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175) LTFU study (GC-LTFU-001)
Secondary malignancy of T-cell origin	**Routine risk minimisation measures:** SmPC Section 4.4, PL Section 2 - warnings, advice and management SmPC Section 4.8, PL Section 4 - listed as an ADR **Additional risk minimisation measures:** Educational programme for HCPs	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable
Important Potential Risks		
Autoimmune disorders	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001)
Aggravation of GvHD	**Routine risk minimisation measures:** SmPC Section 4.4, PL Section 2 - warnings, advice and management **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Included under the category of Other AEs considered related to liso-cel treatment in PASS (JCAR017-BCM-005) and US registry study (CA082-1175)
Secondary malignancies (except secondary malignancy of T-cell origin)	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175) LTFU study (GC-LTFU-001)
Generation of replication competent lentivirus	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		reactions reporting and signal detection: None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001).
Immunogenicity	**Routine risk minimisation measures:** SmPC Section 4.2 and PL Section 3 - premedication with paracetamol and diphenhydramine or another H1-antihistamine SmPC Section 4.8 - listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None.
Transmission of infectious agents	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 (Risk of transmission of infectious agents exists. Guidance on monitoring patients for signs and symptoms of infections), and 6.6, PL Section 2 and Labelling Section 10 - handling instructions	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Reduced viability of liso-cel due to inappropriate product handling	**Routine risk minimisation measures:** SmPC Sections 4.2, 6.3, 6.4, 6.5 and 6.6, PL Section 5 and Labelling Section 9 - handling instructions	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: 15) Educational programme for HCPs 16) Controlled Distribution Programme	**Additional pharmacovigilance activities:** None.
Missing Information		
Impact on pregnancy and lactation	**Routine risk minimisation measures:** SmPC Section 4.6, PL Section 2- warnings and advice	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) and US registry study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		(CA082-1175) for pregnancy events LTFU study (GC-LTFU-001).
Long-term safety	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175) LTFU study (GC-LTFU-001)
Safety in patients < 18 years old	**Routine risk minimisation measures:** SmPC Section 4.2, PL Section 2 - warnings and advice	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001).
Safety in patients ≥ 75 years	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI for editorial purposes and in addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Iceland

2.8.1. 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:

- the readability of the PL (QRD template) of Breyanzi was assessed during the review of the initial MAA
- the new indication in adults foresees the same route of administration and has a similar safety profile as the previously approved indication (i.e., key safety messages for the existing and new applied for indication are essentially the same).
- Breyanzi is administered by HCP. The instructions for preparation, administration, storage and disposal that are currently reflected in the approved PL were also successfully tested as part of the user consultation performed for the initial MAA and remain unchanged.
- the general design and layout of the proposed PL have not changed compared to the tested one.
- the modifications now proposed in the PL (i.e., those relevant to the new indication) do not represent major changes

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

3.1.2. Available therapies and unmet medical need

According to the current ESMO guidelines (M. Dreyling et al, Annals of Oncology 2017), covalent Bruton-tyrosine kinase inhibitors (BTKis) are the preferred option after failure of 1L treatment (immunochemotherapy, ASCT followed by rituximab). In particular, ibrutinib has been shown to improve outcomes in R/R MCL (Rule S et al, Br J Haematol 2017), but the occurrence of resistance or intolerance limits the long-term benefit with covalent BTKis.

There is no single standard-of-care for R/R MCL in the post-BTKi setting and the optimal approach/sequence to treat R/R MCL is yet to be defined. Treatment choice is further complicated by the lack of data comparing the available treatment options in randomized controlled trials. Treatment choice in R/R MCL is guided by age, performance status, comorbidities, and prior therapy. It is noteworthy that temsirolimus, lenalidomide and bortezomib were all licensed before covalent BTKis, hence limited data are available on their efficacy in the post-BTKi setting, especially for lenalidomide and bortezomib. Chemoimmunotherapy regimens (rituximab, bendamustine ± cytarabine) are additional options that have been associated with high response rates (up to 83%) but their use is often limited by the associated toxicity, often resulting in dose reduction/discontinuation.

