



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 January 2025
EMA/72407/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Breyanzi

International non-proprietary name: Lisocabtagene maraleucel /
Lisocabtagene maraleucel

Procedure No. EMEA/H/C/004731/II/0043/G

Note

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



Table of contents

1. Background information on the procedure	9
1.1. Type II group of variations	9
1.2. Steps taken for the assessment of the product	10
2. Scientific discussion	11
2.1. Introduction	11
2.1.1. Problem statement	11
2.1.2. About the product	14
2.1.3. The development programme/compliance with CAT/CHMP guidance/scientific advice	14
2.1.4. General comments on compliance with GCP	15
2.2. Quality aspects	15
2.2.1. Discussion on quality aspects	17
2.2.2. Conclusion on the quality aspects	17
2.3. Non-clinical aspects	17
2.3.1. Ecotoxicity/environmental risk assessment.....	17
2.4. Clinical aspects	18
2.4.1. Introduction	18
2.4.2. Pharmacokinetics	18
2.4.3. Pharmacodynamics.....	28
2.4.4. Discussion on clinical pharmacology	32
2.4.5. Conclusions on clinical pharmacology	34
2.5. Clinical efficacy	34
2.5.1. Dose response study(ies)	34
2.5.2. Main study	35
2.5.3. Discussion on clinical efficacy	89
2.5.4. Conclusions on the clinical efficacy	95
2.6. Clinical safety	95
2.6.1. Discussion on clinical safety	121
2.6.2. Conclusions on clinical safety	125
2.6.3. PSUR cycle	125
2.7. Risk management plan.....	125
2.8. Update of the Product information	134
2.8.1. User consultation.....	134
3. Benefit-Risk Balance.....	134
3.1. Therapeutic Context	134
3.1.1. Disease or condition.....	134
3.1.2. Available therapies and unmet medical need	135
3.1.3. Main clinical studies	136
3.2. Favourable effects.....	137
3.3. Uncertainties and limitations about favourable effects	138
3.4. Unfavourable effects.....	138
3.5. Uncertainties and limitations about unfavourable effects	139
3.6. Effects Table	139
3.7. Benefit-risk assessment and discussion	140

3.7.1. Importance of favourable and unfavourable effects140

3.7.2. Balance of benefits and risks.....141

3.7.3. Additional considerations on the benefit-risk balance141

3.8. Conclusions.....141

4. Recommendations 141

5. EPAR changes..... 142

List of abbreviations

Abbreviation	Definition
1L	First-line treatment
2L	Having received one line of prior therapy for the disease under study (second-line treatment)
2L+	Having received one or more line of 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 or more lines of prior therapy for the disease under study (fourth-line or later treatment)
ACC	Analytic Comparator cohort
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ASTCT	American Society for Transplantation and Cellular Therapy
ATA	Antitherapeutic antibody
AUC	Area under the blood concentration-time curve
BLA	Biologics License Application
BMB	Bone marrow biopsy
BMS	BristolMyers Squibb Company
B-NHL	B-cell non-Hodgkin lymphoma
BOR	Best overall response
BTki	Bruton tyrosine kinase inhibitor
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
C _{max}	Maximum observed blood concentration
CMR	Complete metabolic response
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response; Continued remission
CRF	Case report form
CRL	Complete Response Letter

CRMTS	Center for Biologics Evaluation and Research (CBER) Regulatory Meetings Management Tracking System
CRP	C-reactive protein
CRR	Complete response rate
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computerized tomography
CV	Coefficient of variation
ddPCR	Digital droplet polymerase chain reaction
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECA	External control arm
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer - Quality of Life C30 questionnaire
EOS	End of study
EQ-5D-5L	European Quality of Life-5 Dimensions health state classifier to 5 levels
ESMO	European Society of Medical Oncology
FACT-LymS	Functionality Assessment of Cancer Therapy Lymphoma Subscale
FDA	Food and Drug Administration
FL	Follicular lymphoma
FL3B	Follicular lymphoma grade 3B
FLIPI	Follicular Lymphoma International Prognostic Index
F/U	Follow up
GELF	Groupe d'Etude des Lymphomes Folliculaires
GM-CSF	Granulocyte macrophage colony-stimulating factor
HCP	Healthcare provider
HGBCL	High grade B cell lymphoma
HGL	High grade lymphoma
HLH	Hemophagocytic lymphohistiocytosis
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
HTA	Health technology assessment
ICANS	Immune effector cell associated neurotoxicity

ICF	Informed consent form
ICU	Intensive care unit
IgG	Immunoglobulin
iiNT	Investigator-identified neurologic toxicity
IL	Interleukin
IND	Investigational New Drug
iNHL	Indolent non-Hodgkin lymphoma
IPTW	inverse probability of treatment weighting
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reaction
ISA	Insertion site analysis
ISS	Integrated Summary of Safety
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
JTEAC	JCAR017-treated Efficacy Analysis Cohort
KM	Kaplan-Meier
LBCL	Large B-cell lymphoma
LDC	Lymphodepleting chemotherapy
LDH	Lactate dehydrogenase
Liso-cel	Lisocabtagene maraleucel
LKC	Leukapheresed cohort
LLOD	Lower limit of detection
LOD	Limit of detection
LOT	Line of therapy
LTFU	Long term follow-up
LVEF	Left ventricular ejection fraction
MAIC	Matching-adjusted indirect comparison
MAS	Macrophage activation syndrome
Max	Maximum
MCL	Mantle cell lymphoma
Min	Minimum
MZL	Marginal zone lymphoma
N.A.	Not applicable
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Neurologic event

NHL	Non-Hodgkin lymphoma
NOS	Not otherwise specified
NT	Neurotoxicity
N.R.	Not Reached
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progressionfree survival
PI3K	Phosphoinositide 3 kinase
PK	Pharmacokinetic(s)
PMBCL	Primary Mediastinal Large B Cell Lymphoma
PML	Progressive multifocal leukoencephalopathy
PMR	Partial metabolic response
POD24	Progression of disease within 24 months of initiation of first-line chemoimmunotherapy with antiCD20 and alkylating agent
POD24-Per protocol	As per protocol definition and case report form: progression of disease within 24 months of diagnosis after initiating treatment with an anti-CD20 and alkylating agent within the first 6 months of initial FL diagnosis
PR	Partial response
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PRR	Partial response rate
PS	Propensity score
PT	Preferred term
Q1	First quartile
Q3	Third quartile
QCC	Qualifying Comparator Cohort
QoL	Quality of life
R2	Rituximab and lenalidomide
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RCL	Replication-competent lentivirus
R-CVP	Rituximab, cyclophosphamide, vincristine, and prednisone
REMS	Risk evaluation and mitigation strategy
RMP	Risk management plan
R/R	Relapsed or refractory
RR	Response ratio
RW	Real world

SAP	Statistical analysis plan
sBLA	Supplemental Biologics License Application
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	Stable disease
SE	Standard error
SLL	Small lymphocytic lymphoma
SLR	Systematic literature review
SOC	System organ class
SPD	Sum of perpendicular diameter
SPM	Second primary malignancy
TARC	Chemokine (C-C motif) ligand 17
T-cell	T-lymphocyte
TE	Transplant eligible
TEAE	Treatment-emergent adverse event
THRBCL	T cell/histiocyte-rich large B-cell lymphoma
TLS	Tumor lysis syndrome
Tmax	Time of maximum observed blood concentration
TNE	Transplant non-eligible
TTNT	Time to next treatment
ULN	Upper limit normal
US	United States
USPI	United States prescribing information
VAS	Visual analog scale(s)

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 29 July 2024 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
B.II.d.1.a	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	Type IB	None
B.II.d.1.a	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	Type IB	None
B.II.d.1.e	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	Type II	None

C.I.6 (Type II): Extension of indication for Breyanzi to include treatment of adult patients with 3rd line + follicular lymphoma (FL) based on final results from the pivotal study JCAR017-FOL-001 (FOL-001, TRANSCEND-FL). This is a phase 2, open-label, single-arm, multicohort, multicenter study to evaluate efficacy and safety of JCAR017 in adult subjects with relapsed or refractory (R/R) follicular Lymphoma (FL) or marginal zone lymphoma (MZL). 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 5.0 of the RMP has been submitted. Furthermore, as part of the application the MAH is requesting a 1-year extension of the market protection.

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

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. During the procedure, the MAH decided to withdraw the claim.

Scientific advice

The MAH received Scientific Advice from the CAT/CHMP on 22 July 2021 (EMA/SA/0000062296). The Scientific Advice pertained to clinical aspects of the application.

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: N/A

Timetable	Actual dates
Submission date	29 July 2024
Start of procedure:	17 August 2024
CAT Rapporteur Assessment Report	11 October 2024
PRAC Rapporteur Assessment Report	14 October 2024
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	24 October 2024
CAT and CHMP members comments	N/A
PRAC Outcome	31 October 2024
Updated CAT Rapporteur(s) (Joint) Assessment Report	4 November 2024
CAT Request for Supplementary Information (RSI)	8 November 2024
CAT Rapporteur Assessment Report	2 January 2025
PRAC Rapporteur Assessment Report	2 January 2025
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	9 January 2025
CAT and CHMP members comments	N/A
PRAC Outcome	16 January 2025
Updated CAT Rapporteur Assessment Report	20 January 2025
CAT Opinion	24 January 2025
CHMP Opinion	30 January 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Follicular lymphoma (FL) is a heterogeneous condition including B-cell malignancies derived from germinal centre B cells. The histological growth pattern of FL is characterised by a nodular appearance that is always present, although, in more advanced stages, it is no longer predominant. The pseudo-follicular structures of FL include both centrocytes (small cleaved follicular centre cells) and centroblasts (large non-cleaved follicular centre cells) and mimics the normal germinal centres of secondary lymphoid follicles. However, unlike reactive follicles, FL neoplastic nodules are usually closely packed and heterogeneous in size and shape.

Centrocytes are typically predominant in classic (Grade 1-3a) FL, while centroblasts might be the main cell component in rare forms with aggressive behaviour (i.e. Grade 3b FL, known under the name follicular large B-cell lymphoma in the latest WHO classification of lymphoid neoplasms). Occasional cases of FL may show plasmacytoid differentiation or foci of marginal zone or monocytoid B cells.

The vast majority of FL cases express HLA-DR and are positive for B cell antigens (CD19, CD20, CD79a), CD21, and CD10 (60 percent). CD23 expression is variable.

Claimed therapeutic indication

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Epidemiology

FL is one of the most common forms of non-Hodgkin lymphoma (NHL), accounting for about 35% of all NHLs. The incidence of FL in the EU is approximately 2.2 cases per 100.000 persons per year, with a higher prevalence in Caucasian populations compared to African and Asians (see e.g. Sant M et al, Blood 2010). FL shows no strong sex predilection, yet its incidence varies with age; with the majority of FL cases arising in middle-aged individuals and older adults (see e.g. Morton LM et al, Blood 2006). The median age at diagnosis is 65 years yet rare cases have been reported also in children and adolescents (see e.g. Lorschach RB et al, Blood 2002).

Aetiology and pathogenesis

The aetiology of FL is largely unknown, and its pathogenesis is not fully understood. The majority of FL cases harbour the t(14;18) translocation, which results in the juxtaposition of the B-cell leukemia/lymphoma 2 gene (Bcl2) with the promoter of the immunoglobulin heavy chain gene (IGH). The Bcl2/IGH translocation event is essential in promoting the overexpression of Bcl2, which act as inhibitor of programmed cell death (apoptosis) and results in prolonged cell survival.

However, since t(14;18) has been detected also in reactive lymphoid tissues and peripheral blood lymphocytes of normal subjects, additional genetic events (e.g. in genes codifying chromatin-modifying enzymes, see Morin RD et al, Nature 2011) are considered to be necessary in order to develop FL. In this regard, approximately 90% of FL demonstrate additional genetic alterations such as loss of 1p, 6q, 10q, and 17p and gains of chromosomes 1, 6p, 7, 8, 12q, X, and 18q/dup. The Ig-mediated B cell receptor (BCR) pathway, for example, has also been shown to play a role in FL pathogenesis.

Clinical presentation, diagnosis and stage/prognosis

Most patients with FL present with enlarged and painless superficial lymph nodes. Although large (mostly asymptomatic) abdominal masses are not uncommon, mediastinal masses are rarer. FL is usually widely disseminated at the time of diagnosis and could involve the spleen (40% of all cases), the liver (50% of all cases) or the bone marrow (80% of all cases, see Anderson T et al, Cancer 1982). Involvement of other “extra-lymphatic” organs is uncommon and invasion of central nervous system is rare compared to other forms of NHL.

Symptoms are uncommon at diagnosis, and only approximately 20% of patients report “B symptoms” (i.e. fever, night sweats, pruritic and/or unintentional weight loss). Laboratory values are usually non-informative and, despite the large tumour burden, increased serum LDH or cytopenias have been reported in less than 25% of patients.

Symptoms in patients with R/R FL are more heterogeneous and might be due to compression/infiltration of visceral organs, peripheral nerves and/or bone tissue.

Management

FL is characterised by an indolent, relapsing/remitting clinical behaviour and, as a general rule, drug resistance increases, and clinical benefit is reduced, with each subsequent line of therapy.

Current treatment guidelines (see e.g. the 2020 ESMO guidelines for newly diagnosed and relapsed FL, or the NCCN guidelines for classic FL v. 3.2024) recommend that conventional immunochemotherapy should form the backbone of treatment early in the course of the disease (e.g. at frontline or at first relapse). In later settings of relapse/progression, alternative approaches are usually preferred. Therefore, with respect to the claimed indication for Breyanzi, only a selected group of patients can be reasonably expected to benefit from the use of classic immune-chemotherapy regimens such as bendamustine plus rituximab (BR), R-CHOP/R-CVP, or other similar regimens. Rituximab, an anti-CD20 monoclonal antibody, is recommended by current guidelines for the treatment of R/R FL in monotherapy or in combination. Rituximab monotherapy is often preferred in older subjects with indolent disease because of its manageable toxicity profile; in the rituximab arm of the Phase III HOMER study (see e.g. Maloney DG et al, Blood Adv 2020) only subjects with rituximab-sensitive disease could be enrolled, the overall response rate (ORR) was 66%, the complete response rate (CRR) was 20% and the median progression-free survival (PFS) was 19.2 months. The SCHOLAR-5, a large observational study investigating the RW outcomes of subjects with R/R NHLs, showed that the ORR and CRR for subjects with R/R FL receiving various rituximab-based salvage treatments in their 3L+ ranged from 43% to 69% and from 20% to 46%, respectively.

The main clinical need in R/R FL patients is, however, represented by the increasing rate of resistance to rituximab-based regimens in later lines of therapy, together with the reduction in the disease-free time between relapses and the accumulation of treatment-related toxicities.

The combination of obinutuzumab (a 2nd generation anti-CD20 mAb) plus bendamustine (BO), followed by obinutuzumab maintenance, is approved for the treatment of for subjects who did not respond or who progressed during or up to 6 months after treatment with rituximab or rituximab-containing regimens. The results from registrational study GAO4753g/GADOLIN showed that the BOR (CR+PR) in the BO arm was 79.7% and the CRR 15.7%. At the time of approval, the median PFS by IRC in the BO arm was not reached with a median FU of 22 months, nor the median duration of response (DoR) and overall survival (OS). Updated results with a median FU of 57.5 months in the BO arm (see Sehn LH et al, Blood 2019) showed that the median PFS was 24.1 months, and the median OS was still not reached.

The therapy landscape for these patients has observed some changes in recent years, with more chemo-free options becoming available.

Idelalisib and duvelisib are PI3K inhibitors (PI3Kis) approved for the treatment as monotherapy of adult patients with FL that is refractory to two prior therapies. The efficacy outcomes from the registrational studies (single-arm, multicentre study 101-09 and single-arm, multicentre study IPI-145-06, respectively) showed ORRs ranging between 40% and 55.6% and CRRs in the range 0% to 16.7%. Long-term outcomes data showed mDoR, mPFS and mOS ranging between 10-12 months, 8-11 months and 28-61 months, respectively. With respect to safety, long-term treatment with PI3Kis is characterised by significant rates of neutropenia, infection, GI ADRs and rash.

Zanubrutinib (a 2nd generation BTK inhibitor) is approved in combination with obinutuzumab (OZ) for the treatment of adult patients with R/R FL who have received at least two prior systemic therapies. Data from Phase 2, randomised, controlled study ROSEWOOD showed in the OZ arm an ORR of 69% (CRR 39.3%), with a 69% DoR rate at 18 months and a median PFS of approximately 28 months.

Lenalidomide is approved in combination with rituximab (RR) for the treatment of adult patients with previously treated FL. The efficacy and safety of the RR regimen was investigated in a phase 3, multicentre, randomised, double-blind controlled study (AUGMENT) which compared RR with rituximab plus placebo in patients with R/R indolent NHLs including FL. With a median follow-up of approximately 28 months, the ORR for FL patients in the RR arm was 80.3%, the CRR 34.7%, the median DoR 36.6 months, the median PFS 39.4 months and the 5-year OS rate was 85.9%.

Mosunetuzumab is an anti-CD20/CD3 T-cell-engaging bispecific mAb approved conditionally for the treatment of adult patients with R/R FL who have received at least two prior systemic therapies. The CMA of Lunsumio was based on the results from a single open-label, multicenter, multi-cohort study (GO29781) in subjects with R/R B-cell NHLs. Efficacy results showed that the ORR was 80%, the CRR 60%, the mDoR 22.8 months, the median PFS 17.9 months and the median OS was not yet reached. Epcoritamab and odronextamab are two additional anti-CD20/CD3 bispecific mABs approved as monotherapy for the treatment of adult patients with R/R FL after two or more lines of systemic therapy that showed similar results to mosunetuzumab.

Tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel) are two anti-CD19 CAR T cell (CARTs) advanced medicinal products (ATMPs). Tisa-cel is approved for the treatment of subjects with R/R FL after two or more lines of systemic therapy. Results from the registrational ELARA trial (a Phase 2, open-label, single-arm study) showed that treatment with tisa-cel resulted in high ORR (86%) and CRR (69%), with a median PFS of 18.4 months and median DoR and OS not yet reached after a median follow-up of 20.8 months.

Axi-cel is approved for treatment of patients with R/R FL after three or more lines of systemic therapy. Supporting efficacy data come from study ZUMA-5, a single-arm Phase 2 trial in subjects with R/R indolent NHLs, and showed that the ORR was 94%, the CRR 78%, the median DoR 38.6 months, the median PFS 39.6 months and the median OS was not yet reached with a median FU of 25.9 months.

The safety profile of T cell engaging immunotherapies (including bispecific mAbs and CARTs) is characterised by CRS, neurotoxicity including ICANS, infections, persisting hypogammaglobulinemia and cytopenias. Rates and severity of AEs vary across different products.

Overall, despite several products are approved for the treatment of subjects with 3L+ FL, with CAR-T therapies offering the most compelling efficacy, there is a continuous need for efficacious treatments with better safety profiles to further enhance patient outcomes. FL, in fact, remains largely incurable, and death occurs mainly due to histological transformation to aggressive LBCL, infection, or because FL becomes refractory to the available options. Further, a higher medical need can be recognised for POD24 patients (i.e. subjects with early progression), who are at high risk of poor long-term outcomes, with an estimated 5-year OS 50% (vs. 90% in the absence of early progression).

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:

- Diffuse large B-cell lymphoma (DLBCL), High grade B cell lymphoma (HGBCL), Primary Mediastinal Large B Cell Lymphoma (PMBCL) and Follicular lymphoma grade 3B (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.

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

On 22-07-2021, the MAH received scientific advice for liso-cel for treatment of FL and received feedback from the CHMP (EMA/SA/0000062296). The Scientific Advice covered different points of development of liso-cel in FL; in respect to protocol JCAR017-FOL-001, the advice focused on the proposed development plan for FL to support the benefit/risk assessment of treatment in R/R FL, and about the opportunity of use of the JCAR017-FOL-001 study data, contextualized with a historic control, to support an earlier benefit/risk assessment for heavily treated R/R FL patients. An evaluation about the study endpoints was also provided.

The Applicant was advised to invert the order of the proposed primary endpoint of CRR with one of the first key secondary endpoint of ORR, because it has been outlined that for most registrational CAR T cell single arm studies on which approvals have been granted, the primary endpoint has been ORR rather than CRR. The Applicant was advised that CHMP will consider DOR as determined by an independent review committee (IRC) of importance in performing benefit risk evaluation. Both suggestions have been implemented in the pivotal study protocol.

The CHMP proposed also to conduct the efficacy analysis in an intent-to-treat (ITT) population defined as “all patients providing informed consent” rather than in the leukapheresed set, because it is considered more in line with the ITT principle. Nevertheless, the use of leukapheresed set is preceded in the setting of CAR-T therapies and the MAH decision to maintain this setting for the

efficacy analysis is considered acceptable; attention should be posed anyway to patient who underwent leukapheresis without meeting all inclusion/exclusion criteria.

The Applicant was also invited to submit results after at least 12 months of follow-up from the initial response; considering the previous experience in the same setting of Idelalisib trial the MAH accepted this request and provided results at a median follow up of 23.13 months (22.93, 23.26).

Finally, the CHMP discussed the proposal of the MAH to provide the results of supportive studies based on published literature in which subjects treated in the real-world setting or clinical trials were included. The MAH proposed data from real world external control arm study, a systematic literature review and an Indirect Treatment Comparison. The CHMP focused the attention on the missed opportunity of a phase 3 trial, considering the previous experiences in the same setting in which an active comparator was successfully implemented. Although data from supporting studies were adjusted in order to improve the similarity with patients included in the FOL-001, the strength of the evidence provided by this indirect comparison was considered sub-optimal when compared to a randomized clinical trial with an active comparator. The CHMP warned that the absence of an active comparator contemporaneously would need to be justified at the time of a MAA.

2.1.4. General comments on compliance with GCP

The MAH stated that the 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 were confirmed to meet the ethical requirements of Directive 2001/20/EC.

2.2. Quality aspects

Introduction

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.

While Study 017001 pertained to patients with relapsed or refractory large B cell lymphoma (LBCL) after two or more lines of systemic therapy (3L+), Study FOL-001 pertains to patients with relapsed or refractory Follicular Lymphoma after at least one (2L+) or two (3L+) 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 drug product, the following studies are included in this section in support of Study FOL-001:

- Phenotypic and functional characterisation of drug product components manufactured in support of Study FOL-001
- Exploratory correlative analysis of quality attributes associations with clinical efficacy, safety, and pharmacokinetics in Study FOL-001

Manufacturing Process Development

The Healthy Donor Leukapheresis Product was reassessed for 3L+ FL to confirm that process characterisation results are still relevant to 3L+ FL. This assessment was presented.

The drug product v4 manufacturing process produces similar drug product 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 Study JCAR017-FOL-001 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 drug product to patient safety and product efficacy is considered low.

Specification

The specification for lisocabtagene maraleucel CD8+ drug product component (liso-cel) covers relevant CQAs. The quality parameters taken into account for each cell component include appearance, identity, purity, strength, potency and safety.

Information on lots of drug product that were manufactured to support the Study JCAR017-FOL-001 clinical trial was provided.

Justification of Specifications (CD8+)

The specification of liso-cel (lisocabtagene maraleucel) drug product has been established to confirm its appearance, identity, purity, strength, potency, and safety. The quality attributes of the drug product components have been determined through process and product understanding gained during development and correlative analyses with clinical outcomes. The analytical procedures that were selected to ensure control of attributes in the specification reflect the experience gained during development and manufacture of liso-cel, knowledge from other autologous gene and cellular therapeutics, and their suitability for routine evaluation of attributes that ensure the quality of released drug product component lots. The acceptance criteria in the specification have been established to ensure that the quality of released drug product component lots remain within experience demonstrated to be safe and effective in Study 017001, JCAR017-BCM-001 (BCM-001), JCAR017-BCM-003 (BCM-003) and Relapsed or Refractory Follicular Lymphoma (R/RFL; JCAR017-FOL-001 [FOL-001]).