Recently, brexucabtagene autoleucel (brexu-cel, autologous CD19-directed CAR T-cell therapy) has been approved in the EU under conditional approval (CMA) for the treatment of patients with R/R MCL after ≥2 prior lines of treatment, including BTKi and pirtobrutinib (a non-covalent BTKi) has been approved in the EU under conditional approval (CMA) for the treatment of patients with R/R MCL who have been previously treated with a BTKi. In both cases, the CMA was based on results from single-arm trials. As also highlighted by the systematic literature review submitted by the MAH, the ORR for the existing non-

CAR-T therapies ranged between 27% and 83% (CRR 9.1-60%) yet the impact on survival was limited, with median OS ranging between 3.6 months and 14 months.

In the single-arm ZUMA-2 study, treatment with the anti-CD19 CAR T cell brexu-cel resulted in high rates of deep and durable responses (ORR 91% (95% CI, 81.8 to 96.7), CRR 68% (95% CI, 55.2 to 78.5), median DOR 28.2 (95% CI 13.5, 47.1) months) (wang et al, 2022), yet non-negligible toxicity was also observed (Grade ≥ ≥3 AEs 98.5%; Grade ≥ 3 CRS 13%, Grade ≥ 3 CART-related encephalopathy syndrome 32%, Grade ≥3 infections 30%).

Overall, subjects with R/R MCL in relapse or refractory after 2 or more lines of therapy, including a covalent BTKi treatment, have limited therapeutic options and generally unsatisfying outcomes. An unmet medical need for effective and safe alternatives can be recognised.

3.1.3. Main clinical studies

Study 017001 is an open-label, multicentre, multicohort, seamless design, Phase 1 study to determine the safety, antitumor activity, and PK of liso-cel in adult subjects with R/R B-cell NHL; the Mantle Cell Lymphoma (MCL) cohort included subjects with R/R MCL who had received ≥ 2 prior lines of systemic therapy, including an alkylating agent, a BTKi, and rituximab (or other CD20-targeted agents).

The target dose of liso-cel used for MCL is consistent with the current posology recommendations in the Breyanzi SmPC for existing indications (i.e. 100 × 10^6 CAR+ viable T cells with a target 1:1 ratio of the CD4+ and CD8+ T cell components, within the acceptability range 44 to 120 × 10^6 CAR+ viable T cells).

The primary endpoint of this study was ORR by IRC according to the 2014 Lugano criteria; CRR by IRC was the key secondary endpoint.

A total of 105 subjects were screened for the MCL cohort; the PAS included a total of 75 patients, corresponding to 72% of the Leukapheresed set (ITT; n=104 subjects).

3.2. Favourable effects

Liso- cell showed consistent efficacy results in the pre-specified final analyses (data cut date 16 May-2024, median follow up of 16.10 months; ORR in the Leukapheresed set (n=104): 70.2% (95% CI: 60.4, 78.8), CRR Per Investigator assessment: 61.5% (95% CI: 51.5%, 70.9%), in the post-hoc defined "Efficacy Set" (n=81), ORR: 82.7% (95% CI: 72.7, 90.2), CRR: 71.6%, (95%CI 60.5%, 81.1%) and in subgroup analyses, including patients aged ≥75 years (N=15) and subjects with high risk factors such as refractoriness to their last therapy, Ki67≥30%, mutated TP53, blastoid morphology and high sMIPI score.

Treatment with liso-cel also resulted in durable responses: in the Leukapheresed set (mDoR 15.2 months, 95%CI 7.0, 24.0), in the analysis by Investigator assessment (mDoR 11.3 months, 95%CI 5.7, 23.3) and in the post-hoc defined "Efficacy Set" (mDoR 11.5 months, 95%CI 6.2, 24.0).

Results from the primary (inferential) analysis from the MCL cohort of study 017001 (data cut date 19 Jan 2023, median follow up of 16.10 months) were overall consistent with those at the time of the final analysis.

3.3. Uncertainties and limitations about favourable effects

- The evidence supporting the efficacy of liso-cel in the target population comes from one single uncontrolled, open-label study, which limited the interpretation of time-to-event endpoints. Significant and clinically relevant improvements in terms of PFS/OS have been historically accepted as adequate basis to inform B/R decisions in NHLs, yet the interpretation of time-to-

event endpoints in the absence of controls is hampered by the difficulties in disentangling the impact of the intervention from the effect of heterogeneity in tumour growth rates.