Analytical Procedures

The appearance, identity, purity, strength, potency, and safety attributes that are included in the drug product 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 (QC) environment.

Acceptance Criteria in the Specification for Drug Product

The acceptance criteria in the specification have been established to ensure that the quality of released drug product component lots remain within experience demonstrated to be safe and effective. In accordance with ICH Q6B, Q8, Q9, and Q10, the following assessment of liso-cel drug product 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

Drug Product Component Lots Included in the Specification Assessment

The acceptance criteria established in the commercial specification for release and stability of drug product considered data that were acquired from drug product component lots manufactured under GMP conditions in the manufacturing process v4.

To maximize patient access to quality drug product that is within experience demonstrated to be safe and effective, the number of quality attributes and stringency of acceptance criteria in the commercial specification were considered. Therefore, redundant controls were eliminated from the drug product specification. In addition, the cumulative impact of acceptance criteria was considered to ensure an appropriate balance between providing the necessary assurances of drug product quality, process control, and patient access to drug product that is within experience demonstrated to be safe and effective in Study 017001, BCM-001, BMC-003 and FOL-001.

2.2.1. Discussion on quality aspects

The MAH has performed a limited set of characterisation studies on the CD8+ and CD4+ cell components manufactured for Study FOL-001, pertaining to patients with r/r Follicular Lymphoma (FL) after at least one (2L+) or two (3L+) prior lines of systemic therapy.

The rationale behind this restricted characterisation dataset is that r/r FL patient populations may differ in the characteristics of their starting materials (e.g., memory T cell phenotypes) and their clinical response to the drug product as compared to the clinical setting investigated so far. A relevant number of FOL-001 batches has been considered for each component in the context of this newly generated data, which do not highlight any remarkable differences or give rise to any further considerations as compared to the assessments performed so far for Breyanzi (MA and 2nd line EoI). The same consideration applies to the correlative analyses performed between cell components' quality attributes and clinical outcomes (efficacy, safety and PK) and to inform inter-quality attributes correlations.

The batch analysis data for Study FOL-001 has been provided, confirming that the product (and process) is in a state of control.

No new CQAs were identified, nor manufacturing process (v4) or control strategy changes were proposed. The release specification test panel remains unchanged following the inclusion of data from study FOL-001 lots in the dataset to justify the acceptance criteria, with two exceptions that are regarded as acceptable.

2.2.2. Conclusion on the quality aspects

In conclusion, the quality aspects linked to the sought EoI are approvable.

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) in Module 1.6.2 of the present Type II variation, which extends the treatment of liso-cel to include adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

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 still unlikely.

As the Type II variation 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. Tabular listing of clinical studies included in the application

Type of Study	Study No.; NCT ID; EudraCT ID; Location of Study Report	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Treatment Duration	No. of Subjects Treated ^a with Liso-cel	Subject Population	Study Status; Type of Report
Efficacy and Safety Studies of Liso-cel Monotherapy: Pertinent to the Claimed Indication (R/R FL)								
Uncontrolled	JCAR017-FOL-001; NCT04245839; 2019-004081-18; 5.3.5.2	Efficacy (ORR) based on IRC of liso-cel in subjects with R/R FL (Cohorts 1, 2, 3)	Phase 2 open-label, single-arm, multicohort, multisite trial	Liso-cel; 100×10 ⁶ CAR+ T cells; intravenous	Single dose	FL (Cohorts 1, 2, 3): 130	Adult indolent B-NHL (2L+ FL Grade 1, 2, or 3A)	Ongoing; Interim CSR (27-Jan-2023 data cut for FL cohorts) Addendum 01 CSR (10-Jan-2024 data cut for FL cohorts) Safety data in the SCS (10-Jan-2024 data cut for FL cohorts)

2.4.2. Pharmacokinetics

The clinical pharmacology profile of Breyanzi in subjects with FL has been characterised based on results from Study FOL-001 Cohorts 1,2 and 3. The secondary objective of this study was to characterize the PK profile of liso-cel; the exploratory objectives were to assess the peripheral biomarkers of liso-cel including soluble factors and changes in immune cell populations and to evaluate the immune responses directed against liso-cel.

Breyanzi dose recommendation of 100 × 10⁶ CAR+ viable T cells in Study FOL-001 was selected based on the dosing experience in Study 017001 (Phase 1 study to determine the safety, antitumour activity, and PK of JCAR017 in adult subjects with R/R B-cell NHL, submitted within the initial MA).

Table 2. Description of Study FOL-001

Study	Design	Study Population	Number of FL Subjects (Cohorts 1, 2 and 3) Enrolled	Dosing	PK Sampling Timepoints by PCR
JCAR017-FOL-001	A Phase 2, open-label, single-arm, multicohort, multicenter trial to evaluate the efficacy and safety of liso-cel in adult subjects with R/R indolent B-cell NHL	Adult subjects with R/R FL and R/R MZL	Screened Set ^a : 154 Eligible Set ^b : 139	100 × 10 ⁶ CAR+ T cells	Days 1, 4, 8, 11, 15, 22, 29, 60, 90, 180, 270, 365, 545 and 730 Months 30, 36, 42, 48, 54, and 60 (EOS)

^a Subjects signed informed consent.

^b Subjects signed consent who meet all inclusion/exclusion criteria.

Methods

The following bioanalytical methods were used to assess the PK, PD and immunogenicity of Breyanzi.

Table 3. Bioanalytical methods

Assessment	Data Cut-off Date	Laboratory	Status
Pharmacokinetic Assessments			
Digital droplet PCR (transgene vector sequences)	10-Jan-2024	MolecularMD (Portland, OR)	Validated
Pharmacodynamic Assessments			
Flow cytometry (B-cell aplasia)	10-Jan-2024	Labcorp (Indianapolis, IN)	Validated
MSD-ECL Immunoassay (Soluble biomarkers)	10-Jan-2024	BioAgilytix, (Boston, MA)	Validated
Serum Ig, CRP, ferritin	10-Jan-2024	Measured by the local labs at individual sites	Validated
Immunogenicity Assessments			
Electrochemiluminescence immunoassay (ATA)	10-Jan-2024	Charles River Laboratories (Reno, NV)	Validated

A validated ddPCR assay (CC-MULT-DMPK-3180 validation report and Biomarker report JCAR017-FOL-001) was used to quantitate gene expression and a validated ATA assay (JCAR017-DMPK-2774-ADA) was used to evaluate immune responses to the ECD of liso-cel.

In the current application, the Applicant used a validated industry-standard assay to monitor B-cell aplasia that replaced the original method, a research-use-only flow cytometry used in the initial Marketing Authorisation.

Soluble biomarkers were analysed using multiplex MSD-ECL immunoassays (validation submitted within the II/05 variation; 00970). Serum Ig, CRP, and ferritin were measured at a local laboratory.

Transgene measurement: pan gag VCN ddPCR Test (CC-MULT-DMPK-3180)

To evaluate the transduction of the target cells (CAR⁺ cells) with the lentivirus and the persistence of gene transfer the pan gag VCN ddPCR Test was used. The method detects gag DNA sequence of the lentiviral vector and that of the reference gene RPPH1 in nucleic acids isolated from human blood. Calculated data are reported as gag copies per µg (gag copies/ ([genomes x (6.6 pg/genome)] / 106 pg/µg)), % gag positive cells (([gag copies/RPPH1 copies] x 2) x 100), and genomes (RPPH1 copies/2).

Analytical Sensitivity was set as follow: the Limit of Detection of the pan gag VCN ddPCR Test is ≤ 16 copies per 400 ng. The Lower Limit of Quantitation of the Test is 16 copies per 400 ng. The Upper Limit of Quantitation of the Test is 720,000 copies per 400 ng.

Pharmacokinetics results

The PK analyses were based on PCR. Noncompartmental PK parameters such as Cmax, Tmax, and AUC(0-28) were calculated for subjects in the PK Evaluable Analysis Set (subjects who have at least 1 evaluable PK parameter). Persistence of liso-cel transgene in blood was assessed by PCR and defined as a transgene count greater than or equal to the LOD of 16 copies/400 ng reaction which is ~ 40 copies/ μ g. All PK data, including persistence, were summarized descriptively.

The clinical pharmacology of liso-cel has been evaluated in Study FOL-001 in subjects with FL by group and using the analysis datasets described in the tables below.

The MAH submitted an interim clinical pharmacology report (dated September 2023) with data cut-off 27 January 2023 and an Addendum 1 clinical pharmacology report (dated 18 June 2024) with data cut-off 10 January 2024 where the DBL occurred on the same date as for the Study FOL-001 Addendum 01 CSR (06-Mar-2024). As of the latest data cutoff date, the study was still ongoing.

Table 4. Group Information - Study FOL-001

Group Name in Tables/Figures/Listings and Text	Study Cohort(s) Included in the Group
4L+ FL or 4L+	Cohort 1
3L FL or 3L	Cohort 2
3L+ FL or 3L+	Cohort 1 and Cohort 2
2L FL or 2L	Cohort 3
2L+ FL or 2L+	All Cohorts (1, 2, and 3)

Table 5. Analysis Populations Presented in this SCP - Study FOL-001

Analysis Population	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2	2L FL Cohort 3	Total 2L+ FL (Cohorts 1, 2, 3)
Leukapheresed Set - Subjects signed consent who undergo leukapheresis and meet all inclusion/exclusion criteria.	65 (100.0)	49 (100.0)	114 (100.0)	25 (100.0)	139 (100.0)
Liso-cel-treated Set - Subjects received a dose of liso-cel	59 (90.8)	48 (98.0)	107 (93.9)	23 (92.0)	130 (93.5)
Liso-cel -treated Efficacy Set - Subjects received a dose of liso-cel with positive disease present before liso-cel administration per IRC. Subjects without baseline assessment repeated after anticancer therapy for disease control and before liso-cel administration excluded	55 (84.6)	48 (98.0)	103 (90.4)	23 (92.0)	126 (90.6)

Table 5. Analysis Populations Presented in this SCP - Study FOL-001

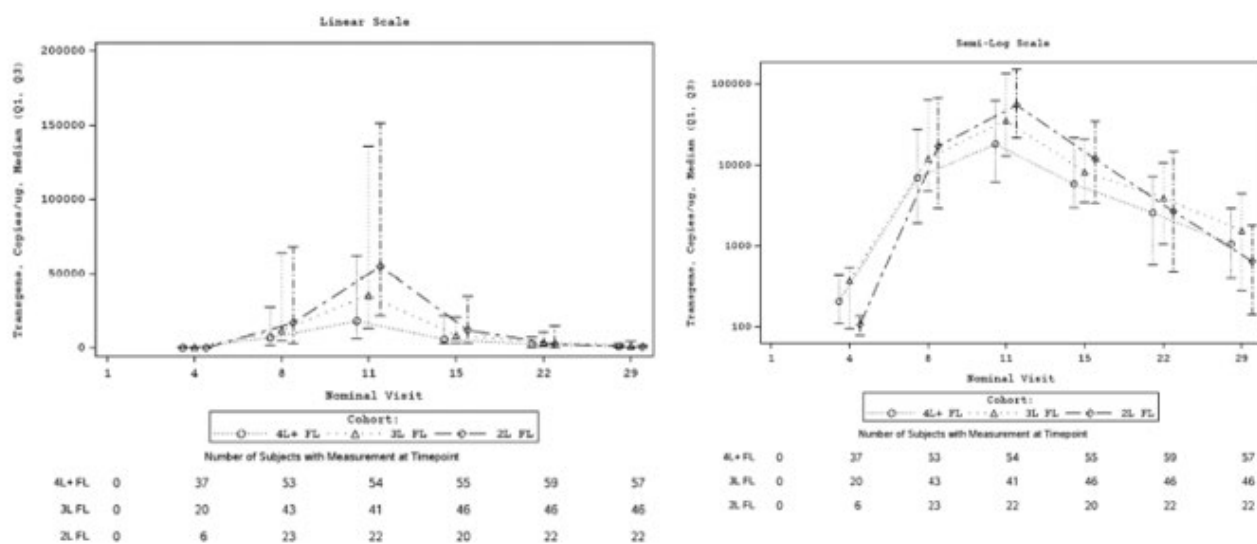
Analysis Population	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2	2L FL Cohort 3	Total 2L+ FL (Cohorts 1, 2, 3)
PK Analysis Set - Subjects with any available PK measurements by PCR in the liso-cel-treated set	59 (90.8)	48 (98.0)	107 (93.9)	23 (92.0)	130 (93.5)
PK Evaluable Analysis Set - Subjects with at least one evaluable PK parameter in the liso-cel-treated set	59 (90.8)	47 (95.9)	106 (93.0)	23 (92.0)	129 (92.8)

Percentages are based on Leukapheresed Set.

Peripheral blood samples for PK by ddPCR were collected up to 60 months (pre-treatment, D1, 4, 8, 11, 15, 22, 29, 60, 90, 180, 270, 365, 545, 730 (24 months), 30 months, 36 months, 42 months, 48 months, 54 months, 60 months).

The PK section highlight the results in the 3L+ (cohort 1 and 2) and 2L+ groups (Cohort 1, 2 and 3) that were evaluated for PK-safety relationship, while the 3L+ group was evaluated for PK-efficacy relationship.

Liso-cel concentration in peripheral blood over time showed a similar pattern in the 4L+, 3L, and 2L groups. In all 3 groups, the liso-cel concentration in the peripheral blood detected by PCR exhibited a rapid expansion followed by a monophasic decline up to 28 days after infusion.

Figure 1. Median PK Concentration Data by Group (Linear and Semi-log Scales) – PK Analysis Set

Upper error bar represents the third quartile, lower error bar represents the first quartile.
Liso-cel was given on Study Day 1. Only nominal visits up to Day 29 are included in this figure. Values after the start of subsequent anti-follicular lymphoma therapy are excluded.

In the 3L+ group, median C_{max}, AUC(0-28), and T_{max} were 31336 copies/μg, 253400 day*copies/μg, and 10.0 days, respectively.

In the 2L+ group, median C_{max}, AUC(0-28), and T_{max} were 41315 copies/μg, 260274 day*copies/μg, and 10.0 days, respectively.

Median Tmax reached 10 days in the 4L+, 3L, and 2L groups. Median Cmax and AUC(0-28) in the 2L group were higher than the 3L group, followed by the 4L+ group. However, inter-subject variability was large for Cmax and AUC(0-28) (geometric CV% > 150%) with exposure ranges overlapping across the groups.

Table 6. Summary of Liso-cel PK parameters in Peripheral Blood by Group – PK Evaluable Analysis Set

	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2	2L FL Cohort 3	Total 2L+ FL Cohorts 1, 2, 3
	N=59	N=47	N=106	N=23	N=129
Cmax (copies/μg)					
n	59	47	106	23	129
Median	29170	35815	31336	62091	41315
Q1, Q3	10039, 82196	13804, 124019	12693, 96795	45428, 176273	13717, 100239
Min, Max	565, 688672	238, 399591	238, 688672	1975, 541191	238, 688672
Geometric Mean	26247	35828	30130	67209	34763
Geometric CV%	303	312	307	184	295
Tmax (days)					
n	59	47	106	23	129
Median	10.0	10.0	10.0	10.0	10.0
Q1, Q3	7.00, 13.0	9.00, 10.0	8.00, 11.0	9.00, 10.0	8.00, 11.0
Min, Max	6.00, 22.0	7.00, 21.0	6.00, 22.0	7.00, 11.0	6.00, 22.0
AUC(0-28) (day*copies/μg)					
n	57	45	102	20	122
Median	213741	281820	253400	385668	260274
Q1, Q3	79297, 485787	112745, 905908	106099, 603488	194260, 921947	107494, 645997
Min, Max	7895, 6986370	7998, 2733453	7895, 6986370	12599, 6849741	7895, 6986370
Geometric Mean	203158	292732	238682	376523	257202
Geometric CV%	256	204	235	260	240

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: $CV (\%) = 100 \times \sqrt{\exp(S^2) - 1}$, where S^2 denotes the variance of the log-transformed values.

Persistence

Persistence of liso-cel transgene in the peripheral blood is defined as a transgene count $\geq$ the LOD. In the 3L+ and 2L+ groups, with longer follow-up based on the 10-Jan-2024 data cut compared to the Interim Clinical Pharmacology report (cut-off Jan 2023, data up to Day 730) persistence of liso-cel transgene was observed up to Month 36 (Day 1095). However, the number of evaluable subjects at Month 36 (Day 1095) was small in the 3L+ and 2L+ groups (N = 2 and N = 3, respectively). At Month 30 (Day 910), persistence of liso-cel transgene was observed in 25.0% (7 of 28 subjects) and 23.5% (8 of 34 subjects) in the 3L+ and 2L+ groups, respectively.

Table 7. Summary of Persistence of Liso-cel in Peripheral Blood by PCR Over Time – PK Analysis Set

Transgene, n/N (%)	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2	2L FL Cohort 3	Total 2L+ FL Cohorts 1, 2, 3
	N=59	N=48	N=107	N=23	N=130
Day 29	55/57 (96.5)	44/46 (95.7)	99/103 (96.1)	21/22 (95.5)	120/125 (96.0)
Day 60	47/53 (88.7)	37/44 (84.1)	84/97 (86.6)	12/17 (70.6)	96/114 (84.2)
Day 90	33/56 (58.9)	34/46 (73.9)	67/102 (65.7)	8/21 (38.1)	75/123 (61.0)
Day 180	23/49 (46.9)	16/39 (41.0)	39/88 (44.3)	6/20 (30.0)	45/108 (41.7)
Day 270	22/48 (45.8)	19/41 (46.3)	41/89 (46.1)	5/20 (25.0)	46/109 (42.2)
Day 365	22/46 (47.8)	17/38 (44.7)	39/84 (46.4)	5/19 (26.3)	44/103 (42.7)
Day 545	18/40 (45.0)	15/36 (41.7)	33/76 (43.4)	6/20 (30.0)	39/96 (40.6)
Day 730	10/26 (38.5)	10/31 (32.3)	20/57 (35.1)	3/11 (27.3)	23/68 (33.8)
Month 30 (Day 910)	4/15 (26.7)	3/13 (23.1)	7/28 (25.0)	1/6 (16.7)	8/34 (23.5)
Month 36 (Day 1095)	0	1/2 (50.0)	1/2 (50.0)	0/1	1/3 (33.3)

Persistence is defined as a transgene count $\geq$ the LOD.

Concentration values after another anticancer treatment are excluded from the summaries.

n/N = (number of subjects persistent)/(number of subjects for evaluation). For timepoints where there were no evaluable subjects, n/N was reported as 0.

Subgroup analysis

Subgroup analysis were performed to assess the effect on transgene PK parameters (C_{max}, T_{max}, AUC[0-28]) by age (< 65, $\geq$ 65 to < 75, $\geq$ 75 years old), sex (male, female), region (North America, Europe, Japan), bulky disease (defined as any mass > 7 cm, or 3 or more masses [each > 3 cm] at screening based on investigator assessment, yes/no), pre-LDC SPD status per IRC ($\geq$ 50 cm², < 50 cm²), FLIPI risk category (low/intermediate/high), and modified GELF criteria (yes/no).

In the 3L+ group, no relevant differences were observed.

In the 2L+ group, a potential association was observed between longer T_{max} and the presence of bulky disease, however, the median T_{max} of subjects with and without bulky disease was the same (10 days). A potential association was also observed between longer T_{max} and higher FLIPI risk category, however, the median T_{max} was generally comparable between low-, intermediate-, and high-risk groups (9, 10, and 10 days, respectively).

Non-conforming product

In PK evaluable analysis set, three subjects in 4L+ cohort, one in 3L and one in 2L cohorts received a non-conforming product.

Comparison with data from BCM-003 (2L LBCL)

The clinical pharmacology of Breyanzi has been characterised in LBCL in studies BCM-003, 017006, 017001 and BCM-001, however a comparison with BMC-003 has been reported since the same ddPCR method has been used to analyse the samples.

Table 8. Summary of Liso-cel Transgene PK Parameters

Parameter Statistic	Study FOL-001	Study BCM-003
	3L+ FL	2L LBCL
	N = 106	N = 84
Cmax (copies/μg)		
N	106	84
Median	31336	33285
Q1, Q3	12693, 96795	13848, 94913
Tmax (days)		
N	106	84
Median	10.0	10.0
Q1, Q3	8.0, 11.0	9.0, 11.0
AUC(0-28) (day•copies/μg)		
N	102	84
Median	253400	268911
Q1, Q3	106099, 603488	114626, 779701

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

PK/efficacy and PK/safety Relationship

The efficacy and safety endpoints are defined as follow:

Table 9. Endpoints

Efficacy Endpoints

BOR	IRC assessment	BOR is the best disease response recorded from the time of the liso-cel infusion until disease progression, end of study, or the start of another anticancer therapy.^a BOR is assigned according to the following order: CR, PR, SD, PD, not evaluable, or not done. Responders are defined as subjects that achieved a BOR of either a CR or a PR up to 60 months after liso-cel infusion. Complete responders are defined as subjects that achieved a BOR of CR up to 60 months after liso-cel infusion.
-----	----------------	--

PFS	IRC assessment	Time from start of liso-cel to disease progression or death from any cause, whichever occurs first.
DOR	IRC assessment	Time from first response (CR or PR) to disease progression or death from any cause, whichever occurs first.
DOR if BOR is CR	IRC assessment	For subjects with a BOR of CR, time from first response (CR or PR) to disease progression or death from any cause, whichever occurs first.

Safety Endpoints

Treatment-emergent adverse event of CRS, categorized as Grade 0 ^b versus Grade ≥ 1	Investigator assessment	A CRS event was captured on the AE CRF using preferred term of “Cytokine release syndrome” and graded according to the grading scale adapted from Lee. ⁴
Treatment-emergent adverse event of CRS, categorized as Grade ≤ 2 versus Grade ≥ 3		
Treatment-emergent adverse event of iiNT, categorized as Grade 0 ^b versus Grade ≥ 1		CAR T-cell-related iiNT was captured on the AE CRF using the preferred term “neurotoxicity” and graded using NCI CTCAE v5.0 on the basis of the highest individual symptom grade.
Treatment-emergent adverse event of iiNT, categorized as Grade ≤ 2 versus Grade ≥ 3		
Treatment-emergent adverse event of hypersensitivity as Grade 0 ^b versus Grade ≥ 1		Hypersensitivity events were selected using pre-defined list of preferred terms from MedDRA v26.0.
Treatment-emergent adverse event of hypersensitivity as Grade ≤ 2 versus Grade ≥ 3		

^a New anticancer therapy - anti-lymphoma therapy including both allo- and auto-HSCT is considered as a new antineoplastic therapy

^b Grade 0 indicates no CRS, iiNT, or hypersensitivity events.

The relationship between PK parameters (C_{max}, T_{max}, and AUC[0-28]) and dichotomous parameters (BOR, CRS and iiNT) were assessed by Wilcoxon tests. The relationship between PK parameters (C_{max} and AUC[0-28]) and time-to-event parameters (PFS, DOR, and DOR if BOR is CR) were assessed by univariable Cox proportional hazards models. The 3L+ group was used for assessment of PK-efficacy relationships. The 3L+ and 2L+ groups were used for assessment of PK-safety relationships.

In the 3L+ group, a potential relationship was observed between higher transgene PK parameters (C_{max} and AUC[0-28]) and longer PFS, DOR and DOR if BOR is CR per IRC charter. The relationships between transgene PK parameters and response (BOR of either CR or PR) were not assessed because the number of evaluable non-responders was less than 5. A potential relationship was observed between higher C_{max} and higher CRR per IRC charter, however the number of evaluable non-CR subjects was small for the assessment (N = 5).

Table 10. Relationship Between PK Parameters of Liso-cel and Efficacy (3L+ Group) - Subjects from Both Liso-cel-treated Efficacy Analysis Set and PK Evaluable Analysis Set

Variable/ Statistic	Yes	No	p-value
Response (BOR of either CR or PR) per IRC charter			
Cmax (copies/μg)			
n	100	2	NA
Median	31336.0	15567.6	
Q1, Q3	11876.5, 90643.6	12692.9, 18442.3	
Tmax (days)			
n	100	2	NA
Median	10.0	17.5	
Q1, Q3	8.0, 11.0	14.0, 21.0	
AUC(0-28) (day•copies/μg)			
n	96	2	NA
Median	245730.2	161934.9	
Q1, Q3	96528.0, 622704.0	142725.2, 181144.6	
Complete Response (BOR of CR) per IRC charter			
Cmax (copies/μg)			
n	97	5	0.0300
Median	35066.0	12692.9	
Q1, Q3	12862.8, 96795.0	5569.8, 17689.9	
Tmax (days)			
n	97	5	0.2763
Median	10.0	11.0	
Q1, Q3	8.0, 11.0	9.0, 14.0	
AUC(0-28) (day•copies/μg)			
n	93	5	0.0681
Median	259171.9	142725.2	
Q1, Q3	106099.1, 641920.4	37402.8, 181144.6	
PFS per IRC charter			
Cmax			
Hazard ratio	0.37		< 0.0001
95% CI	0.23, 0.59		
AUC(0-28)			
Hazard ratio	0.32		0.0005
95% CI	0.17, 0.61		
DOR per IRC charter			
Cmax			
Hazard ratio	0.36		< 0.0001
95% CI	0.22, 0.58		
AUC(0-28)			
Hazard ratio	0.30		0.0005
95% CI	0.16, 0.59		
DOR if BOR is CR per IRC charter			
Cmax			
Hazard ratio	0.37		0.0002
95% CI	0.22, 0.63		
AUC(0-28)			

Table 10. Relationship Between PK Parameters of Liso-cel and Efficacy (3L+ Group) - Subjects from Both Liso-cel-treated Efficacy Analysis Set and PK Evaluable Analysis Set

Variable/ Statistic	Yes	No	p-value
Hazard ratio	0.33		0.0026
95% CI	0.16, 0.68		

A response is defined as a complete response or partial response. For response and CR, p-values were based on the Wilcoxon test. The statistical test was only performed if there were at least five subjects in each subgroup.

For PFS, DOR, and DOR if BOR is CR, p-value, hazard ratio for a one-unit increase in log₁₀ transformed Cmax or AUC(0-28), and associated 95% CI were based on a Cox proportional hazards model.

In the 3L+ group, a potential relationship was observed between higher transgene PK parameters (Cmax and AUC[0-28]) and higher incidence of any-grade CRS and any-grade iiNT. A potential relationship was also observed between earlier transgene Tmax and higher incidence of any-grade CRS and any-grade iiNT; however, the difference in median Tmax was small (1 day and 2 days, respectively).

The relationship between PK parameters and Grade ≥ 3 CRS or Grade ≥ 3 iiNT was not assessed because the number of evaluable subjects with Grade ≥ 3 CRS and Grade ≥ 3 iiNT was each less than 5 (N = 1 and N = 3, respectively). Results in the 2L+ group were consistent with those in the 3L+ group.

Table 11. Relationship Between Pharmacokinetic Parameters of Liso-cel and Safety (3L+ and 2L+ Groups) - PK Evaluable Analysis Set

Variable/ Statistic	3L+ FL (Cohorts 1 + 2)			Total 2L + FL (Cohorts 1, 2, 3)		
	Yes	No	p-value	Yes	No	p-value
CRS Status (Any-grade CRS)						
Cmax (copies/μg)						
n	63	43		75	54	
Median	44539.2	17689.9	0.0058	46862.1	25476.7	0.0033
Q1, Q3	20103.0, 126346.5	6834.8, 59617.0		22610.2, 151400.3	9000.6, 62091.3	
Tmax (days)						
n	63	43		75	54	
Median	9.0	10.0	0.0272	9.0	10.0	0.0093
Q1, Q3	7.0, 10.0	9.0, 12.0		7.0, 10.0	9.0, 11.0	
AUC(0-28) (day•copies/μg)						
n	61	41		72	50	
Median	301949.0	142725.2	0.0027	329731.4	147561.1	0.0009
Q1, Q3	149587.8, 905908.3	68130.4, 299104.9		182040.4, 970457.9	68130.4, 337709.2	
iiNT Status (Any-grade iiNT)						
Cmax (copies/μg)						
n	17	89		21	108	
Median	124019.2	28588.6	0.0008	156159.8	33604.2	<0.0001
Q1, Q3	46142.7, 176559.0	11582.1, 71373.0		61771.6, 196958.2	12304.9, 74763.1	
Tmax (days)						
n	17	89		21	108	
Median	8.0	10.0	0.0070	8.0	10.0	0.0049

Table 11. Relationship Between Pharmacokinetic Parameters of Liso-cel and Safety (3L+ and 2L+ Groups) - PK Evaluable Analysis Set

Variable/ Statistic	3L+ FL (Cohorts 1 + 2)			Total 2L + FL (Cohorts 1, 2, 3)		
	Yes	No	p-value	Yes	No	p-value
Q1, Q3	7.0, 10.0	9.0, 12.0		7.0, 10.0	9.0, 11.0	
AUC(0-28) (day•copies/μg)						
n	17	85		20	102	
Median	912020.3	213457.0	0.0008	970422.8	235723.4	0.0001
Q1, Q3	377546.3, 1258803.0	82990.9, 423360.9		431666.4, 1317570.0	87330.4, 465744.6	

P-values are based on the Wilcoxon test.

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

PD was investigated in A Phase 2, Open-label, Single-arm, Multicohort, Multicenter Trial to Evaluate the Efficacy and Safety of JCAR017 in Adult Subjects with Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma (TRANSCEND FL).

The incidence of B-cell aplasia (defined as < 3% of CD19+ B-cells in peripheral blood lymphocytes) was assessed over time. Peripheral blood samples for flow cytometry (B-cell aplasia) were collected pre-treatment, Day 1, 8, 11, 15, 22, 29, 60, 90, 180, 270, 365, 545, 730 and on Months 36, 48 and 60.

Overall, the results and profiles for B-cell aplasia were similar across the groups over time.

Overall, the trends for serum immunoglobulins (IgA, IgG, IgM) were similar across the groups. The median levels of the 4L+ and 3L were comparable to the 3L+ Group.

The analysis of serum IgG levels did not take into account potential confounding by the administration of IVIG for the treatment of hypogammaglobulinemia.

Immunogenicity

Samples for immunogenicity assessment were collected pre-treatment, Day 15, 29, 60, 90, 180, 270, 365, 545, 730 (24 months).

In the 3L+ group, the prevalence of ATA was 1.9% (2 of 103 subjects); the incidence of ATA was 21.6% (22 of 102 subjects) (see Table below). The median time to first positive ATA titer in subjects with treatment-induced ATA was 8.77 months (range: 5.7 - 23.9 months). One subject had treatment-boostered ATA. Similar results were observed in the 2L+ group (see Table below).

Table 15. Summary of ATA – Liso-cel-treated Analysis Set

	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2	2L FL Cohort 3	Total 2L+ FL Cohorts 1, 2, 3
	N=59	N=48	N=107	N=23	N=130
Prevalence of ATA^a					
n	57	46	103	21	124
Yes, n (%)	2 (3.5)	0	2 (1.9)	0	2 (1.6)
No, n (%)	55 (96.5)	46 (100.0)	101 (98.1)	21 (100.0)	122 (98.4)
Incidence of ATA^b					
n	57	45	102	21	123
Yes, n (%)	12 (21.1)	10 (22.2)	22 (21.6)	11 (52.4)	33 (26.8)
No, n (%)	45 (78.9)	35 (77.8)	80 (78.4)	10 (47.6)	90 (73.2)
Treatment-induced ATA					
n	55	45	100	21	121
Yes, n (%)	11 (20.0)	10 (22.2)	21 (21.0)	11 (52.4)	32 (26.4)
No, n (%)	44 (80.0)	35 (77.8)	79 (79.0)	10 (47.6)	89 (73.6)
Treatment-boostered ATA					
n	2	0	2	0	2
Yes, n (%)	1 (50.0)	0	1 (50.0)	0	1 (50.0)
No, n (%)	1 (50.0)	0	1 (50.0)	0	1 (50.0)

^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-boostered antibodies that bind to liso-cel. In a subject without pre-existing antibodies, development of antibodies after infusion of liso-cel is considered treatment induced. In a subject with pre-existing antibodies, an increased level of antibodies after infusion of liso-cel is considered treatment boosted.

There was no clear difference in the prevalence of ATA across the groups. The incidence of ATA was generally comparable in the 4L+ and 3L groups (21.1% [12 of 57 subjects] and 22.2% [10 of 45 subjects], respectively) whereas higher incidence of ATA was observed in the 2L group (52.4% [11 of 21 subjects]) (Table 4.5.1-1). The median time to first positive ATA titer in subjects with treatment induced ATA were comparable across the groups. In addition, there was no clear difference in the maximum post-treatment ATA titers observed in subjects with treatment-induced ATA among the groups.

Clinical parameters (BOR, CRS, iINT, and hypersensitivity) and transgene PK parameters (C_{max} and AUC[0-28]) were summarized by prevalence and incidence of ATA. All endpoints were evaluated in a descriptive manner and formal statistical comparison were not made. The 3L+ group were used for assessment of ATA with efficacy relationships, while the 3L+ and 2L+ groups were used for assessment of ATA with safety or PK relationships. Overall, no apparent relationships of treatment-induced or treatment-boostered ATA were observed with efficacy, and safety. The number of subjects with pre-existing ATA was too low to assess any potential relationship with efficacy, safety, or PK.

Effect of ATA on efficacy

In the 3L+ group, for subjects who had pre-existing ATA, the ORR and CRR per IRC charter were 100% (2 of 2 subjects) (Table below). There were no clear differences in both ORR and CRR per IRC charter between subjects who had treatment-induced or treatment-boosted ATA and subjects who did not have treatment-induced or treatment-boosted ATA.

Table 13. Summary of Response Status vs ATA in Serum – Liso-cel-treated Analysis Set – 3L+ Group

	ATA Prevalence ^a		ATA Incidence ^b	
	Yes (N=2)	No (N=97)	Yes (N=22)	No (N=76)
Efficacy (assessed per IRC charter)				
Response				
Yes, n (%)	2 (100.0)	94 (96.9)	22 (100.0)	74 (97.4)
No, n (%)	0	3 (3.1)	0	2 (2.6)
Complete Response				
Yes, n (%)	2 (100.0)	91 (93.8)	21 (95.5)	72 (94.7)
No, n (%)	0	6 (6.2)	1 (4.5)	4 (5.3)

^a Prevalence of anti-therapeutic antibodies is defined as the percentage of subjects with pre-existing antibodies that bind to the ECD of liso-cel (at the pre-liso-cel infusion evaluation).

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

Effect of ATA on safety

In the 3L+ group, of two subjects who had pre-existing ATA, one subject experienced Grade ≥ 3 CRS. There was no incidence of any-grade iiNT or hypersensitivity in subjects who had pre-existing ATA (0 of 2 subjects). There were no clear differences in the incidence of any-grade CRS, Grade ≥ 3 CRS, any-grade iiNT, Grade ≥ 3 iiNT, or Grade ≥ 3 hypersensitivity between subjects who had treatment-induced or treatment-boosted ATA compared with subjects who did not have treatment-induced or treatment-boosted ATA. However, a higher incidence of any-grade hypersensitivity was observed in subjects who had treatment-induced ATA. Similar results were observed in the 2L+ group (see table below).

Table 14. Summary of CRS, iiNT or Hypersensitivity vs ATA in Serum – Liso-cel-treated Analysis Set – 3L+ and 2L+ Group

	3L+ FL (Cohorts 1 + 2)				Total 2L+ FL (Cohorts 1, 2, 3)			
	ATA Prevalence ^a		ATA Incidence ^b		ATA Prevalence ^a		ATA Incidence ^b	
	Yes (N=2)	No (N=101)	Yes (N=22)	No (N=80)	Yes (N=2)	No (N=122)	Yes (N=33)	No (N=90)
Any CRS								
Yes, n (%)	1 (50.0)	61 (60.4)	14 (63.6)	48 (60.0)	1 (50.0)	71 (58.2)	20 (60.6)	52 (57.8)
No, n (%)	1 (50.0)	40 (39.6)	8 (36.4)	32 (40.0)	1 (50.0)	51 (41.8)	13 (39.4)	38 (42.2)
CRS Grade ≥ 3								
Yes, n (%)	1 (50.0)	0	0	1 (1.3)	1 (50.0)	0	0	1 (1.1)
No, n (%)	1 (50.0)	101 (100.0)	22 (100.0)	79 (98.8)	1 (50.0)	122 (100.0)	33 (100.0)	89 (98.9)
Any iiNT								
Yes, n (%)	0	16 (15.8)	3 (13.6)	13 (16.3)	0	19 (15.6)	5 (15.2)	14 (15.6)
No, n (%)	2 (100.0)	85 (84.2)	19 (86.4)	67 (83.8)	2 (100.0)	103 (84.4)	28 (84.8)	76 (84.4)
iiNT Grade ≥ 3								
Yes, n (%)	0	3 (3.0)	0	3 (3.8)	0	3 (2.5)	0	3 (3.3)
No, n (%)	2 (100.0)	98 (97.0)	22 (100.0)	77 (96.3)	2 (100.0)	119 (97.5)	33 (100.0)	87 (96.7)
Any hypersensitivity								
Yes, n (%)	0	6 (5.9)	2 (9.1)	4 (5.0)	0	8 (6.6)	4 (12.1)	4 (4.4)
No, n (%)	2 (100.0)	95 (94.1)	20 (90.9)	76 (95.0)	2 (100.0)	114 (93.4)	29 (87.9)	86 (95.6)
Hypersensitivity Grade ≥ 3								
Yes, n (%)	0	0	0	0	0	0	0	0
No, n (%)	2 (100.0)	101 (100.0)	22 (100.0)	80 (100.0)	2 (100.0)	122 (100.0)	33 (100.0)	90 (100.0)

^a Prevalence of anti-therapeutic antibodies is defined as the percentage of subjects with pre-existing antibodies that bind to the ECD of liso-cel (at the pre-liso-cel infusion evaluation).

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

Effect of ATA on pharmacokinetics

In the 3L+ group, transgene C_{max} and AUC(0-28) of two subjects who had pre-existing ATA were lower than the median values of subjects who did not have pre-existing ATA. There were lower values in transgene AUC(0-28) in subjects who had treatment-induced or treatment-boostered ATA if compared to subjects who did not have treatment-induced or treatment-boostered ATA, however the difference seems small and not clear if related to ATA status. Similar results were observed in the 2L+ group (see table below).

Table 15. Summary of Liso-cel in Peripheral Blood by PCR vs ATA in Serum – PK Evaluable Analysis Set – 3L+ and 2L+ Groups

	3L+ FL (Cohorts 1 + 2)			Total 2L+ FL (Cohorts 1, 2, 3)		
	C _{max} (copies/μg)	T _{max} (days)	AUC(0-28) (day*copies/μg)	C _{max} (copies/μg)	T _{max} (days)	AUC(0-28) (day*copies/μg)
Pre-Existing ATA						
n	2	2	2	2	2	2
Median	4445.050	10.5	43877.54	4445.050	10.5	43877.54
Q1, Q3	2580.610, 6309.490	8.0, 13.0	19624.72, 68130.35	2580.610, 6309.490	8.0, 13.0	19624.72, 68130.35
No Pre-Existing ATA						
n	100	100	97	121	121	116
Median	33604.200	10.0	259171.93	41314.710	10.0	260274.11
Q1, Q3	13153.260, 96891.610	7.5, 11.0	107887.94, 603487.56	14010.300, 100239.030	8.0, 11.0	109709.64, 673556.12
Treatment-Induced/Boosted ATA						
n	22	22	21	33	33	30
Median	31051.735	9.0	220205.52	44655.040	9.0	245941.29
Q1, Q3	18853.100, 46436.690	7.0, 10.0	149587.77, 299104.86	28588.570, 124019.240	7.0, 10.0	169034.53, 701115.37
No Treatment-Induced/Boosted ATA						
n	80	80	78	90	90	88
Median	32797.820	10.0	260274.11	36822.180	10.0	265889.27
Q1, Q3	11722.740, 98985.455	8.0, 11.5	80717.34, 905908.32	12692.850, 96988.260	8.0, 11.0	81854.10, 642291.27

Pre-existing antibodies are antibodies that bind to the ECD of liso-cel at the pre-liso-cel infusion evaluation.

In a subject without pre-existing antibodies, development of antibodies after infusion of liso-cel is considered treatment-induced.

In a subject with pre-existing antibodies, an increased level of antibodies after infusion of liso-cel is considered treatment-boosted.

Peripheral blood samples for flow cytometry (T-cell phenotype) were collected pre-treatment, Day 1, 8, 11, 15, 22, 29, 60 and 90. However, results related to this parameter are not available.

2.4.4. Discussion on clinical pharmacology

Breyanzi dose recommendation of 100×10^6 CAR+ viable T cells in Study FOL-001 was selected based on the dosing experience from Study 017001.

The clinical pharmacology profile of liso-cel in subjects with FL has been characterized based on the results from Cohorts 1, 2 and 3 of clinical study FOL-001 and includes a characterization of the PK profile of liso-cel as described above.

Methods

Methods for the Pharmacology data collections, as described above, have been considered acceptable and duly validated.

Pharmacokinetic

Data from ddPCR of samples collected from Study FOL-001 showed that a higher expansion of cells occurred at Day 10 post-infusion with a decline up to day 29, that is in line with data previously observed in the initial MA and in the clinical study BCM-003 supporting the extension of indication in 2L Large B-Cell Lymphoma (LBCL).

The median Tmax in Cohorts 1 and 2 (4L+ FL and 3L FL) is 10 days with a minimum of 6 days to a maximum of 22; in Cohort 3 (2L FL) the range of Tmax is narrower (9-10 days), but a lower number of patients are included.

In terms of median Cmax, Cohort 3 (2L FL) showed a higher expression (62091 copie/μg) compared to Cohort 1 (29170 copie/μg) and 2 (35815 copie/μg) and lower variability; however, the range of Cmax in Cohort 3 is within that of Cohort 1 and 2.

The median AUC(0-28) in Cohort 3 showed the same trend of the median Cmax, with higher expression and range included in that of Cohort 1 and 2. The variability is high in all cohorts.

The higher expression in Cohort 2 could be due to a higher burden of disease, however no clear conclusions can be drawn due to the high variability and overlapping of expression ranges between cohorts. Some patients showed low level of transgene copies (e.g. CCTH 1081001, CCTH 1101001) and although a relationship has been observed between PK parameters and efficacy endpoints, no conclusion can be drawn on expansion threshold that guarantees efficacy.

Data on persistence are collected until Month 36 (Day 1095), however at this time point very few data are available (3 patients). At Month 30 (day 910) data from 34 patients are available and 23.5% showed persistence. Patients showing a high gag copies/μg showed a longer persistence, however there are patients in which the persistence was maintained until day 730 although the gag copies/μg were low.

It is of note that persistence in FOL-001 was analysed for a longer period than in Study BCM-003 (i.e. until 17 Months).

Among the subgroup analysis no significant differences were observed on transgene PK parameters (Cmax, Tmax, AUC0-28) by age, sex, region, modified GELF criteria. In Cohort 2L+ (Cohorts 1, 2, 3) a trend of higher median Cmax is observed in pre-LDC SPD status ≥ 50 cm² and FLIPI risk category low, however this difference is not statistically significant. Regarding the bulky disease Cohort 3L+ and Cohort 2L+ showed a slightly higher median Cmax, however not statistically significant. In Cohort 2L+ a potential association was observed between longer Tmax and the presence of bulky disease, however, the median Tmax of subjects with and without bulky disease was the same (10 days).

In the PK evaluable analysis set, three subjects in 4L+ cohort, one in 3L and one in 2L cohorts received a non-conforming product, however PK parameters fall within the ranges observed in patients taking the conforming product.

The MAH compared the PK parameters between study FOL-001 and BCM-003 in which the same ddPCR has been used. Cmax, Tmax and AUC0-28 showed similar median values and overlapping of exposure quartiles.

PK/Efficacy and PK/safety relationship

The 3L+ group (cohort 1 and 2) was used for assessment of PK-efficacy relationships and a potential relationship was observed between higher transgene PK parameters (Cmax and AUC0-28) and efficacy endpoints (longer PFS, DOR and DOR if BOR is CR per IRC charter). A potential relationship was observed between higher Cmax and higher Complete response per IRC charter, however the number of evaluable non-CR subjects was small for the assessment (N = 5).

The 3L+ and 2L+ groups were used for assessment of PK-safety relationships. As expected, a potential relationship is observed between PK parameters (C_{max}, T_{max} and AUC₀₋₂₈) and any-grade CRS and any-grade iiNT. The difference in median T_{max} in patients showing any grade of CRS or iiNT compared to patients free of these events is very small (max 2 hours); considering the setting of use and the monitoring foreseen after the infusion, this does not represent an issue.

Pharmacodynamics

PD was investigated in A Phase 2, Open-label, Single-arm, Multicohort, Multicenter Trial to Evaluate the Efficacy and Safety of JCAR017 in Adult Subjects with Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma (TRANSCEND FL).

The PD parameters assessed were the incidence of B-cell aplasia (defined as < 3% of CD19+ B-cells in peripheral blood lymphocytes), serum immunoglobulins (IgA, IgG, IgM), and a total of 37 soluble biomarkers (analyzed to examine changes in cytokine and chemokine levels following liso-cel infusion).

Overall, the results and profiles for B-cell aplasia over time and the trends for serum immunoglobulins were similar across the groups. B-cell aplasia was maintained through Day 90

Immunogenicity

Immunogenicity was investigated till 24 months. There was no clear difference in the prevalence of ATA across the groups. The incidence of ATA was generally comparable in the 4L+ and 3L groups (21.1% [12 of 57 subjects] and 22.2% [10 of 45 subjects], respectively) whereas higher incidence of ATA was observed in the 2L group (52.4% [11 of 21 subjects]). The median time to first positive ATA titer in subjects with treatment induced ATA were comparable across the groups. In addition, there was no clear difference in the maximum post-treatment ATA titers observed in subjects with treatment-induced ATA among the groups.

Overall, no apparent relationships of treatment-induced or treatment-boosted ATA were observed with efficacy and safety, with the exception any-grade hypersensitivity, where a higher incidence was observed in subjects who had treatment-induced ATA. The number of subjects with pre-existing ATA was too low to assess any potential relationship with efficacy, safety, or PK. There were lower values in transgene AUC(0-28) in subjects who had treatment-induced or treatment-boosted ATA if compared to subjects who did not have treatment-induced or treatment-boosted ATA, however the difference seems small and not clear if related to ATA status.