- The sample size was too limited to adequately characterize the efficacy of liso-cel in clinically relevant subgroups
- All subjects in the MCL cohort of study 017001 were screened at 14 sites in the US. Although the substantial uniformity in terms of guidelines and approved treatments between US and EU at the time study 017001 was conducted is acknowledged, uncertainties on results generalizability to the EU setting remain, due to possible differences in treatment access or positioning (e.g. with respect to ASCT/alloHSCT). The MAH agreed on amending the ongoing PASS JCAR017-BCM-005 study to include the collection of data on EU subjects with R/R MCL treated with liso-cel.

3.4. Unfavourable effects

The unfavorable effects with liso-cel are the generally known identified risks, i.e., CRS, neurotoxicity and prolonged cytopenias.

The most common **adverse reactions** of any grade were **CRS** (61.4%), **neutropenia** (59.1%), and **anaemia** (44.3%) fatigue (35%), thrombocytopenia (30%), and headache (23%).

The most common **serious adverse reactions** were **CRS** (23.9%), **confusional state** (5.7%), and **pyrexia** (3.4%) mental status changes (2%), encephalopathy (2%), upper respiratory tract infection (2%), and pleural effusion (2%).

The most common **Grade 3 or higher adverse reactions** included **neutropenia** (55.7%), **anaemia** (37.5%), and **thrombocytopenia** (25.0%), hypophosphataemia (9%), and leukopenia (7%).

CRS occurred in **61.4%** of patients, **1.1% of whom experienced Grade 3 or 4 CRS** (no fatal events). The median time to CRS onset from the time of liso-cel infusion was 4 days (range: 1 to 10 days) with a median time to resolution of 4 days (range: 1 to 14 days). The most common manifestations of CRS included pyrexia (60%), hypotension (22%), hypoxia (11%), tachycardia (10%), chills (8%), headache (8%), nausea (3%), and dyspnea (2%). In the TRANSCEND-MCL Cohort, 24 of 88 (27%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi.

iiNT occurred in **30.7%** of patients receiving Breyanzi, including **Grade 3 or 4 in 9%** of patients (no fatal events). The most common neurologic toxicities included encephalopathy (26.1%), tremor (6.8%), and aphasia and delirium (5.7%, each). Seizures (1%) have occurred in patients treated with Breyanzi. The median time to onset was 8 days (range: 1 to 25 days). Among the 27 subjects with first onset iiNT, 26 resolved (96.3%); the median time to resolution was 5 days (range: 1 to 45 days).

Grade 3 or higher cytopenias, present at Day 29 following Breyanzi administration, occurred in **39.8%** of patients. Of the 88 total patients treated in the MCL Cohort, Grade 3-4 thrombocytopenia (n= 28, 31.8%), Grade 3-4 neutropenia (n= 21, 23.9%) or Grade 3-4 anaemia (n= 4, 4.5%) recovered to Grade ≤ 2 by Month 2.

Grade 3 infections occurred in 14.8% of patients.

3.5. Uncertainties and limitations about unfavourable effects

The safety database included 88 R/R MCL patients treated with liso-cel in pivotal Study 017001 (TRANSCEND NHL-001). Generally, the spectrum of the unfavourable effects of liso-cel is known, and currently no major additional issues seem to arise. The safety profile of liso-cel in the intended target population appears manageable, and no new safety concerns have been identified.

With a median follow up of 19.53 months (min, max: 0.4, 72.0) months, no new safety concerns with liso-cel were identified in subjects in the R/R MCL Treated Set. However, while this period would be enough to identify the earlier and immediate AEs, there are some potential risks for which conclusive data could not be obtained due to the limited sample size and limited follow-up time, including the long-term safety profile. The MAH agreed to collect further long-term safety data in R/R MCL within the ongoing registry-based PASS JCAR017-BCM-005 and in Study GC-LTFU-001.

3.6. Effects Table

Table 63. Effects Table for Liso-cel for the Treatment of Adult Patients with R/R MCL after 2 or More Lines of Systemic Therapy, including a BTKi (Study 017001 MCL Cohort) (Data cut-off 16 May-2024).