2.4.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology profile of liso-cel in subjects with FL has been adequately characterized and no major differences were noted in the extended FL patient population based on data available.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The Liso-cel dosing recommendation of a target dose of 100×10^6 CAR+ viable T cells in Study FOL-001 was selected based on the dosing experience in Study 017001, a Phase 1 study in adult subjects with R/R DLBCL NOS (de novo and transformed from indolent lymphoma), HGBCL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL, FL grade 3B, and MCL, object of the initial Marketing authorisation for Breyanzi (Breyanzi EPAR).

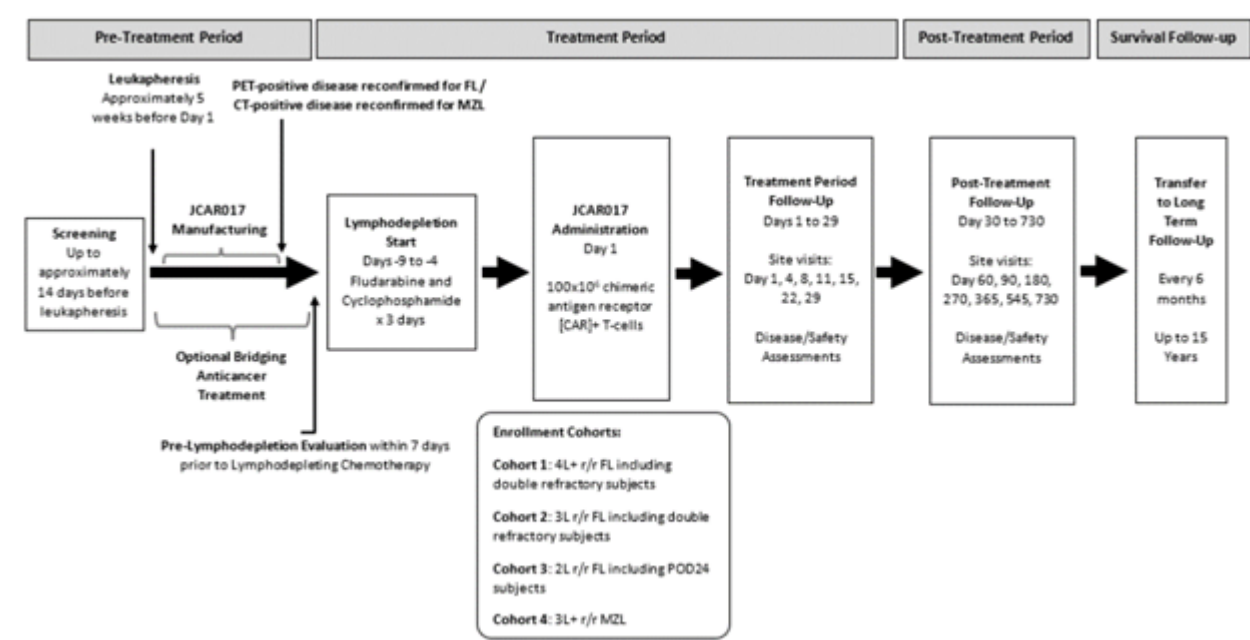
2.5.2. Main study

Title of Study

JCAR017-FOL-001 (TRANSCEND FL; Study FOL-001): A phase 2, open-label, single-arm, multicohort, multicenter trial to evaluate the efficacy and safety of liso-cel in adult subjects with relapsed or refractory indolent B-cell non-hodgkin lymphoma (NHL)

A specific cohort of patients affected by Marginal Zone Lymphoma was also included in this trial, but it was not considered in the efficacy analysis evaluation. The study contemplates three different phases: Pretreatment, Treatment, and Post-treatment Follow-up. Upon completion or early discontinuation, subjects were asked to participate in a LTFU study (GC-LTFU-001) for up to 15 years after the dose of Liso-cel.

Figure 2. Study Design



Methods

Study participants

The target study population included adult subjects with R/R FL and R/R MZL.

Depending on cohort assignment, subjects must have received previous treatment as follows:

- **Cohort 1 (4L+ R/R FL):** received at least 3 prior lines of systemic therapy. At least 1 of these lines must be a combination which included an anti-CD20 antibody and an alkylating agent. Prior HSCT was permitted as part of a line of prior therapy along with the preceding salvage regimen. A group of 4L+ double-refractory subjects was to be enrolled in this cohort.

- **Cohort 2 (3L R/R FL):** received 2 prior lines of systemic therapy. At least 1 of these lines must be a combination which included an anti-CD20 antibody and an alkylating agent. Prior HSCT was permitted as part of a line of prior therapy along with the preceding salvage regimen.
- **Cohort 3 (2L R/R FL):** received 1 prior line of combination systemic therapy, which included an anti-CD20 antibody and an alkylating agent. A group of POD24-Per Protocol subjects was to be enrolled to this cohort. The 2L subjects that did not meet this definition must instead meet one of the modified GELF criteria.
- **Cohort 4 (3L+ R/R MZL):** received at least 2 prior systemic therapies, including at least one line of combination systemic therapy, therapy with an anti-CD20 antibody and an alkylating agent, or relapsed after HSCT.

Main inclusion and exclusion criteria

Eligible subjects must have had:

- histologically confirmed FL (Grade 1, 2, or 3a) or MZL, as assessed by local pathology, within 6 months of screening
- relapsed or refractory disease as assessed by the Investigator defined as follow:
 - a. Relapsed lymphoma is defined as relapse after an initial response of CR or PR to the prior therapy
 - b. Refractory lymphoma is defined as a best response of SD or PD after prior therapy
- measurable disease defined as PET-positive disease with at least one PET positive lesion and at least one measurable nodal or extranodal lesion according to the 'Celgene interpretation of the Lugano Classification'.
- ECOG performance status of 0 or 1, and adequate organ functions.

Main exclusion criteria included evidence or history of composite DLBCL and FL, or transformed FL, CNS-only involvement by malignancy (secondary CNS involvement was allowed), or prior CAR T-cell or other genetically-modified cell therapy.

A retrospective central pathology confirmation of the FL diagnosis was required per study protocol.

Treatments

Protocol-related treatments were relegated to pre-treatment and treatment period as reported below:

Pretreatment Period

Leukapheresis

Following screening and enrolment, an unstimulated leukapheresis collection was performed on each subject to obtain a sufficient quantity of PBMCs for the production of the Liso-cel investigational product. Leukapheresis was to occur approximately 5 weeks prior to Liso-cel administration on Day 1. Leukapheresis was required to be scheduled as soon as possible after meeting eligibility requirements, in coordination with the Sponsor. If Liso-cel could not be manufactured, the subject could have had a second leukapheresis procedure performed, as long as they continued to meet eligibility requirements.

Optional Bridging Treatment Between Leukapheresis and LDC

Anticancer treatment as bridging was allowed for disease control while Liso-cel was manufactured, if deemed necessary by the Investigator (i.e., after leukapheresis and prior to Lymphodepleting Chemotherapy (LDC)).

Treatment Period

The treatment period was defined as the period of time from the date on which LDC was first administered to Day 29 after Liso-cel infusion. All subjects, including those who prematurely withdrew after the one dose of Liso-cel and those with progressive disease (PD), were asked to complete the post-treatment follow-up visits at the following intervals: Days 60, 90, 180, 270, 365, 545, 730 (Month 24), and Months 30, 36, 42, 48, 54, and 60 (EOS) after Liso-cel administration for disease status and survival, unless otherwise specified.

Subjects were required to be clinically stable, and recovered from any prior toxicities, to receive LDC and proceed with Liso-cel infusion. Neither LDC nor Liso-cel was administered if there was a worsening of performance status (PS) (compared to initial assessment), rapid clinical deterioration, or evidence of rapidly progressive disease. Prior to LDC and Liso-cel administration, subjects were evaluated for evidence of ongoing infection and if an infection was suspected, it was treated, while LDC and Liso-cel treatment were postponed until infection resolution.

Lymphodepleting Chemotherapy

Upon notification from the Sponsor that Liso-cel was available, LDC was timed so as to be completed 2 to 7 days prior to Liso-cel administration. A low-intensity LDC regimen of fludarabine IV (30 mg/m²/day for 3 days) and cyclophosphamide IV (300 mg/m²/day for 3 days) was administered prior to Liso-cel administration: LDC administration denoted the start of the Treatment Period.

Liso-cel Administration

Subjects were premedicated with 500 to 650 mg acetaminophen per os (PO) and 25 to 50 mg diphenhydramine hydrochloride (PO or intravenous (IV)) 30 to 60 minutes prior to Liso-cel administration. These medications were to be repeated every 6 hours as needed based on the Investigator's assessment of symptoms. Premedication with steroids was not allowed. Liso-cel administration was given as a single dose of 100×10^6 CAR+ T cells (including CD8+ CAR+ T cells and CD4+ CAR+ T cells) on Study Day 1, 2 to 7 days after completion of LDC. Each Liso-cel dose consisted of CD8+ CAR+ T cells and CD4+ CAR+ T cells. Liso-cel was infused on Day 1 at a single dose of 100×10^6 CAR-positive viable T cells (CAR+ T cells), 2 to 7 days after completion of LDC. Subjects were continuously monitored during Liso-cel administration. Vital signs (temperature, respiratory rate, heart rate, blood pressure, and SaO₂ by pulse oximetry) were measured approximately every 15 minutes ($\pm$ 5 minutes), starting from 15 minutes prior to the first IV administration until one hour after the last IV administration, and hourly for the next 2 hours.

Concomitant medications

Concomitant medications were allowed during the protocol.

Prohibited prior treatments included: alemtuzumab treatment within 6 months of leukapheresis, fludarabine or cladribine treatment within 3 months of leukapheresis, and prior CAR T-cell or other genetically-modified cell therapy.

Objectives

The primary objective of the study was to determine the antitumoral activity of Liso-cel in patients affected by R/R FL.

The secondary objectives included to evaluate other measures of efficacy and safety of liso-cel.

Outcomes/endpoints

Primary Endpoint

The primary endpoint was the ORR as assessed by PET-CT (for FL) using the “Lugano Classification”, and defined as the percentage of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) up to 60 months after liso-cel infusion as determined by an IRC (see table below).

Per Study FOL-001 protocol, PET scan was used to evaluate bone marrow lymphoma involvement.

Table 16. Estimands for the primary objective

Population	Adult patients with FL who are refractory or relapsed to the prior therapy in Cohort 1 (4L+), Cohort 2 (3L), Cohort 3 (2L) who <u>would</u> encounter the Intercurrent Event of achieving a response (CR or PR) at any time up to 60 months after liso-cel infusion, which is assessed by PET-CT by IRC using the Lugano Classification
Treatment condition<s>	Assignment to liso-cel, single administration, in a single arm trial
Endpoint (variable)	ORR: Achieving a response (CR or PR) at any time up to 60 months after liso-cel infusion, which is assessed by PET-CT by IRC using the 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	
Intercurrent event n 1 Lost to follow-up before achieving a CR/PR	Strategy Composite: subjects are counted as non-responders
Intercurrent event n 2 Subsequent anti-lymphoma Therapy	Strategy While-on-treatment: Observations after the intercurrent event are excluded.
Intercurrent event n 3	Strategy

HSCT as consolidation therapy	Treatment Policy: Disease assessments after the intercurrent event are included regardless of intercurrent event. Subjects who receive HSCT post infusion (but no other anticancer treatment) should continue to undergo scans, unless they have progressive disease
Intercurrent event n 4 Progression assessed by IRC	Strategy While-on treatment: Disease assessments after the intercurrent event are excluded.
Intercurrent event n 5 Death on the same day as CR/PR achieved	Strategy Treatment Policy: Subjects are counted as Responders

Secondary and exploratory objectives/Endpoints

Table 17. Efficacy and PRO Endpoints - Study FOL-001

Secondary Endpoints	Endpoint description
Complete response rate (CRR) as assessed by PET-CT (for FL) using the "Lugano Classification" ^a	Percentage of subjects achieving a CR at any time up to 60 months after liso-cel treatment (EOS)
Duration of Response (DOR) as assessed by PET-CT and/or CT using the "Lugano Classification" ^a	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 treatment (EOS)
DOR if best overall responses (BOR) is CR, as assessed by PET-CT and/or CT ^b using the "Lugano Classification" ^a	For subjects with a BOR of CR, time from first response (CR or PR) to disease progression or death from any cause up to 60 months after liso-cel infusion (EOS) ^c
Progression free survival (PFS) as assessed by PET-CT and/or CT using the "Lugano Classification" ^a	Time from start of liso-cel to disease progression or death from any cause, whichever occurs first up to 60 months after liso-cel treatment (EOS)
Overall survival (OS)	Time from start of liso-cel to time of death due to any cause up to 60 months after liso-cel treatment (EOS)
Health related quality of life (HRQoL)	HRQoL primary domains of interest assessed by EORTC QLQ-C30 (global health/QoL, physical functioning,

cognitive functioning, fatigue, pain) and FACT-LymS up to 24 months after liso-cel treatment

Exploratory

HRQoL	HRQoL parameters assessed by the remaining subscales of: EORTC QLQ-C30, up to 24 months after liso-cel treatment
Health Utility and Global Health Assessment	EQ-5D-5L health utility and VAS scores up to 60 months after liso-cel treatment (EOS)
Hospital Resource Utilization	Number of inpatient ICU days and outpatient visits up to 60 months after liso-cel treatment (EOS)

a Per Study FOL-001 protocol, PET scan was used to evaluate bone marrow lymphoma involvement.

b PET-CT was not required for subjects who reached a PET-CT CR and these subjects could subsequently be monitored by CT only.

c Definition above per protocol. Of note, per SAP version 3.0, DOR if BOR is CR was defined as the time from first complete response to disease progression or death from any cause up to 60 months after liso-cel infusion.

Complete Response Rate (CRR), DOR, PFS and OS were defined as key secondary endpoints and were all assessed by PET-CT scans based on the Lugano Classification.

Regarding the definition of DOR and PFS, the EMA censoring rules were applied, while in the OS analysis all available survival information, including the information from the long-term follow-up study were included.

Estimands for the key secondary objectives

Table 18. First key secondary endpoint: complete response (CR)

Population	Adult patients with FL who are refractory or relapsed to the prior therapy in Cohort 1 (4L+), Cohort 2 (3L), Cohort 3 (2L) who <u>would</u> encounter the Intercurrent Event of achieving a CR at any time up to 60 months after liso-cel infusion, which is assessed by PET-CT by IRC using the Lugano Classification
Treatment condition<s>	Assignment to liso-cel, single administration, in a single arm trial
Endpoint (variable)	CR: Achieving a response of CR at any time up to 60 months after liso-cel infusion, which is assessed by PET-CT by IRC using the 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	
Intercurrent event n 1	Strategy Composite: subjects are counted as non-responders

Lost to follow-up before achieving a CR/PR	
Intercurrent event n 2 Subsequent anti-lymphoma Therapy	Strategy While-on-treatment: Observations after the intercurrent event are excluded.
Intercurrent event n 3 HSCT as consolidation therapy	Strategy Treatment Policy: Disease assessments after the intercurrent event are included regardless of intercurrent event. Subjects who receive HSCT post infusion (but no other anticancer treatment) should continue to undergo scans, unless they have progressive disease
Intercurrent event n 4 Progression assessed by IRC	Strategy While-on treatment: Disease assessments after the intercurrent event are excluded.
Intercurrent event n 5 Death on the same day as CR achieved	Strategy Treatment Policy: Subjects are counted as Responders

Table 19. Second key secondary endpoint: Duration of response (DOR)

Population	Adult patients with FL who are refractory or relapsed to the prior therapy in Cohort 1 (4L+), Cohort 2 (3L), Cohort 3 (2L) who <u>would</u> encounter the Intercurrent Event of achieving a CR at any time up to 60 months after liso-cel infusion, which is assessed by PET-CT by IRC using the Lugano Classification
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 Classification
Population-level summary	Median DOR with 95% CI
Intercurrent events and strategy to handle them	
Intercurrent event n 1 Lost to follow-up before PD or death	Strategy Hypothetical: Censored at last adequate response assessment before the intercurrent event
Intercurrent event n 2 Start a new anti-lymphoma Therapy before PD/death	Strategy Treatment policy: All data are used regardless of this intercurrent event.

Table 20. Third key secondary endpoint: Progression free survival (PFS)

Population	Adult patients with FL who are refractory or relapsed to the prior therapy in Cohort 1 (4L+), Cohort 2 (3L), Cohort 3 (2L) who <u>would</u> encounter the Intercurrent Event of achieving a CR at any time up to 60 months after liso-cel infusion, which is assessed by PET-CT by IRC using the Lugano Classification
Treatment condition<s>	Assignment to liso-cel, single administration, in a single arm trial
Endpoint (variable)	PFS is defined as the time from start of liso-cel to disease progression or death from any cause, whichever occurs first up to 60 months after liso-cel infusion (EOS).
Population-level summary	Median PFS with 95% CI
Intercurrent events and strategy to handle them	
Intercurrent event n 1 Lost to follow-up	Strategy Hypothetical: Censored at last adequate response assessment before the intercurrent event

Intercurrent event n 2 Start a new anti-lymphoma Therapy before PD/death	Strategy Treatment policy: All data are used regardless of this intercurrent event.
---	---

Table 21. Forth key secondary endpoint: overall survival (OS)

Population	Adult patients with FL who are refractory or relapsed to the prior therapy in Cohort 1 (4L+), Cohort 2 (3L), Cohort 3 (2L) who <u>would</u> encounter the Intercurrent Event of achieving a CR at any time up to 60 months after liso-cel infusion, which is assessed by PET-CT by IRC using the Lugano Classification
Treatment condition<s>	Assignment to liso-cel, single administration, in a single arm trial
Endpoint (variable)	OS is defined as the time from start of liso-cel to time of death due to any cause up to 60 months after liso-cel infusion (EOS).
Population-level summary	Median OS with 95% CI
Intercurrent events and strategy to handle them	
Intercurrent event n 1 Lost to follow-up	Strategy Hypothetical: Censored at last adequate response assessment before the intercurrent event
Intercurrent event n 2 Start a new anti-lymphoma Therapy before death	Strategy Treatment policy: All data are used regardless of this intercurrent event.

According to Study FOL-001 protocol subjects were considered enrolled in the trial once they underwent leukapheresis. The Leukapheresed Analysis Set corresponds, therefore, to the ITT Set and includes all subjects who had signed informed consent, met all inclusion/exclusion criteria, and underwent leukapheresis.

Study assessment

Efficacy has been assessed by radiographic tumour evaluation by diagnostic quality computed tomography (CT)/magnetic resonance imaging (MRI) scans (chest, neck, abdomen and pelvis) and/or positron emission tomography (PET) scans according to the Lugano Classification (Cheson, 2014) and

has been reviewed by an independent review committee (IRC). For this study, a “Modified Lugano Classification Criteria” has been used; FL subjects have been primarily be assessed using PET scans.

Notably, PET scans were not required after a subject achieved a complete response (CR) unless progressive disease (PD) was suspected on follow- up CT/MRI scan. Assessment of bone marrow involvement by lymphoma was not routinely used at screening, while a confirmatory bone marrow biopsy (BMB) has been conducted as soon as logistically feasible after initial PET CR in all FL subjects who did not have a negative BMB between their most recent disease progression prior to screening and initiation of lymphodepleting chemotherapy.

In respect to the risk of Indeterminate Response (IR) due to immunologic-related tumour flare, if a subject demonstrated early tumour progression (defined as occurring prior to 3 months after liso-cel infusion), the investigator was responsible for evaluating whether the subject was experiencing a possible pseudoprogression (i.e., tumour flare, a local inflammatory reaction indicating early tumour response at sites of disease such as lymph nodes). Per protocol, if tumour flare was suspected it was recommended that either a biopsy be performed or the lesion be reassessed in at least 2 weeks, and if there was continued evidence of tumour progression, the date of progressive disease was that of the previous evaluation.

Sensitivity analyses

Sensitivity analyses of primary and secondary efficacy endpoints, including ORR, CRR, DOR, and PFS, referred as per FDA algorithm, were performed based on the IRC Procedures Document and the use of FDA censoring rules for DOR and PFS, as reported in the table below.

Table 22. Definitions of FDA Algorithm and IRC Charter

Terminology	FDA algorithm	IRC charter
Response evaluation	IRC Procedures Document using the Lugano Classification	IRC charter using a modified Lugano Classification (using PET scan instead of BMB for lymphomatous bone marrow involvement)
Censoring rules	FDA censoring rules for DOR and PFS	EMA censoring rules for DOR and PFS
Per-protocol analyses	Sensitivity analyses; referred as “FDA criteria” in the statistical outputs	Primary analyses; referred as “IRC assessment” in the statistical outputs

In particular, attention has been posed on:

- 1) BMB was required to confirm metabolic CR in subjects with a positive, missing, or inconclusive BMB at study entry. Subjects with a negative study entry BMB were exempt from confirmatory biopsies
- 2) The following scenarios were categorized as PD regardless of PET-based metabolic response at that time point:
 - a. Complete metabolic response/partial metabolic response on PET and disease progression on CT scan
 - b. Stable metabolic disease on PET and disease progression on CT scan

- c. New lesion on CT scan regardless of whether the new lesion is FDG avid on PET
- d. The application of FDA censoring rules to determine DOR and PFS

Subgroup analyses

Efficacy subgroup analyses were performed based on demographic variables from subject's baseline status such as:

- Age
- Sex
- Ethnicity
- Anticancer treatment for disease control (yes vs no)
- Concomitant G-CSF (yes vs no)

Subgroup analyses and forest plots were performed by cohort for the primary and secondary efficacy endpoints of ORR, CRR, DOR, PFS, and OS.

Sample size

Assuming a 20% drop out rate, a total of approximately 213 subjects may be enrolled to ensure a total of 170 treatments with Liso-cel divided into 4 cohorts as follows:

- Cohort 1 (4L+ R/R FL): approximately 50 treated subjects
- Cohort 2 (3L R/R FL): approximately 40 treated subjects
- Cohort 3 (2L R/R FL): approximately 20 treated subjects, with a minimum of 10 POD24-Per Protocol subjects
- Cohort 4 (3L+ R/R MZL): approximately 60 treated subjects

The statistical hypothesis for the definition of the ORR threshold was set on literature data about the efficacy of PI3K inhibitors Idelalisib (in 3L+ subjects double refractory, assessed by CT: ORR 54%, CRR 14%, median DOR 11 months and median PFS 11 months; 4 median prior lines of therapy), Copanlisib (3L+ subjects r/r, received rituximab and alkylating agent, assessed by CT: ORR 59%, CRR 14%, median DOR 12 months and median PFS 11 months; 4 median prior lines of therapy) and Duvelisib (3L+ subjects double refractory, assessed by CT: ORR 42%, CRR 1%, median DOR 11 months and median PFS 8 months; 3 median prior lines of therapy).

Based on the literature for 3L+ r/r Marginal Zone Lymphoma (MZL) subjects, the following results have been reported: Ibrutinib data (n=63), 3L+ subjects, assessed by CT: ORR 48%, CRR 3%, median DOR not reached, median PFS 14 months; 2 median prior lines of therapy.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

The hypothesis testing was planned for each of the following analysis group:

Analysis Group 1: 4L+ r/r FL (Cohort 1)

Analysis Group 2: 3L+ r/r FL (Cohort 1 and Cohort 2)

Analysis Group 3: 2L r/r FL (Cohort 3)

Analysis Group 4: 3L+ r/r MZL (Cohort 4)

All patients included in the 3L + were eligible regardless of the presence of POD24 status or GELF criteria.

Analysis Group 1: 4L+ r/r FL (Cohort 1): The null hypotheses for each endpoint are as follows as assessed by PET-CT: H0: ORR = 50%, CRR = 20%. With a sample size of 50 treated subjects, using 1-sided 0.025 level testing, there would be 90% power to detect an ORR of 74% versus 50%, or a CRR of 42% versus 20%, using exact binomial one sample tests unadjusted for the hierarchical testing procedure.

Analysis Group 2: 3L+ FL (Cohort 1 and Cohort 2): The analysis of the 3L+ FL population will include approximately 90 treated subjects (approximately 40 3L and 50 4L+). The null hypotheses for each endpoint are as follows as assessed by PET-CT: H0: ORR = 60%, CRR = 30%. With a sample size of 90 subjects, using 1- sided 0.025 level testing there would be 90% power to detect an ORR of 77% versus 60%, or a CRR of 48% versus 30%, using exact binomial one sample tests unadjusted for the hierarchical testing procedure.

Analysis Group 3: 2L r/r FL (Cohort 3): The targets for each endpoint are as follows as assessed by PET-CT: Ha: ORR = 80%, CRR = 50%. The analysis of this cohort is for proof of concept. With a sample size of 20 treated subjects, using 1-sided 0.025 level testing, there would be 80% power to detect an ORR of 80% versus 50%, or a CRR of 50% versus 19%, using exact binomial one sample tests unadjusted for the hierarchical testing procedure.

Analysis Group 4: 3L+ r/r MZL (Cohort 4): The null hypotheses for each endpoint are as follows as assessed by CT: H0: ORR = 50%, CRR = 5%. With a sample size of 60 treated subjects, using 1-sided 0.025 level testing, there would be 90% power to detect an ORR of 72 % versus 50%, or a CRR of 19 % versus 5%, using exact binomial one sample tests unadjusted for the hierarchical testing procedure.

For each of these analysis groups, hierarchical testing was used to control type 1 error with the endpoints being tested in the following order: ORR, CRR.

Since Cohort 1 is included in Analysis Groups 1 and 2, a multiplicity adjustment procedure was used between these groups. The following three testing sequences were treated independently:

Sequence 1 (Analysis Groups 1 and 2)

Sequence 2 (Analysis Group 3)

Sequence 3 (Analysis Group 4)

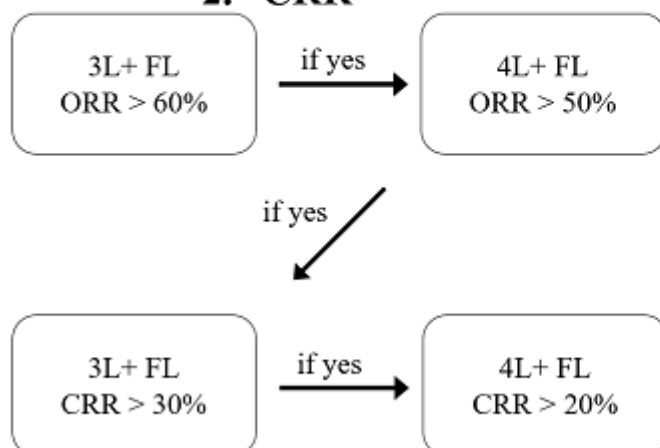
Figure 3. Testing sequences

Testing Sequence 1

3L+ FL and 4L+ FL:

1. ORR

2. CRR

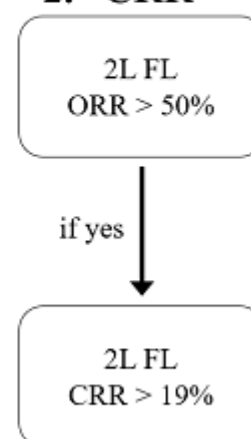


Testing Sequence 2

2L FL:

1. ORR

2. CRR



Primary Endpoint

For each analysis group described above, the ORR analysis was a one-sided 0.025 level exact binomial test for whether the ORR was greater than the null hypothesis rate. The primary efficacy analysis tested, for each analysis group, the null hypothesis of $ORR \leq p_0$, against the alternative hypothesis that $ORR > p_0$ at a 1-sided 0.025 level of significance at the primary analysis, ie,

$H_0: ORR \leq p_0$ vs. $H_1: ORR > p_0$.

The primary analysis for Analysis Groups 1 and 2 was planned for when the approximate number of planned treated subjects in both groups was followed for DOR for approximately 12 months after first response of CR or PR per the Investigator's assessment or until death, disease progression, or withdrawal from the study. The approximate number of treated subjects was 50 for Analysis Group 1 (4L+ R/R FL) and 90 for Analysis Group 2 (3L+ R/R FL).

The primary analysis for Analysis Group 3 was planned when the approximate number of planned treated subjects was followed for DOR for approximately 12 months after first response of CR or PR per the Investigator's assessment or until death, disease progression, or withdrawal from the study. The approximate number of treated subjects was 20 for Analysis Group 3 (2L R/R FL).

Secondary Endpoint of CRR

For each analysis group reported before, the CRR analysis will be a one-sided 0.025 level exact binomial test for whether the CRR is greater than the null hypothesis rate; similar to what reported for the primary endpoint, a multiplicity adjustment procedure was required considering that cohort 1 was included in both analysis group 1 and 2.

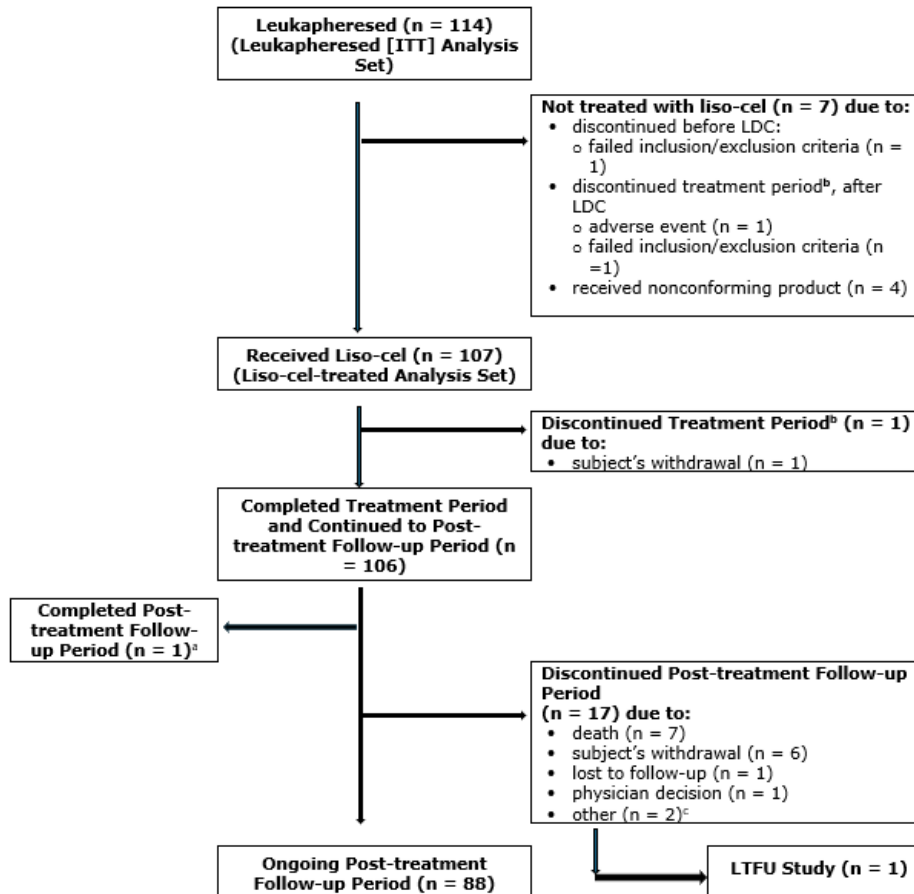
The efficacy analysis of CRR will test, for each analysis group, the null hypothesis of $CRR \leq p_0$ against the alternative hypothesis that $CRR > p_0$ at a 1-sided 0.025 level of significance at the primary analysis, i.e.:

$H_0: CRR \leq p_0$ vs. $H_1: CRR > p_0$

Results

Participant flow

Data cutoff date of 10-Jan-2024.



Recruitment

As of the clinical data cut-off date (10-Jan-2024), all FL subjects (Cohorts 1, 2, and 3) were enrolled (MZL subjects in Cohort 4 were still enrolling), and 115 FL subjects had 12 months of DOR follow up.

Subject Disposition

As of the data cut-off date (10-Jan-2024), all FL cohorts (Cohorts 1, 2, and 3) had been enrolled. All but one subject in the 3L+ FL group (Cohorts 1 and 2) completed the treatment period (Days 1 to 29). As of the data cut-off date, the median follow-up was 29.96 (24.67, 32.76) months, with the majority (82.2%) of 3L+ FL subjects were ongoing in the post-treatment follow-up period (Day -30 to Month 60).

Table 23. Key Dates and Follow-up - Study FOL-001

First Subject First Visit	14-Jul-2020
First FL Subject Enrolled (Day of Leukapheresis)	29-Jul-2020
Last FL Subject Enrolled (and Treated)	10-Feb-2022 (04-Apr-2022)

Primary Analysis (hypothesis testing)

Clinical Data Cutoff	27-Jan-2023
Database Lock	31-Mar-2023
Median on-study follow-up, months (range: min, max) ^a	18.89 (0.3, 28.2)

Updated Analysis - EU submission (SmPC)

Clinical Data Cutoff	10-Jan-2024
Database Lock	06-Mar-2024
Median on-study follow-up (3L+ FL), months (range: min, max) ^a	29.96 (24.67, 32.76)

^a Study follow-up time in months is defined as: (EOS date - date of liso-cel infusion + 1) / 30.4375. For subjects continuing on-study follow-up time is defined as: (data cutoff date - date of liso-cel infusion + 1) / 30.4375.

Table 24. Subject Disposition, Pre-liso-cel Treatment - Screened Set

	4L+ FL Cohort 1 N = 65	3L FL Cohort 2 N = 49	3L+ FL Cohorts 1 + 2 N = 114	2L FL Cohort 3 N = 25	Total 2L+ FL Cohorts 1, 2, 3 N = 139	Total N = 154
Total Number of Subjects Screened						154
Number of Subjects Who Discontinued Screening Period ^a						15 (9.7)
Primary Reason for Discontinuing Screening Period ^b						
Withdrawal by Subject						1 (6.7)
Screen Failure						14 (93.3)
Inclusion/ Exclusion Criteria Failed ^c						14 (93.3)
Subjects Who Met Screening Eligibility						139 (90.3)
Leukapheresed	65 (100.0)	49 (100.0)	114 (100.0)	25 (100.0)	139 (100.0)	139 (90.3)
Leukapheresed but did not Receive Liso-cel	6 (9.2)	1 (2.0)	7 (6.1)	2 (8.0)	9 (6.5)	9 (5.8)
Reason for Not Receiving Liso-cel						
Received Nonconforming Product	3 (4.6)	1 (2.0)	4 (3.5)	1 (4.0)	5 (3.6)	5 (3.2)
Adverse Event	1 (1.5)	0	1 (0.9)	0	1 (0.7)	1 (0.6)
Failure to Meet Inclusion/Exclusion Criteria	1 (1.5)	0	1 (0.9)	1 (4.0)	2 (1.4)	2 (1.3)
Not Reported	1 (1.5)	0	1 (0.9)	0	1 (0.7)	1 (0.6)
Completed Pre-Treatment Period	64 (98.5)	49 (100.0)	113 (99.1)	24 (96.0)	137 (98.6)	137 (89.0)
Discontinued Pre-Treatment Period After Leukapheresis And Prior to LDC	1 (1.5)	0	1 (0.9)	1 (4.0)	2 (1.4)	2 (1.3)
Reason for Discontinuing Pre-Treatment Period						
Failure to Meet Treatment Criteria	1 (1.5)	0	1 (0.9)	1 (4.0)	2 (1.4)	2 (1.3)

Inclusion/Exclusion Criteria Failed ^c	1 (1.5)	0	1 (0.9)	1 (4.0)	2 (1.4)	2 (1.3)
Subjects Entered Treatment Period	64 (98.5)	49 (100.0)	113 (99.1)	24 (96.0)	137 (98.6)	137 (89.0)
Subjects Completed LDC But Did Not Receive Liso-cel	5 (7.7)	1 (2.0)	6 (5.3)	1 (4.0)	7 (5.0)	7 (4.5)

a Percentages are based on the number of subjects screened

b Percentages are based on the number of subjects who discontinued screening period

c Subjects may have more than one inclusion/exclusion criteria failed. inclusion/exclusion criteria were checked again prior to LDC and prior to liso-cel infusion

Table 25. Subject Disposition - Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Subjects Received Liso-cel	59 (100.0)	48 (100.0)	107 (100.0)	23 (100.0)	130 (100.0)
Subjects Ongoing on Treatment Period	0	0	0	0	0
Subjects Completed Treatment Period	59 (100.0)	47 (97.9)	106 (99.1)	22 (95.7)	128 (98.5)
Subjects Discontinued Treatment Period	0	1 (2.1)	1 (0.9)	1 (4.3)	2 (1.5)
Primary Reason for Treatment Period Discontinuation					
Adverse Event	0	0	0	1 (4.3)	1 (0.8)
Withdrawal by Subject	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Subjects Continued to Posttreatment Follow-Up Period	59 (100.0)	47 (97.9)	106 (99.1)	22 (95.7)	128 (98.5)
Subjects Ongoing on Posttreatment Follow-Up Period	51 (86.4)	42 (87.5)	93 (86.9)	22 (95.7)	115 (88.5)
Subjects Completed Posttreatment Follow-Up Period ^a	0	0	0	0	0
Subjects Discontinued Posttreatment Follow-Up Period	8 (13.6)	5 (10.4)	13 (12.1)	0	13 (10.0)
Primary Reason for Discontinuing Posttreatment Follow-Up Period					
Death	5 (8.5)	2 (4.2)	7 (6.5)	0	7 (5.4)
Withdrawal by Subject	2 (3.4)	2 (4.2)	4 (3.7)	0	4 (3.1)
Physician Decision	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Other	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Discontinued Posttreatment Follow-Up Period Due to Covid-19 Pandemic	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Subjects Continued to LTFU Protocol ^b					
Yes	1 (1.7)	0	1 (0.9)	0	1 (0.8)
No	7 (11.9)	6 (12.5)	13 (12.1)	1 (4.3)	14 (10.8)
Reason Subject Did Not Continue to LTFU Protocol					
Death	5 (8.5)	3 (6.3)	8 (7.5)	1 (4.3)	9 (6.9)
Progressive Disease	1 (1.7)	0	1 (0.9)	0	1 (0.8)

Withdrawal by Subject	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Subject Refused	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Withdrawal by Subject After Initial Consent	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Other	1 (1.7)	0	1 (0.9)	0	1 (0.8)

Treatment Period is defined as the initiation of lymphodepleting chemotherapy and concludes at Day 29 after liso-cel infusion. Posttreatment Follow-up period is defined as the period starting on day 30 post-liso-cel visit and ending at the 60-month post-liso-cel visit.

a Includes subjects that completed the posttreatment follow-up period based on the prior protocol that only required 2 years.

b Per protocol, all subjects who either complete the follow-up period specified in the protocol or prematurely withdraw after infusion of liso-cel, would be eligible to enroll in the LTFU study (GC-LTFU-001; to be continued for up to 15 years after liso-cel infusion) at the end of study visit or at the time of withdrawal, respectively; a separate ICF was to be provided for the LTFU study.

Conduct of the study

Impact of COVID-19 Pandemic

This study was conducted in 10 countries for FL cohorts including Austria, Canada, France, Germany, Italy, Japan, Spain, Sweden, United Kingdom, and United States. The clinical cutoff date and data base lock (DBL) of the study occurred on 27-Jan-2023 and 31-Mar-2023, respectively, during the global COVID-19 (coronavirus) pandemic. The FDA and EMA both issued guidelines on the management of clinical trials during the COVID-19 pandemic. In response to this public health emergency, the Sponsor developed overarching principles and guidance for the conduct of the Sponsor's clinical research in light of COVID-19.

Impact on data integrity: All CRF data entries were completed, and all critical queries were addressed in all countries. Throughout the duration of the study, no site has required an increase in Source Data Verification (SDV) due to compliance issues. Mitigation included increased remote data listing review. Therefore, the outstanding SDVs were assessed as not having a significant impact on the integrity of the data.

Protocol deviations: 23 COVID-19 related protocol deviations were captured prior to the clinical cutoff date. None of these protocol deviations had an impact on the quality of the data in this study.

A COVID-19 Safety Surveillance Plan was created by the Sponsor, and newly released MedDRA v23.0 (effective date 04-May-2020) was adopted to retrospectively search for AEs related to COVID-19 in the database. There were 2 cases reporting the COVID-19 PTs (see below) for JCAR017-FOL-001 from 27-Jan-2023 (LSLV) to 27-Jan-2023 (cutoff date). The COVID-19 PTs include the following:

- COVID-19
- COVID-19 pneumonia
- SARS-CoV-2 test positive

Prior to the DBL, a comprehensive situational analysis was performed by the Sponsor's Data Review Committee to assess the potential impact on the DBL and data quality, and concluded that the DBL should proceed as planned.

Changes to Planned Analyses

Changes to planned analyses prior to the cutoff date included the following:

SAP Version 2.0 (08-Jul-2021): added the following subgroup analysis: Anticancer treatment for disease control: yes vs. no

SAP Version 3.0 (05-Oct-2022): added details about the timing of primary analysis; extended the timing for analyses. Clarified that the PRO analyses are based on change from pre-LDC measurement; changed from selected domains of interest to all domains for EORTC QLQ-C30; added analysis for EQ-5D-5L. Added sensitivity analyses of primary and secondary efficacy endpoints, including ORR, CRR, DOR and PFS, based on the description in the IRC Procedures Document and using FDA censoring rules for DOR and PFS. To satisfy any EU and US regulatory requirements, updated age categories for subgroup analysis to Age: < 65, ≥ 65 to < 75, ≥ 75 at screening.

Protocol deviations

GCP Deviations and Serious Breach

There were no GCP deviations impacting the study, and no sites were closed for GCP issues. No serious breaches were reported.

Important Protocol Deviations

Table 26. Summary of Protocol Deviations - Leukapheresed Analysis Set

	4L+ FL Cohort 1 N = 65	3L FL Cohort 2 N = 49	3L+ FL Cohorts 1 + 2 N = 114	2L FL Cohort 3 N = 25	Total 2L+ FL Cohorts 1, 2, 3 N = 139
Subjects With at Least One Protocol Deviation	53 (81.5)	42 (85.7)	95 (83.3)	22 (88.0)	117 (84.2)
Subjects With at Least One Important Protocol Deviation	2 (3.1)	1 (2.0)	3 (2.6)	0	3 (2.2)
Protocol Deviations					
Procedures/Tests	32 (49.2)	27 (55.1)	59 (51.8)	14 (56.0)	73 (52.5)
Laboratory	14 (21.5)	21 (42.9)	35 (30.7)	7 (28.0)	42 (30.2)
ICF Issues	11 (16.9)	11 (22.4)	22 (19.3)	11 (44.0)	33 (23.7)
Visit Schedule	47 (72.3)	34 (69.4)	81 (71.1)	18 (72.0)	99 (71.2)
Study Drug	1 (1.5)	1 (2.0)	2 (1.8)	1 (4.0)	3 (2.2)
Inclusion/ Exclusion	0	1 (2.0)	1 (0.9)	0	1 (0.7)
Other	4 (6.2)	1 (2.0)	5 (4.4)	0	5 (3.6)
Number of Subjects With					
One Deviation	10 (15.4)	5 (10.2)	15 (13.2)	4 (16.0)	19 (13.7)
Two Deviations	6 (9.2)	3 (6.1)	9 (7.9)	2 (8.0)	11 (7.9)
>2 Deviations	37 (56.9)	34 (69.4)	71 (62.3)	16 (64.0)	87 (62.6)
Important Protocol Deviations					
Procedures/Tests	2 (3.1)	0	2 (1.8)	0	2 (1.4)
Inclusion/Exclusion	0	1 (2.0)	1 (0.9)	0	1 (0.7)
Number of Subjects With					
One Important Deviation	2 (3.1)	1 (2.0)	3 (2.6)	0	3 (2.2)

Protocol amendments

The original protocol for this study was dated 11-Nov-2019. As of the 27-Jan-2023 cutoff date, there were a total of 2 global amendments, 2 country specific amendments (Great Britain and Japan) and 1 country specific addendum (Sweden).

The primary endpoint was changed from CRR to ORR and secondary endpoint from ORR to CRR in Protocol Amendment 1.0 (06-Jul-2021), while the study was ongoing, since ORR has been traditionally used as an endpoint in indolent NHL trial. The interpretation of ORR generally remains consistent across response criteria, while different versions of response criteria are used to define CRR in clinical trials. Importantly, this decision was not influenced by JCAR017-FOL-001 trial data, as no efficacy analyses based on IRC data had been conducted before the protocol amendment.

Table 27. Summary of Key Changes to Protocol JCAR017-FOL-001

Protocol Amendment/Date	Summary of Key Changes	Planned Sample Size	Subjects Enrolled at Time of Amendment
Protocol Amendment 2.0/ 10-Jul-2022	The posttreatment follow-up period was extended from 2 years (24 months) to 5 years (60 months); assessment planning updated accordingly Extended timing for statistical analyses Added new assessment for PD/relapse: local results on target antigen expression if available (ie, CD19 expression in subjects who received prior CD19-directed therapy) Increased total number of subjects from approximately 188 to approximately 213	213	181
Protocol Amendment 1.0/ 06-Jul-2021	Changed primary endpoint from CRR to ORR and secondary endpoint from ORR to CRR Added requirement for BMB to confirm all CMRs in FL subjects as part of a sensitivity analysis Broadened third line population from 'high risk' to 'all comers' given that for FL subjects in the third line of therapy the five-year survival rate is only 20%, highlighting the urgent need for treatment of the 'all comers' population. The hierarchical testing was updated to first test the 3L+ 'all comers' group, followed by the 4L+ group. This was done to acknowledge that the main population of unmet need is the 3L+ population. Increased the number of subjects enrolled in the 4L+ cohort (from 40 to 50) and decreased the number of subjects enrolled in the 3L cohort (from 50 to 40) Added requirement of upper gastrointestinal endoscopy/biopsy for subjects with gastric MALT lymphoma	188	116
Original Protocol/ 11-Nov-2019	N/A	188	None

COVID-19-Related Protocol Deviations

Based on the number and types of protocol deviations, the study primary and secondary endpoints were not impacted by COVID-19, as well as the ability to monitor and manage subjects' safety during the conduct of the study; less than 2% of more than 2 deviations were recorded during the trial.