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects					
Overall Response Rate	Best Overall Response(CR or PR) per IRC based on the Lugano classification	% (n)	Efficacy Set: 82.7% (95% CI%=72.7, 90.2) (n=81) ITT Set: 70.2% (95% CI=60.4, 78.8) (n=104)	Unc: Single arm studySoE: consistent results across primary and sensitivity analyses, as well as secondary endpoints	Study 017001
Duration of response	Median Time from first response (CR or PR) to PD or death from any cause (whichever occurs first) per IRC	Months	Efficacy Set (n=81): 11.5 (95%CI 6.2-24) ITT Set (n=104: 15.2 (95% CI: 7.0, 24.0)		
Unfavourable Effects					
CRS	Cytokine-release syndrome	N (%)	54/88 (61.4%)	Unc: Single-arm study Limited sample size Limited follow-up for long-term evaluations	Study 017001
iiNT	Investigator identified neuro-toxicity	N (%)	27/88 (30.7%)		
Prolonged cytopenia	≥ Grade 3	N (%)	35/88 (39.8%)		
Infections	≥ Grade 3	N (%)	13/88 (14.8%)		
SPM (treatment emergent period)	Any grade	N (%)	3/88 (3.4%)		
SPM (post-treatment emergent period)	Any grade		14/88 (17.1%)		
Hypogammaglobulinaemia		N (%)	6/88 (6.8%)		

Abbreviation: SPM= secondary primary malignancies, CRS = cytokine release syndrome, iiNT = investigator-identified neurologic toxicity.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

MCL is an aggressive form of NHL that is currently incurable with conventional treatment options. MCL is characterised by a relapsing/remitting disease course, with increasing resistance to treatment with each relapse. Despite novel medicinal products have been approved (e.g., the non-covalent BTKi pirtobrutinib and the anti-CD19 CAR T cell therapy brexu-cel), the life-expectancy for patients with R/R MCL after at least 2 prior lines of therapy which included a BTKi is still reduced compared to the general population, and the unmet need for additional safe and effective treatment options can be recognised.

Results from the MCL cohort of pivotal study 017001 showed that treatment with liso-cel in a post-BTKi setting of R/R MCL was associated with a clinically relevant antitumoral effect, as highlighted by the high rates of ORR and CRR (a pre-requisite to experience prolonged disease control) in patients intended to be treated with liso-cel (70.2% and 61.5%, respectively). Responses with liso-cel were rapidly induced (mTTR 0.95 months) and a subgroup of patients in complete remission was able to achieve a long-lasting disease control (24-month DOR rate 44.8%), which is uncommon with conventional treatments in such an advanced setting of relapse.

The unfavourable effects observed with liso-cel were generally limited to the known identified risks with CARTs, including CRS, neurotoxicity and prolonged cytopenias. The low rates of severe CAR-T-related toxicity compared favourably with those previously observed in R/R MCL, although the limits of the uncontrolled study design hampered any reliable comparison across different studies, especially when the clinical heterogeneity of MCL is taken into consideration.

3.7.2. Balance of benefits and risks

Based on the available data, the overall B/R of liso-cel in the claimed indication is considered favourable. The clinically relevant rates of deep and durable responses observed in an advanced setting of R/R MCL balance the known risks associated to anti-CD19 CAR T cell therapy, especially considering the limited occurrence of severe CRS and iiNT events.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Breyanzi is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CAT-CHMP considers the following group of variations acceptable and therefore recommends by consensus the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
B.II.d.1.e	B.II.d.1.e Change outside the approved specifications limits range	Variation type II	

C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

A grouped application comprised of two Type II variations, as follows:

- Type II (C.I.6): Extension of indication to include the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor for BREYANZI, based on results from the pivotal Study 017001 MCL Cohort (TRANSCEND-NHL-001); this is a Phase 1, Multicenter, Open-Label Study of JCAR017, CD19-targeted Chimeric Antigen Receptor (CAR) T Cells, for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL). As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package leaflet is updated in accordance. Version 9.1 of the RMP was also submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to the Package Leaflet.
- Type II (B.II.d.1.e): Change outside the approved specifications limits range

The group of variations leads to amendments to the annex(es) I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

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

Similarity with authorised orphan medicinal products

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

5. EPAR changes

The EPAR will be updated following the Commission Decision for this group of variations. In particular, the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion "Breyanzi-H-C-4731- EMA/VR/0000265024"