Table 28. COVID-19 Related Protocol Deviations - Leukapheresed Set

4L+ FL Cohort 1 N = 65	3L FL Cohort 2 N = 49	3L+ FL Cohorts 1 + 2 N = 114	2L FL Cohort 3 N = 25	Total 2L+ FL Cohorts 1, 2, 3 N = 139

Subjects With at Least One Covid-19-Related Protocol Deviation	10 (15.4)	10 (20.4)	20 (17.5)	3 (12.0)	23 (16.5)
Protocol Deviations					
Procedures/Tests	2 (3.1)	1 (2.0)	3 (2.6)	1 (4.0)	4 (2.9)
Visit Schedule	8 (12.3)	10 (20.4)	18 (15.8)	2 (8.0)	20 (14.4)
Number of Subjects With					
One Deviation	6 (9.2)	9 (18.4)	15 (13.2)	2 (8.0)	17 (12.2)
Two Deviations	4 (6.2)	0	4 (3.5)	1 (4.0)	5 (3.6)
>2 Deviations	0	1 (2.0)	1 (0.9)	0	1 (0.7)

Baseline data

Table 29. Key Demographic and Baseline Characteristics - Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Age (Years)					
N	59	48	107	23	130
Median	64	60	62	53	60
Q1, Q3	56.0, 70.0	53.5, 67.0	55.0, 69.0	42.0, 62.0	53.0, 68.0
Min, Max	23, 80	27, 78	23, 80	34, 69	23, 80
Age Group (Years) - N (%)					
< 65	34 (57.6)	31 (64.6)	65 (60.7)	18 (78.3)	83 (63.8)
≥ 65 - < 75	18 (30.5)	14 (29.2)	32 (29.9)	5 (21.7)	37 (28.5)
≥ 75	7 (11.9)	3 (6.3)	10 (9.3)	0	10 (7.7)
Sex - N (%)					
Female	24 (40.7)	17 (35.4)	41 (38.3)	6 (26.1)	47 (36.2)
Male	35 (59.3)	31 (64.6)	66 (61.7)	17 (73.9)	83 (63.8)
Ethnicity - N (%)^a					
Hispanic or Latino	4 (6.8)	1 (2.1)	5 (4.7)	1 (4.3)	6 (4.6)
Not Hispanic or Latino	39 (66.1)	35 (72.9)	74 (69.2)	15 (65.2)	89 (68.5)
Not Reported	16 (27.1)	12 (25.0)	28 (26.2)	7 (30.4)	35 (26.9)
Primary Race - N (%)^b					
Asian	7 (11.9)	3 (6.3)	10 (9.3)	2 (8.7)	12 (9.2)
Black or African American	3 (5.1)	0	3 (2.8)	1 (4.3)	4 (3.1)
White	31 (52.5)	29 (60.4)	60 (56.1)	9 (39.1)	69 (53.1)
Not Collected or Unknown	18 (30.5)	16 (33.3)	34 (31.8)	11 (47.8)	45 (34.6)
Region - N (%)					
Europe	27 (45.8)	34 (70.8)	61 (57.0)	12 (52.2)	73 (56.2)
Japan	6 (10.2)	3 (6.3)	9 (8.4)	1 (4.3)	10 (7.7)

North America	26 (44.1)	11 (22.9)	37 (34.6)	10 (43.5)	47 (36.2)
Type of Lymphoma and Histological Subtype/Grade at Screening - N (%)					
Grade 1	3 (5.1)	6 (12.5)	9 (8.4)	6 (26.1)	15 (11.5)
Grade 2	41 (69.5)	31 (64.6)	72 (67.3)	11 (47.8)	83 (63.8)
Grade 3A	15 (25.4)	10 (20.8)	25 (23.4)	6 (26.1)	31 (23.8)
Unknown	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Time From Initial B-NHL Diagnosis to Liso-cel Infusion (Years)					
N	59	48	107	23	130
Median	7.288	4.62	5.136	1.993	4.709
Q1, Q3	4.164, 12.134	2.509, 6.341	3.370, 8.794	1.131, 4.394	2.968, 7.860
Min, Max	1.87, 35.27	0.70, 18.74	0.70, 35.27	0.76, 11.38	0.70, 35.27
Time From Completion of Most Recent Systemic Regimen to Progression (Months)					
N	58	46	104	23	127
Median	1.13	3.55	1.87	3.71	1.91
Q1, Q3	0.03, 5.62	0.49, 13.04	0.20, 10.20	0.56, 12.91	0.20, 10.81
Min, Max	-4.4, 115.0	-2.2, 43.7	-4.4, 115.0	-4.0, 106.1	-4.4, 115.0
Within ≥ 0 - ≤ 6 Months - N (%)	31 (52.5)	18 (37.5)	49 (45.8)	11 (47.8)	60 (46.2)
Within > 6 - ≤ 12 Months - N (%)	5 (8.5)	7 (14.6)	12 (11.2)	2 (8.7)	14 (10.8)
Subjects Progressed Before Regimen Completion - N (%)	13 (22.0)	7 (14.6)	20 (18.7)	4 (17.4)	24 (18.5)
Time From Completion of Most Recent Systemic Regimen to Progression (or Stable Disease if Missing Progression Date) (Months)					
N	59	48	107	23	130
Median	1.08	2.61	1.81	3.71	1.82
Q1, Q3	0.03, 5.62	0.49, 13.04	0.20, 9.59	0.56, 12.91	0.20, 9.59
Min, Max	-4.4, 115.0	-2.2, 43.7	-4.4, 115.0	-4.0, 106.1	-4.4, 115.0
Within ≥ 0 - ≤ 6 Months - N (%)	31 (52.5)	20 (41.7)	51 (47.7)	11 (47.8)	62 (47.7)
Within > 6 - ≤ 12 Months - N (%)	5 (8.5)	7 (14.6)	12 (11.2)	2 (8.7)	14 (10.8)
Subjects Progressed or With Stable Disease Before Regimen Completion - N (%)	14 (23.7)	7 (14.6)	21 (19.6)	4 (17.4)	25 (19.2)
FLIPI at Screening - N (%)					
Low Risk (0-1)	9 (15.3)	3 (6.3)	12 (11.2)	11 (47.8)	23 (17.7)
Intermediate Risk (2)	14 (23.7)	20 (41.7)	34 (31.8)	4 (17.4)	38 (29.2)
High Risk (3-5)	36 (61.0)	25 (52.1)	61 (57.0)	8 (34.8)	69 (53.1)
Ann Arbor Stage at Screening - N (%)					
Stage I	1 (1.7)	0	1 (0.9)	1 (4.3)	2 (1.5)
Stage II	4 (6.8)	7 (14.6)	11 (10.3)	5 (21.7)	16 (12.3)
Stage III	18 (30.5)	21 (43.8)	39 (36.4)	6 (26.1)	45 (34.6)
Stage IV	36 (61.0)	20 (41.7)	56 (52.3)	11 (47.8)	67 (51.5)
Presence of B-Symptoms at Screening - N (%)					

Yes	11 (18.6)	7 (14.6)	18 (16.8)	2 (8.7)	20 (15.4)
No	46 (78.0)	41 (85.4)	87 (81.3)	19 (82.6)	106 (81.5)
Unknown	2 (3.4)	0	2 (1.9)	2 (8.7)	4 (3.1)
ECOG Performance Status at Screening - N (%)					
0	30 (50.8)	35 (72.9)	65 (60.7)	17 (73.9)	82 (63.1)
1	29 (49.2)	13 (27.1)	42 (39.3)	6 (26.1)	48 (36.9)
ECOG Performance Status Pre-Liso-cel Infusion - N (%)					
0	24 (40.7)	28 (58.3)	52 (48.6)	16 (69.6)	68 (52.3)
1	33 (55.9)	17 (35.4)	50 (46.7)	7 (30.4)	57 (43.8)
2	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Not Reported	1 (1.7)	3 (6.3)	4 (3.7)	0	4 (3.1)
C-Reactive Protein Prior to Liso-cel - N (%)					
< 20 Mg/L	38 (64.4)	34 (70.8)	72 (67.3)	17 (73.9)	89 (68.5)
≥ 20 Mg/L	19 (32.2)	14 (29.2)	33 (30.8)	4 (17.4)	37 (28.5)
Not Reported	2 (3.4)	0	2 (1.9)	2 (8.7)	4 (3.1)
Lactate Dehydrogenase (LDH) Prior to Lymphodepleting Chemotherapy - N (%)					
≤ ULN	32 (54.2)	28 (58.3)	60 (56.1)	17 (73.9)	77 (59.2)
> ULN	27 (45.8)	20 (41.7)	47 (43.9)	6 (26.1)	53 (40.8)
≥ 500 U/L	4 (6.8)	0	4 (3.7)	1 (4.3)	5 (3.8)
< 500 U/L	55 (93.2)	48 (100.0)	103 (96.3)	22 (95.7)	125 (96.2)
Modified GELF Criteria Met at Time of Most Recent Relapse - N (%)					
Yes	31 (52.5)	26 (54.2)	57 (53.3)	16 (69.6)	73 (56.2)
Symptoms Attributable to FL	8 (13.6)	5 (10.4)	13 (12.1)	6 (26.1)	19 (14.6)
Threatened End-Organ Function/ Cytopenia Secondary to Lymphoma/ Bulky Disease	12 (20.3)	12 (25.0)	24 (22.4)	7 (30.4)	31 (23.8)
Splénomegaly	1 (1.7)	3 (6.3)	4 (3.7)	0	4 (3.1)
Steady Progression Over at Least 6 Months	10 (16.9)	6 (12.5)	16 (15.0)	3 (13.0)	19 (14.6)
No	28 (47.5)	22 (45.8)	50 (46.7)	7 (30.4)	57 (43.8)
Double Refractory Status Per CRF - N (%)^c					
Yes	36 (61.0)	33 (68.8)	69 (64.5)	11 (47.8)	80 (61.5)
No	23 (39.0)	15 (31.3)	38 (35.5)	12 (52.2)	50 (38.5)
POD24 Status Per CRF - N (%)^d					
Yes	21 (35.6)	25 (52.1)	46 (43.0)	12 (52.2)	58 (44.6)
No	38 (64.4)	23 (47.9)	61 (57.0)	11 (47.8)	72 (55.4)
POD24 of First Line Therapy with Anti-CD20 and Alkylator - N (%)^e					
Yes	27 (45.8)	31 (64.6)	58 (54.2)	15 (65.2)	73 (56.2)
No	32 (54.2)	16 (33.3)	48 (44.9)	8 (34.8)	54 (43.1)
Not Estimable	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Refractory to Last Line of Therapy per CRF - N (%)					
Yes	24 (40.7)	14 (29.2)	38 (35.5)	3 (13.0)	41 (31.5)

No	35 (59.3)	34 (70.8)	69 (64.5)	20 (87.0)	89 (68.5)
----	-----------	-----------	------------------	-----------	-----------

Baseline characteristic is defined as the latest measurement on or prior to the date of liso-cel infusion.

- ^a Ethnicity "Not reported" is auto populated due to local privacy regulations for France, Germany, Sweden, United Kingdom.
- ^b Race "Not Collected or Unknown" is auto populated due to local privacy concerns for France, Germany, Sweden, United Kingdom.
- ^c Double refractory status can be met at any line of therapy that includes an anti-CD20 antibody and alkylating agent. Definition per protocol: double refractory subjects are those who are refractory to both an anti-CD20 antibody and an alkylating agent (defined as subjects who did not respond or progressed during or up to 6 months after completing treatment with an anti-CD20 monoclonal antibody and an alkylating agent) or refractory to anti-CD20 maintenance therapy (defined as subjects who did not respond or progressed during or up to 6 months after completing maintenance treatment with an anti-CD20 monoclonal antibody).
- ^d Definition of POD-24 per protocol. As per protocol and CRF, progression of disease within 24 months of diagnosis after initiating treatment with an anti-CD20 and alkylating agent within the first 6 months of initial FL diagnosis.
- ^e POD24 definition: progression of disease within 24 months of initiation of first-line chemoimmunotherapy with anti CD20 and alkylating agent.

Central diagnosis confirmation

Out of the 139 subjects in the second-line therapy or later (2L+) FL Leukapheresed, the diagnosis of FL was retrospectively confirmed by the central pathology laboratory for 128 subjects (92%). Eleven subjects (third-line therapy or later [3L+] FL, n = 7; second line [2L FL, n = 4) did not have a central pathology confirmation of FL diagnosis due to: For 4 subjects (3L+ FL, n = 3; 2L FL, n = 1) FL diagnosis could not be confirmed by the central pathology laboratory due to insufficient or inadequate sample availability. For these 4 subjects, central pathology analyses could not be performed, and no results are available.

For 4 subjects (3L+ FL, n = 2; 2L FL, n = 2), the central pathology laboratory was able to confirm diagnosis of B-cell lymphoma but was unable to complete testing in order to confirm FL diagnosis in the samples provided. This was due to insufficient or inadequate tissue to complete the immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH) testing, hence precluding subclassification of lymphoma.

For one 3L+ FL subject, no B-cell lymphoma was detected in the sample analysed by the central pathology laboratory.

For 2 subjects who had central pathology laboratory diagnosis different from FL:

- a) One 2L FL subject had findings not compatible with a B-lymphoid neoplasm according to the central pathology laboratory.
- b) One 3L+ FL subject had findings consistent with large B-cell lymphoma of follicular center origin according to the central pathology laboratory. Per investigator and according to local pathology assessment, the subject had transformed disease to diffuse large B-cell lymphoma, reported after leukapheresis. The subject was then discontinued from the study before receiving any study treatment, because not meeting the required inclusion criterion of FL diagnosis.

Prior anticancer therapy

Table 30. Summary of Prior Anticancer Therapies - Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Number of Lines of Prior Therapies					
N	59	48	107	23	130
Median	4	2	3	1	2
Q1, Q3	3.0, 5.0	2.0, 2.0	2.0, 4.0	1.0, 1.0	2.0, 4.0

Min, Max	3, 10	2, 3	2, 10	1, 3	1, 10
Number of Lines of Prior Therapies - N (%)					
1	0	0	0	22 (95.7)	22 (16.9)
2	0	47 (97.9)	47 (43.9)	0	47 (36.2)
3	24 (40.7)	1 (2.1)	25 (23.4)	1 (4.3)	26 (20.0)
4	18 (30.5)	0	18 (16.8)	0	18 (13.8)
≥ 5	17 (28.8)	0	17 (15.9)	0	17 (13.1)
Number of Prior Radiation Therapies					
N	59	48	107	23	130
Median	0	0	0	0	0
Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
Min, Max	0, 5	0, 2	0, 5	0, 2	0, 5
Number of Prior Radiation Therapies - N (%)					
0	50 (84.7)	45 (93.8)	95 (88.8)	22 (95.7)	117 (90.0)
1	5 (8.5)	2 (4.2)	7 (6.5)	0	7 (5.4)
2	2 (3.4)	1 (2.1)	3 (2.8)	1 (4.3)	4 (3.1)
4	1 (1.7)	0	1 (0.9)	0	1 (0.8)
≥ 5	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Number of Lines of Prior Radiation Therapies ^a					
N	59	48	107	23	130
Median	0	0	0	0	0
Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
Min, Max	0, 5	0, 1	0, 5	0, 2	0, 5
Number of Lines of Prior Radiation Therapies ^a - N (%)					
0	54 (91.5)	47 (97.9)	101 (94.4)	22 (95.7)	123 (94.6)
1	2 (3.4)	1 (2.1)	3 (2.8)	0	3 (2.3)
2	2 (3.4)	0	2 (1.9)	1 (4.3)	3 (2.3)
≥ 5	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Number of Lines of Prior Systemic Therapies					
N	59	48	107	23	130
Median	4	2	3	1	2
Q1, Q3	3.0, 4.0	2.0, 2.0	2.0, 4.0	1.0, 1.0	2.0, 4.0
Min, Max	3, 10	2, 2	2, 10	1, 1	1, 10
Number of Lines of Prior Systemic Therapies - N (%)					
1	0	0	0	23 (100.0)	23 (17.7)
2	0	48 (100.0)	48 (44.9)	0	48 (36.9)
3	26 (44.1)	0	26 (24.3)	0	26 (20.0)
4	19 (32.2)	0	19 (17.8)	0	19 (14.6)
≥ 5	14 (23.7)	0	14 (13.1)	0	14 (10.8)

Type of Last Line of Therapy Prior to Liso-cel (Reported in ≥ 10% of subjects)

Systemic Treatment Only	50 (84.7)	45 (93.8)	95 (88.8)	22 (95.7)	117 (90.0)
Rituximab	19 (32.2)	32 (66.7)	51 (47.7)	20 (87.0)	71 (54.6)
Cyclophosphamide	6 (10.2)	15 (31.3)	21 (19.6)	15 (65.2)	36 (27.7)
Prednisone	6 (10.2)	10 (20.8)	16 (15.0)	11 (47.8)	27 (20.8)
Doxorubicin	4 (6.8)	11 (22.9)	15 (14.0)	11 (47.8)	26 (20.0)
Vincristine	4 (6.8)	10 (20.8)	14 (13.1)	10 (43.5)	24 (18.5)
Cytarabine	7 (11.9)	15 (31.3)	22 (20.6)	0	22 (16.9)
Obinutuzumab	10 (16.9)	9 (18.8)	19 (17.8)	2 (8.7)	21 (16.2)
Etoposide	6 (10.2)	11 (22.9)	17 (15.9)	0	17 (13.1)
Lenalidomide	11 (18.6)	5 (10.4)	16 (15.0)	0	16 (12.3)
Bendamustine	0	10 (20.8)	10 (9.3)	6 (26.1)	16 (12.3)
Radiotherapy Only	0	0	0	0	0
Both Systemic Treatment and Radiotherapy	9 (15.3)	3 (6.3)	12 (11.2)	1 (4.3)	13 (10.0)
Time From Start of Last Systemic Regimen Prior to Liso-cel (Years)					
N	59	48	107	23	130
Median	0.97	1.64	1.22	1.84	1.35
Q1, Q3	0.50, 2.34	0.69, 2.21	0.64, 2.24	1.10, 3.15	0.67, 2.59
Min, Max	0.2, 13.1	0.2, 5.6	0.2, 13.1	0.5, 11.3	0.2, 13.1
Number of Prior Anticancer Surgeries					
N	59	48	107	23	130
Median	0	0	0	0	0
Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
Min, Max	0, 1	0, 1	0, 1	0, 1	0, 1
Number of Prior Anticancer Surgeries - N (%)					
0	56 (94.9)	47 (97.9)	103 (96.3)	22 (95.7)	125 (96.2)
1	3 (5.1)	1 (2.1)	4 (3.7)	1 (4.3)	5 (3.8)
Refractory or Relapsed to Last Systemic Therapy - N (%)					
Refractory	24 (40.7)	14 (29.2)	38 (35.5)	3 (13.0)	41 (31.5)
Relapsed	35 (59.3)	34 (70.8)	69 (64.5)	20 (87.0)	89 (68.5)
Prior Hematopoietic Stem Cell Transplantation - N (%)					
No	43 (72.9)	31 (64.6)	74 (69.2)	23 (100.0)	97 (74.6)
Yes	16 (27.1)	17 (35.4)	33 (30.8)	0	33 (25.4)
If Yes					
Autologous	16 (27.1)	17 (35.4)	33 (30.8)	0	33 (25.4)
Best Response to Last Prior Systemic Regimen N (%)					
Complete Response (CR)	19 (32.2)	21 (43.8)	40 (37.4)	13 (56.5)	53 (40.8)
Partial Response (PR)	17 (28.8)	13 (27.1)	30 (28.0)	9 (39.1)	39 (30.0)

Stable Disease (SD)	8 (13.6)	5 (10.4)	13 (12.1)	0	13 (10.0)
Progressive Disease (PD)	15 (25.4)	9 (18.8)	24 (22.4)	1 (4.3)	25 (19.2)
Received Prior PI3K Inhibitors - N (%)					
Yes	26 (44.1)	1 (2.1)	27 (25.2)	0	27 (20.8)
No	33 (55.9)	47 (97.9)	80 (74.8)	23 (100.0)	103 (79.2)
Received Prior Rituximab and Lenalidomide (R2) - N (%)					
Yes	18 (30.5)	5 (10.4)	23 (21.5)	0	23 (17.7)
No	41 (69.5)	43 (89.6)	84 (78.5)	23 (100.0)	107 (82.3)
Last Line of Prior Systemic Therapy - N (%)					
PI3K Inhibitors	15 (25.4)	1 (2.1)	16 (15.0)	0	16 (12.3)
Rituximab and Lenalidomide (R2)	11 (18.6)	5 (10.4)	16 (15.0)	0	16 (12.3)

Prior therapies include any therapies that were stopped before the Leukapheresis.

Systemic therapy includes chemotherapy, immunotherapy and radioimmunotherapy.

Prior systemic anticancer therapies do not include stem cell transplant but do include conditioning regimens for stem cell transplant.

HSCT is considered a line of systemic therapy, but is grouped with preceding chemotherapy regimen and any intervening conditioning regimen including radiation.

^a Includes only stand-alone radiotherapies

Optional Bridging Therapy for Disease Control Prior to LDC

Table 31. Summary of Anticancer Therapies for Disease Control - Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Anticancer Treatment ^a					
Yes	29 (49.2)	15 (31.3)	44 (41.1)	5 (21.7)	49 (37.7)
No	30 (50.8)	33 (68.8)	63 (58.9)	18 (78.3)	81 (62.3)
Type of Treatment					
Systemic Treatment Only	26 (44.1)	14 (29.2)	40 (37.4)	4 (17.4)	44 (33.8)
Radiotherapy Only	3 (5.1)	1 (2.1)	4 (3.7)	1 (4.3)	5 (3.8)
Both Systemic and Radiotherapy	0	0	0	0	0
Systemic Anticancer Medication for Disease Control					
Antineoplastic and Immunomodulating Agents (Reported in ≥ 5% of subjects)	26 (44.1)	14 (29.2)	40 (37.4)	4 (17.4)	44 (33.8)
Rituximab	9 (15.3)	9 (18.8)	18 (16.8)	2 (8.7)	20 (15.4)
Cyclophosphamide	10 (16.9)	6 (12.5)	16 (15.0)	1 (4.3)	17 (13.1)
Gemcitabine	7 (11.9)	4 (8.3)	11 (10.3)	1 (4.3)	12 (9.2)
Vincristine	6 (10.2)	5 (10.4)	11 (10.3)	0	11 (8.5)
Oxaliplatin	6 (10.2)	3 (6.3)	9 (8.4)	1 (4.3)	10 (7.7)

Doxorubicin	5 (8.5)	4 (8.3)	9 (8.4)	0	9 (6.9)
Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins (Reported in ≥ 2% of subjects)	9 (15.3)	7 (14.6)	16 (15.0)	3 (13.0)	19 (14.6)
Prednisolone	3 (5.1)	2 (4.2)	5 (4.7)	0	5 (3.8)
Prednisone	3 (5.1)	2 (4.2)	5 (4.7)	1 (4.3)	6 (4.6)
Dexamethasone	2 (3.4)	1 (2.1)	3 (2.8)	2 (8.7)	5 (3.8)

^a Anticancer treatment for disease control is defined as any systemic therapy or radiation therapy provided to subjects for disease control after leukapheresis and before LDC.

Table 32. Baseline characteristics in all leukapheresed patients

Characteristic	All leukapheresed (N=114)
Median age, years (range)	62.0 (23, 80)
≥ 65 to <75 years, n (%)	36 (31.6)
≥ 75 years, n (%)	10 (8.8)
Male gender, n (%)	72 (63.2)
Prior HSCT, n (%)	
Autologous HSCT	34 (29.8)
High FLIPI score (3-5), n (%)	66 (57.9)
Stage III-IV disease at screening, n (%)	102 (89.4)
ECOG performance status (at screening)	
ECOG 0, n (%)	68 (59.6)
ECOG 1, n (%)	46 (40.4)
Double refractory, n (%)	74 (64.9)
Progression within 24 months of first line therapy with anti-CD20 and alkylator, n (%)	
Yes	
No	63 (55.3)
Not estimable	50 (43.9)
	1 (0.9)
Median number of prior systemic treatments (range)	3 (2,10)

Numbers analysed

The Liso-cel-treated Efficacy Analysis Set was the primary population used for the efficacy analyses and the Liso-cel-treated Analysis Set was the primary population used for the safety analyses.

The difference in numbers between the Liso-cel *Treated Analysis Set* and the Liso-cel *Treated Efficacy Analysis Set* is due to the exclusion of patients without an assessment prior to liso-cel infusion, or evidence of Complete Response to the bridging therapy. At last data cutoff, in 3L+ cohort 4 subjects were excluded from the former 107 subjects included in the treated analysis set; therefore, the resulting efficacy analysis set was constituted by 103 patients. The main reason for exclusion of infused patients from the EAS were represented by "disease evaluation before the end of bridging therapy" (2 cases) and "absence of PET-positive disease at baseline per IRC assessment" (2 cases); all 4 subjects excluded from the EAS were in CR at the most recent follow-up.

Table 33. Analysis Populations - Screened Set

Analysis Population	4L+ FL	3L FL	3L+ FL	2L FL	2L+ FL	Total
Screened Set ^a						154
Eligible Set ^b						139
Leukapheresed (ITT) Set ^c	65 (100.0)	49 (100.0)	114 (100.0)	25 (100.0)	139 (100.0)	139 (100.0)
Liso-cel-treated Set ^d	59 (90.8)	48 (98.0)	107 (93.9)	23 (92.0)	130 (93.5)	130 (93.5)
Liso-cel-treated Efficacy Set ^e	53 (81.5)	48 (98.0)	101 (88.6)	23 (92.0)	124 (89.2)	124 (89.2)
Outpatient Analysis Set ^f	12 (18.5)	2 (4.1)	14 (12.3)	1 (4.0)	15 (10.8)	15 (10.8)
PK Analysis Set ^g	59 (90.8)	48 (98.0)	107 (93.9)	23 (92.0)	130 (93.5)	130 (93.5)
PK Evaluable Analysis Set ^h	59 (90.8)	46 (93.9)	105 (92.1)	23 (92.0)	128 (92.1)	128 (92.1)
PRO Analysis Set ⁱ	56 (86.2)	46 (93.9)	102 (89.5)	20 (80.0)	122 (87.8)	122 (87.8)

Percentages are based on number of Leukapheresed Set.

a Subjects signed informed consent.

b Subjects signed consent who meet all inclusion/exclusion criteria.

c Subjects signed consent who undergo leukapheresis and meet all inclusion/exclusion criteria.

d Subjects received a dose of conforming liso cel.

e Subjects received a dose of liso-cel with PET positive disease present before liso-cel administration per IRC. Subjects without baseline assessment repeated after anticancer therapy for disease control and before liso-cel administration were excluded.

f Subjects monitored as an outpatient in liso-cel-treated set.

g Subjects with any available PK measurements by PCR in the liso-cel-treated set.

h Subjects with at least one evaluable PK parameter in the liso-cel-treated set.

i Subjects completed pre-LDC PRO questionnaires and with at least one post-baseline measurement in the liso-cel -treated set.

Extent of exposure

Lymphodepleting Chemotherapy Exposure

In the Liso-cel-treated Analysis Set, a total 10.0% of subjects received an adjusted dose of fludarabine (11.2% in 3L+ subject and 4.3% in 2L subjects). One (0.9%) subject received an interrupted dose of fludarabine. One (0.9%) 3L+ subject received an adjusted dose of cyclophosphamide. No subjects received an interrupted dose of cyclophosphamide. The median time from end of LDC to liso-cel infusion (4 days; range, 3 to 12) was consistent with the protocol-specified time (2 to 7 days).

Manufacturing

Table 34. Manufacturing Summary - Leukapheresed Set

	4L+ FL Cohort 1 N = 65	3L FL Cohort 2 N = 49	3L+ FL Cohorts 1 + 2 N = 114	2L FL Cohort 3 N = 25	Total 2L+ FL Cohorts 1, 2, 3 N = 139
Time From Leukapheresis to Liso-cel Product Availability (Day) ^a					
N	60	48	108	24	132
Median	28.5	29	29	28	29
Q1, Q3	23.5, 31.5	27.5, 31.5	26.0, 31.5	25.0, 30.0	25.5, 31.0
Min, Max	20, 55	22, 49	20, 55	19, 38	19, 55
Time From Leukapheresis to Liso-cel Infusion (Day) ^a					
N	59	48	107	23	130
Median	47	51.5	50	48	49
Q1, Q3	41.0, 53.0	47.0, 64.5	42.0, 56.0	37.0, 54.0	41.0, 55.0
Min, Max	31, 313	35, 287	31, 313	33, 72	31, 313

^a Among subjects receiving conforming liso-cel product. Data from nonconforming product is not included in the calculation.

^b Manufacturing failure rate is defined as (number of subjects for whom liso-cel product [conforming at time of release] could not be manufactured)/ (number of subjects who had leukapheresis and manufacturing information available) × 100. Rejected lots are excluded from the calculation.

In one case, a delayed infusion was recorded at 313 days after leukapheresis due to persistently positive COVID-19; the subject was infused after the infection resolved. An additional subject also had a delayed infusion 287 days after leukapheresis due to the absence of PET positive disease in non-irradiated lymph nodes after bridging radiation therapy; the subject was infused after disease progression and a PET/CT scan documented PET positive measurable disease.

The reported manufacturing failure in the whole population was similar in the 3L+; the global rate of manufacturing failure was higher in the 4L+ patients, but it is expected considering that this cohort enrolled highly pre-treated patients.

Liso-cel Exposure

In the 3L+ Liso-cel-treated Analysis Set the median number of total (CD8+ and CD4+) liso-cel administered dose cell counts infused was 100.02×10^6 CAR+ T cells (range: 93.4×10^6 to 109.2×10^6).

Table 35. Liso-cel Exposure - Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Liso-cel CD8+ Cells					
Planned Volume (mL)					
N	59	48	107	23	130
Median	2	2.15	2	1.8	2
Q1, Q3	1.70, 3.20	1.60, 2.65	1.60, 2.90	1.40, 2.40	1.60, 2.70
Min, Max	1.3, 8.2	1.1, 12.5	1.1, 12.5	1.2, 6.5	1.1, 12.5
Actual Volume (mL)					
N	59	48	107	23	130
Median	2	2.15	2	1.8	2
Q1, Q3	1.70, 3.20	1.60, 2.65	1.60, 2.90	1.40, 2.40	1.60, 2.70

Min, Max	1.3, 8.2	1.1, 12.5	1.1, 12.5	1.2, 6.5	1.1, 12.5
Total Number of Liso-cel CD8+ Cell Counts Infused (10⁶ Cells)					
N	59	48	107	23	130
Median	49.9	49.76	49.82	50.11	49.85
Q1, Q3	49.47, 50.53	49.37, 50.30	49.39, 50.42	48.96, 50.30	49.36, 50.41
Min, Max	42.3, 51.7	47.9, 51.6	42.3, 51.7	48.1, 51.7	42.3, 51.7
Was the Infusion Delayed?					
Yes	2 (3.4)	0	2 (1.9)	0	2 (1.5)
No	57 (96.6)	48 (100.0)	105 (98.1)	23 (100.0)	128 (98.5)
Reason for Delay					
Adverse Event	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Not Reported	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Was the Infusion Interrupted?					
Yes	1 (1.7)	0	1 (0.9)	0	1 (0.8)
No	58 (98.3)	48 (100.0)	106 (99.1)	23 (100.0)	129 (99.2)
Reason for Interruption					
Not Reported	1 (1.7)	0	1 (0.9)	0	1 (0.8)

Liso-cel CD4+ Cells

Planned Volume (mL)

N	59	48	107	23	130
Median	1.7	1.75	1.7	1.5	1.7
Q1, Q3	1.40, 2.10	1.30, 2.15	1.40, 2.10	1.30, 1.80	1.40, 2.10
Min, Max	0.9, 7.6	0.9, 4.4	0.9, 7.6	1.1, 4.5	0.9, 7.6

Actual Volume (mL)

N	59	48	107	23	130
Median	1.7	1.75	1.7	1.5	1.7
Q1, Q3	1.40, 2.10	1.30, 2.15	1.40, 2.10	1.30, 1.80	1.40, 2.10
Min, Max	0.9, 7.6	0.9, 4.4	0.9, 7.6	1.1, 4.5	0.9, 7.6

If the Volume Delivered is <90% of Assigned

Other	1 (1.7)	0	1 (0.9)	0	1 (0.8)
-------	---------	---	----------------	---	---------

Total Number of Liso-cel CD4+ Cell Counts Infused (10⁶ Cells)

N	59	48	107	23	130
Median	50.2	49.75	49.99	50.29	50.02
Q1, Q3	49.64, 50.74	49.21, 50.58	49.39, 50.66	49.10, 50.74	49.28, 50.66
Min, Max	43.1, 58.8	48.0, 52.0	43.1, 58.8	47.9, 52.0	43.1, 58.8

Was the Infusion Delayed?

Yes	2 (3.4)	0	2 (1.9)	0	2 (1.5)
No	57 (96.6)	48 (100.0)	105 (98.1)	23 (100.0)	128 (98.5)

Reason for Delay

Adverse Event	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Other	1 (1.7)	0	1 (0.9)	0	1 (0.8)

Was the Infusion Interrupted?

No	59 (100.0)	48 (100.0)	107 (100.0)	23 (100.0)	130 (100.0)
Combined Liso-cel Dose					
Total Volume of liso-cel CD4+ And CD8+ (mL)					
N	59	48	107	23	130
Median	4	3.75	4	3.5	3.8
Q1, Q3	3.20, 5.00	3.15, 5.10	3.20, 5.00	2.80, 3.90	3.10, 4.90
Min, Max	2.2, 15.8	2.4, 16.7	2.2, 16.7	2.5, 9.3	2.2, 16.7
Total Number of Liso-cel CD4+ and CD8+ Cell Counts Infused (10⁶ Cells)					
N	59	48	107	23	130
Median	100.13	99.73	100.02	99.92	100.02
Q1, Q3	99.26, 100.88	98.81, 100.78	99.13, 100.87	99.09, 100.67	99.13, 100.73
Min, Max	93.4, 109.2	96.6, 101.8	93.4, 109.2	97.4, 102.9	93.4, 109.2
Ratio of CD4+: CD8+ Cell Counts					
N	59	48	107	23	130
Median	1	1	1	1	1
Q1, Q3	0.99, 1.02	0.99, 1.02	0.99, 1.02	0.99, 1.02	0.99, 1.02
Min, Max	0.9, 1.2	1.0, 1.1	0.9, 1.2	0.9, 1.1	0.9, 1.2

Subsequent Anticancer Therapy

There were 8 (6.2%) subjects who received subsequent anticancer therapy and the most frequently prescribed systemic therapy regimen were antineoplastic and immunomodulating agents (7 [5.4%] subjects). One (0.8%) subject received radiotherapy. No subjects received surgery or HSCT.

Outcomes and estimation

Primary Efficacy Endpoint - Overall Response Rate

Table 36. Overall Response Rate - Per IRC Charter - Sensitivity Analyses -Leukapheresed (ITT) and Per Investigator - Study FOL-001

	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2
ORR per IRC Charter (Liso-cel-treated Efficacy Analysis Set)			
N = 55	N = 48	N = 103	
n (%)	53 (96.4)	47 (97.9)	100 (97.1)
95% CI ^a	(87.5, 99.6)	(88.9, 99.9)	(91.7, 99.4)
Sensitivity Analyses			
ORR (Leukapheresed [ITT] Set)			
N = 65	N = 49	N = 114	
n (%)	58 (89.2)	48 (98.0)	106 (93.0)
95% CI ^a	(79.1, 95.6)	(89.1, 99.9)	(86.6, 96.9)
ORR per Investigator (Liso-cel-treated Efficacy Analysis Set)			
N = 55	N = 48	N = 103	
n (%)	54 (98.2)	47 (97.9)	101 (98.1)

95% CI^a

(90.3, 100.0)

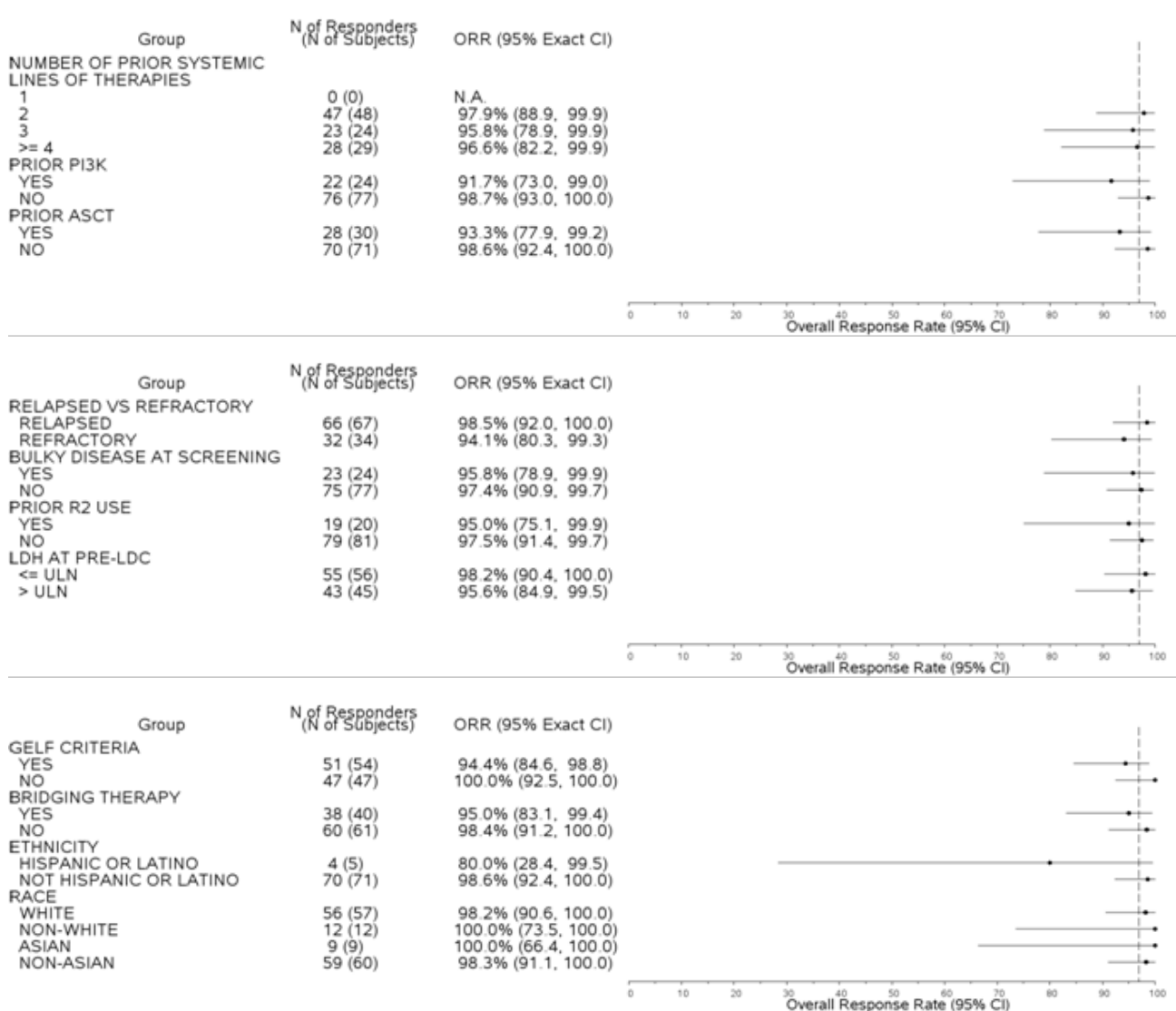
(88.9, 99.9)

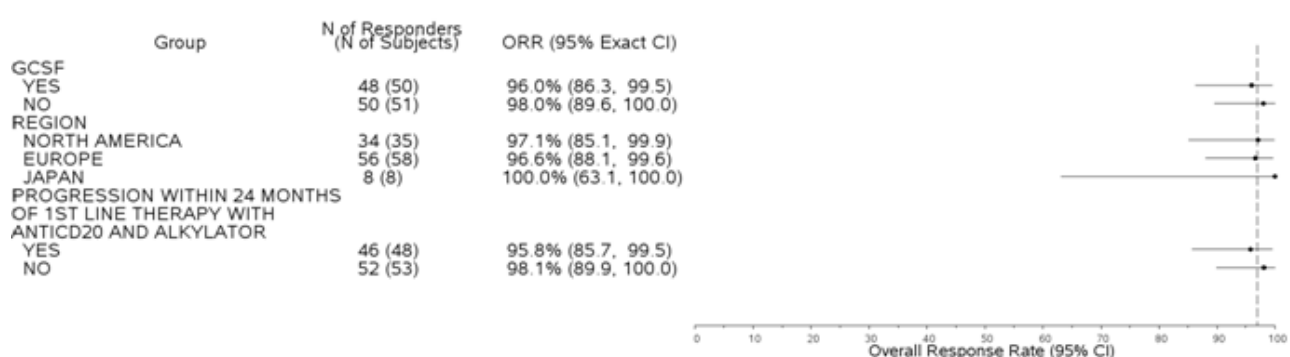
(93.2, 99.8)

The median time to first response (CR or PR) and median time to first CR was 0.95 months (range: 0.6 to 3.3 months).

Subgroup analyses

Figure 4. Forest Plot of ORR per IRC Charter - Liso-cel-treated Efficacy Analysis Set, Subjects from 3L+ R/R FL (Cohort 1 and Cohort 2) Analysis Group





Secondary Efficacy endpoints

Complete Response Rate

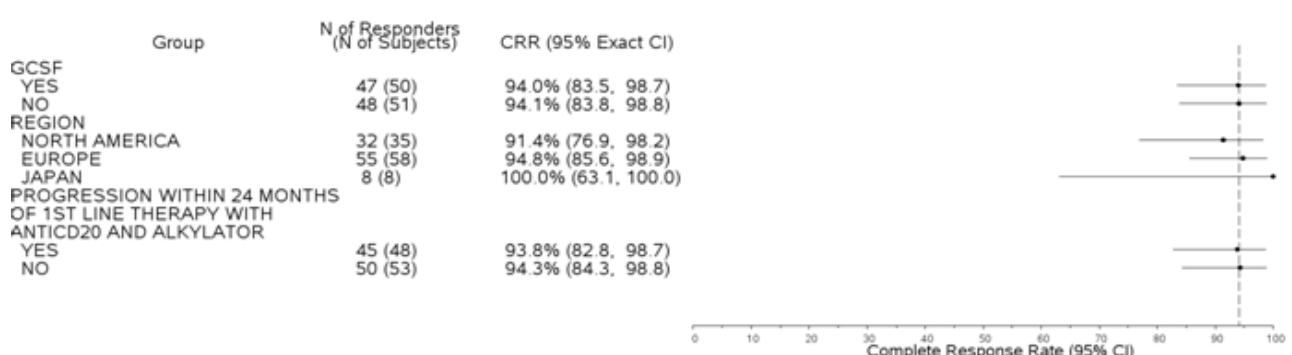
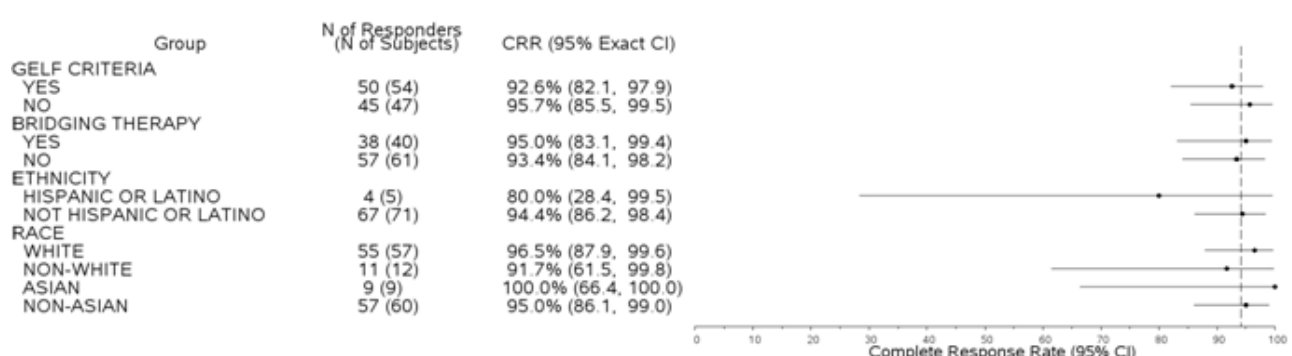
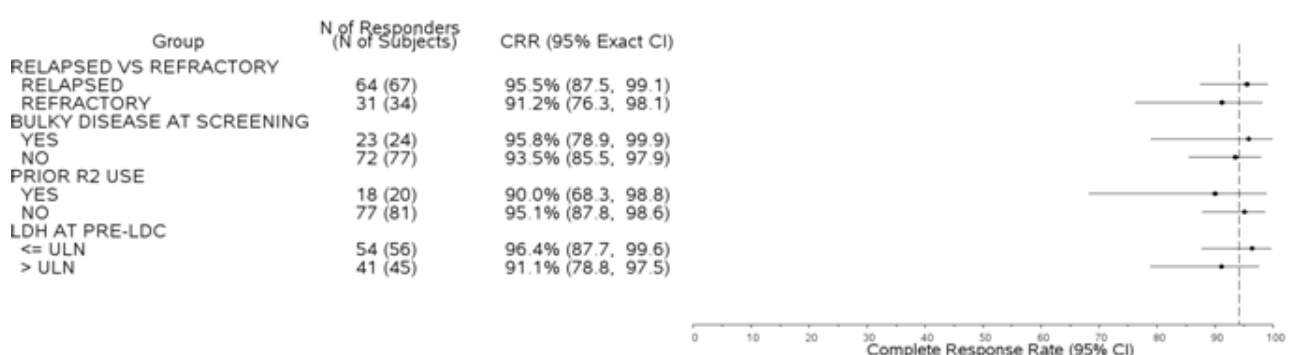
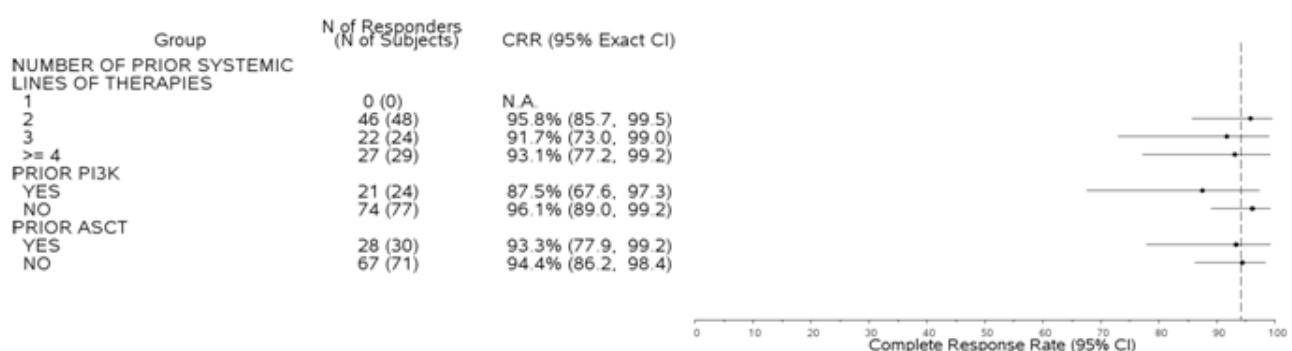
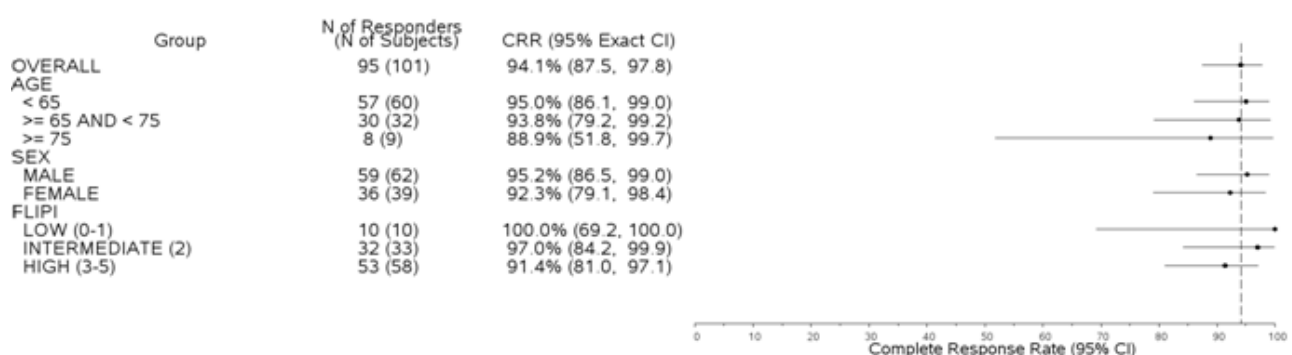
Table 37. CRR - Per IRC Charter - Sensitivity Analyses -Leukapheresed (ITT) and Per Investigator - Study FOL-001

	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2
CRR per IRC Charter (Liso-cel-treated Efficacy Analysis Set)	N = 55	N = 48	N = 103
n (%)	51 (92.7)	46 (95.8)	97 (94.2)
95% CI ^a	(82.4, 98.0)	(85.7, 99.5)	(87.8, 97.8)
Sensitivity Analyses			
CRR (Leukapheresed [ITT] Set)	N = 65	N = 49	N = 114
n (%)	56 (86.2)	47 (95.9)	103 (90.4)
95% CI ^a	(75.3, 93.5)	(86.0, 99.5)	(83.4, 95.1)
CRR per Investigator (Liso-cel-treated Efficacy Analysis Set)	N = 55	N = 48	N = 103
n (%)	51 (92.7)	46 (95.8)	97 (94.2)
95% CI ^a	(82.4, 98.0)	(85.7, 99.5)	(87.8, 97.8)

A sensitivity analyses using the “FDA algorithm” (i.e. requiring a bone marrow biopsy [BMB] to confirm CR) showed a lower CRR compared to the primary analysis per IRC charter. When the FDA algorithm was applied, 22 subjects were downgraded from CR to PR: 19/22 subjects because the BMB results at time of CR were not available, 2/22 had BMB with unknown result, and 1/22 had evidence of lymphomatous BM involvement. Overall, when analyses were performed according to the FDA algorithm, in 3L+ subjects the proportion of reported CRR was consistently lower (72.3%, 95% CI: 62.5, 80.7) and the proportion of PR was higher (25%, 95% CI: 16.4-33.7).

A post-hoc subgroup analysis of time-to-event efficacy outcomes for the 22 subjects with a BOR of CR per IRC charter that was not confirmed using the FDA algorithm showed a trend towards reduced DOR (expected 24-months DOR rate: 58% [34.6-75.5]) and PFS (expected 24-month PFS rate: 58% [34.6-75.5]) when compared with patients with confirmed CR (expected 24-month DOR rate: 76.9% [67.1-84.2]) and PFS (expected 24-month PFS rate: 77% [67.2-84.2]).

Figure 5. Forest Plot of CRR per IRC Charter - Liso-cel-treated Efficacy Analysis Set, Subjects from 3L+ R/R FL (Cohort 1 and Cohort 2) Analysis Group



Duration of Response (DOR)

Table 38. DOR - Analyses per IRC Charter, Leukapheresed (ITT), and Per Investigator - Study FOL-001

	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2
DOR per IRC Charter (Liso-cel-treated Efficacy Analysis Set)	N = 53 responders	N = 47 responders	N = 100 responders
Median (95% CI) ^a	30.85 (30.85, N.A.)	N.A.	N.A. (30.85, N.A.)
Min, Max ^b	1.9, 35.0+	1.9, 34.5+	1.9, 35.0+
Median follow-up (from first response), months (95% CI) ^c	23.03 (22.74, 23.23)	23.26 (22.93, 23.39)	23.13 (22.93, 23.26)
Sensitivity Analyses			
DOR (Leukapheresed [ITT] Set)	N = 58 responders	N = 48 responders	N = 106 responders
Median (95% CI) ^a	N.A. (30.85, N.A.)	N.A.	N.A. (30.85, N.A.)
Min, Max ^b	1.9, 35.0+	1.9, 34.5+	1.9, 35.0+
Median follow-up (from first response), months (95% CI) ^c	23.10 (22.74, 23.26)	23.26 (22.93, 23.39)	23.13 (23.00, 23.26)
DOR if Best Response is CR (Leukapheresed [ITT] Set)	N = 56 responders	N = 47 responders	N = 103 responders
Median (95% CI) ^a	N.A. (30.85, N.A.)	N.A.	N.A. (30.85, N.A.)
Min, Max ^b	2.1, 35.0+	1.9, 34.5+	1.9, 35.0+
DOR per Investigator (Liso-cel-treated Efficacy Analysis Set)	N = 54 responders	N = 47 responders	N = 101 responders
Median (95% CI) ^a	34.76 (30.85, N.A.)	N.A.	34.76 (30.85, N.A.)
Min, Max ^b	2.1, 35.0+	1.9, 34.5+	1.9, 35.0+
Median follow-up (from first response), months (95% CI) ^c	23.06 (22.74, 23.26)	23.26 (22.97, 23.39)	23.13 (23.00, 23.26)

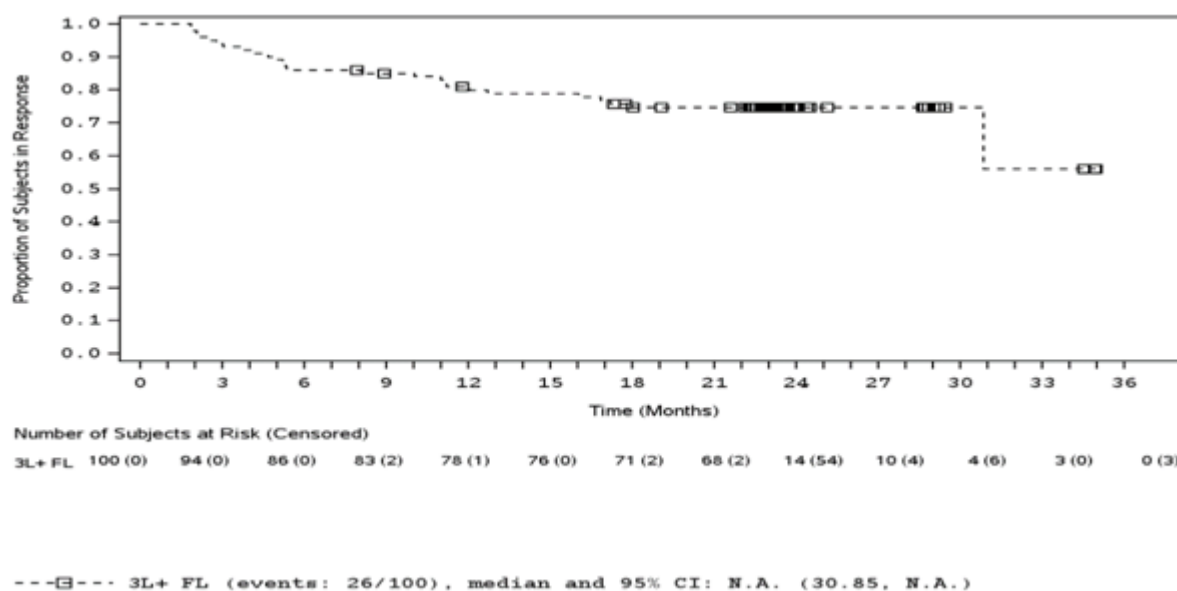
^a Median, Q1, Q3 are estimated from KM product-limit estimates

^b Symbol + indicates a censored value.

^c Reverse KM method is used to obtain the median follow-up and its 95% CIs.

Sensitivity analysis per FDA algorithm confirms that DOR in subjects with CR or PR was not reached in 3L+ subjects (95% CI: 18.04, NA) and 2L subjects (95% CI: 19.32, NA).

Figure 6. KM Plot of DOR per IRC Charter - Liso-cel-treated Efficacy Analysis Set, Subjects who Achieved CR or PR 3L+ Subjects



Symbols represent censored observations.

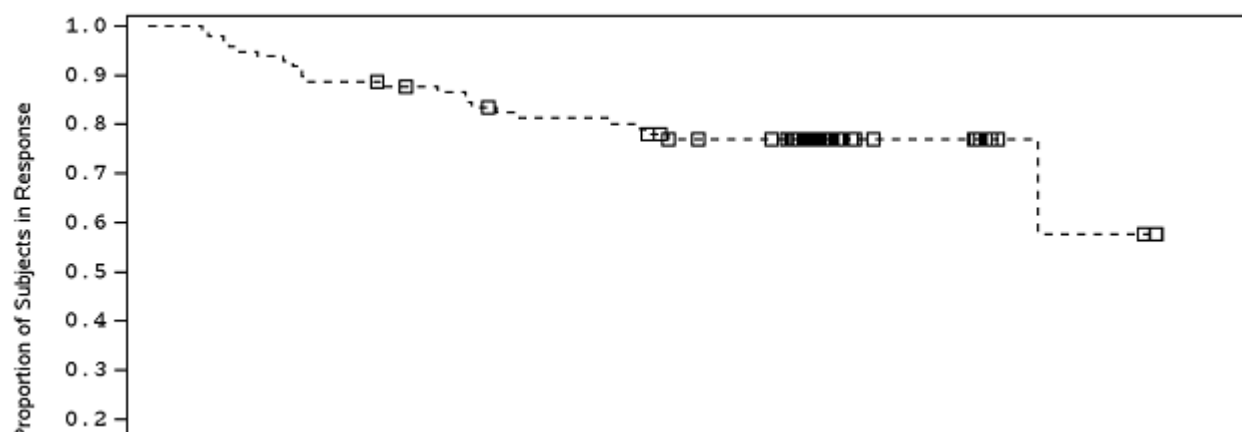
DOR is defined as the interval from the first documentation of response to progressive disease or death from any cause, whichever occurs first.

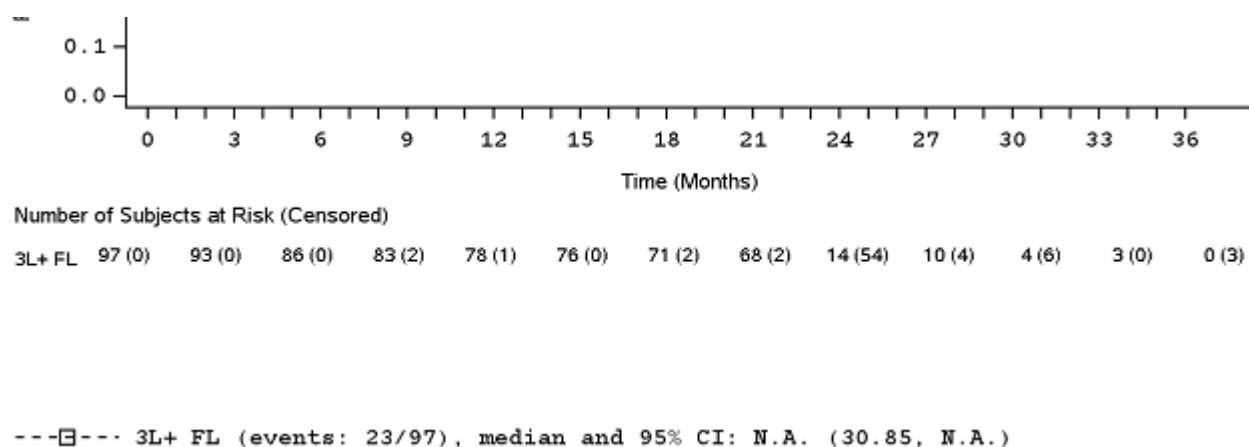
DOR if BOR is CR

The median DOR in subjects with a BOR of CR (per protocol and SAP definitions) per IRC charter was not reached in 3L+ subjects (95% CI: 18.04, NA) and 2L subjects (95% CI: 19.32, NA).

Figure 7. KM Plot of DOR if BOR is CR per IRC Charter - Liso-cel-treated Efficacy Analysis Set - 3L+ FL Subjects

3L+ Subjects





Sensitivity analyses supported these data: per FDA algorithm, the median DOR was not reached in 3L+ subjects (95% CI: NA) and 2L subjects (95% CI: NA). Per Investigator assessment, the median DOR was not reached in 3L+ subjects (95% CI: 20.37, NA) and 2L subjects (95% CI: 19.32, NA).

In the 3L+ FL group, DOR was consistent across all subgroups, including age, sex, region, ethnicity, race, anticancer treatment for disease control (yes vs no), received concomitant GCSF (yes vs no).

Progression Free Survival (PFS)

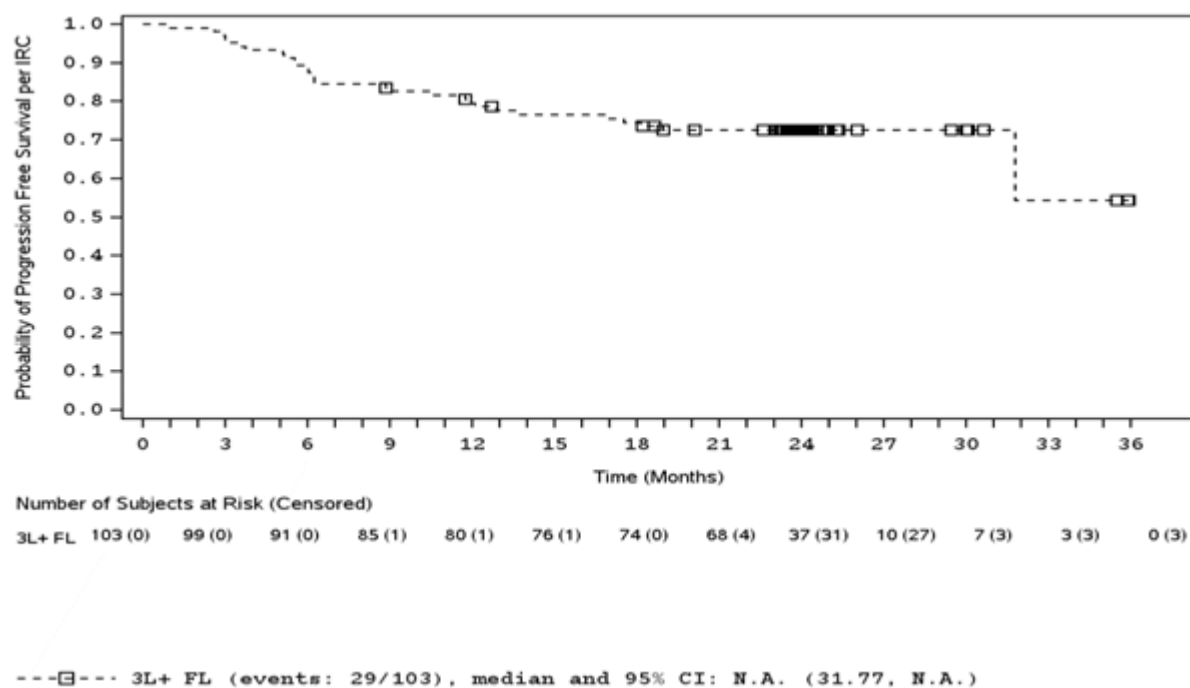
The median follow-up time for PFS was per IRC charter in the 3L+ FL group was 23.98 months (95% CI: 23.82, 24.15).

Table 39. PFS - Analyses Per IRC Charter, Leukapheresed (ITT), and Per Investigator - Study FOL-001

	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2
PFS per IRC Charter (Liso-cel-treated Efficacy Analysis Set)			
N	55	48	103
n (%)	17 (30.9)	12 (25.0)	29 (28.2)
Median (95% CI), months ^a	31.77 (31.77, N.A.)	N.A. (16.99, N.A.)	N.A. (31.77, N.A.)
Sensitivity Analyses			
PFS (Leukapheresed [ITT] Set)			
N	65	49	114
n (%)	20 (30.8)	13 (26.5)	33 (28.9)
Median (95% CI), months ^a	33.45 (30.55, N.A.)	N.A.	33.45 (30.55, N.A.)
PFS per Investigator (Liso-cel-treated Efficacy Analysis Set)			
N	55	48	103
n (%)	17 (30.9)	12 (25.0)	29 (28.2)
Median (95% CI), months ^a	36.14 (31.77, N.A.)	N.A.	36.14 (31.77, N.A.)

a Median, Q1, Q3 are estimated from KM product-limit estimates.

Figure 8. KM Plot of PFS per IRC Charter - Liso-cel-treated Efficacy Analysis Set 3L+ Subjects



Symbols represent censored observations.

In the 3L+ FL group, PFS was consistent across all subgroups, including age, sex, region, ethnicity, race, anticancer treatment for disease control (yes vs no), received concomitant GCSF (yes vs no).

In female subjects, the estimated PFS at 24 months was slightly higher (77.1%, 95% CI 61.6-85.6) than in males (69.6%, 95% CI 56.6-79.4), but given the large overlap of the Confidence Interval between the two groups, the difference was not deemed significant; the same conclusion can be applied to presence of concomitant therapy with G-CSF (24 month PFS if yes: 76% 95% CI 61.6-85.6%, if no: 68.8%, 06% CI 54.1-79.6%).

Overall Survival (OS)

The median follow-up for OS analysis was 29.47 months (95% CI: 26.51, 29.93).

Table 40. Summary of Efficacy Results - Liso-cel-treated Efficacy Analysis Set - Study FOL-001

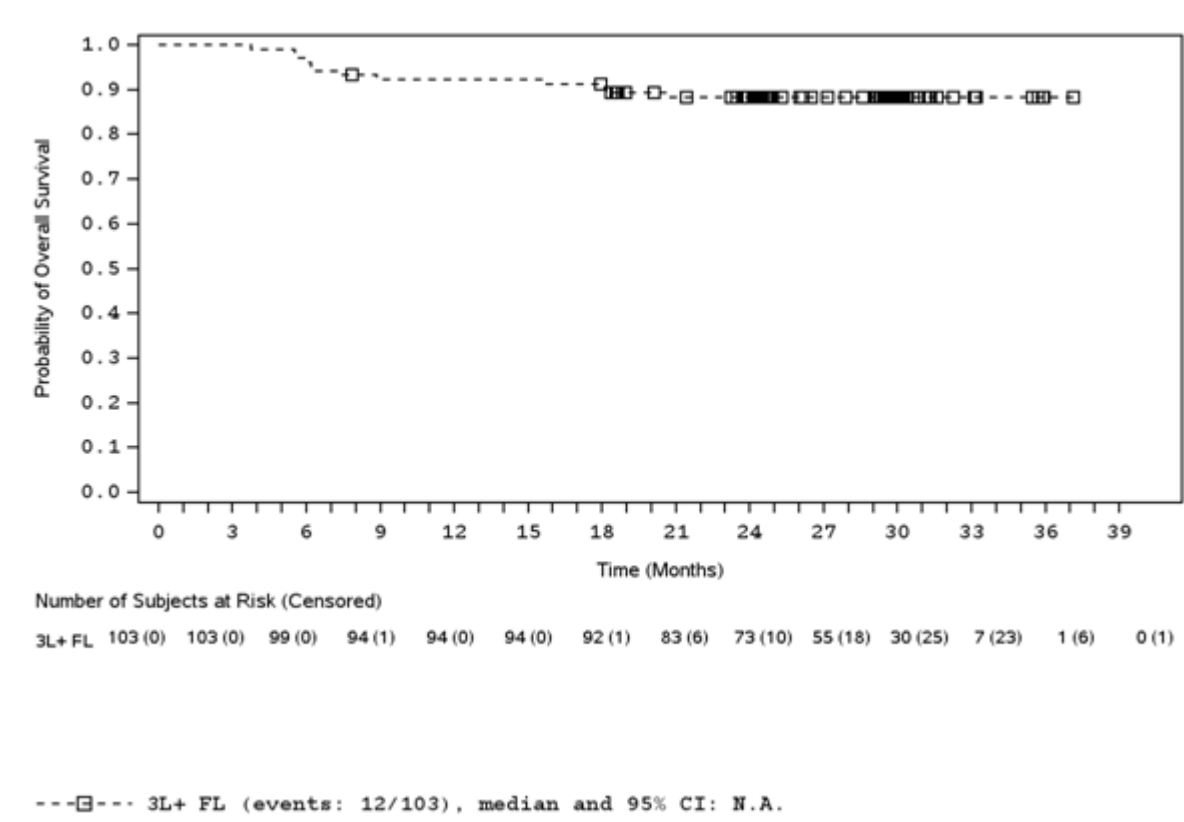
	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2
OS^{a,b}	N = 55	N = 48	N = 103
Events, n (%)	7 (12.7)	5 (10.4)	12 (11.7)
Median (95% CI), months ^c	N.A.	N.A.	N.A.
Min, Max, months ^d	3.7, 37.2+	5.6, 35.7+	3.7, 37.2+
OS rate, % (95% CI)^e			
6 months	94.5 (84.0, 98.2)	97.9 (86.1, 99.7)	96.1 (90.0, 98.5)
12 months	90.9 (79.5, 96.1)	93.7 (81.7, 97.9)	92.2 (85.0, 96.0)
18 months	89.1 (77.3, 94.9)	93.7 (81.7, 97.9)	91.2 (83.8, 95.3)
24 months	87.2 (75.1, 93.7)	89.3 (76.2, 95.4)	88.2 (80.1, 93.1)
30 months	87.2 (75.1, 93.7)	89.3 (76.2, 95.4)	88.2 (80.1, 93.1)
36 months	87.2 (75.1, 93.7)	N.A.	88.2 (80.1, 93.1)
Follow-up (Months)			

Median (95% CI) ^e	29.93 (29.31, 30.00)	26.15 (24.41, 29.47)	29.47 (26.51, 29.93)
Min, Max ^d	3.7, 37.2+	5.6, 35.7+	3.7, 37.2+

- a OS is defined as the interval from the date of liso-cel infusion to the date of death due to any reason.
b The OS analysis includes all available OS information from both Study FOL-001 as well as GC-LTFU-001 studies.
c Median, Q1, Q3 are estimated from KM product-limit estimates.
d Symbol + indicates a censored value.
e Based on KM estimates.

Sensitivity analyses supported OS results in the Leukapheresed (ITT) Set, 15/114 (13.2%) 3L+ FL subjects had died; most (7 subjects, 6.1%) were due to complications of malignant disease under study.

Figure 9. Kaplan-Meier Plot of Overall Survival - Liso-cel-Treated Efficacy Analysis Set - Study FOL-001 - 3L+ FL



Symbols represent censored observations.
The OS analysis includes all available OS information from both Study FOL-001 and GC-LTFU-001 (long-term follow-up) studies.

Ancillary analyses

Subgroup Analysis

In the 3L+ FL group, OS was consistent across all subgroups, including age, sex, region, ethnicity, race, anticancer treatment for disease control (yes vs no), received concomitant GCSF (yes vs no).

Post-hoc Analyses

A sensitivity analysis for patients in 3L+ which comprised all leukapheresed patients excluding subjects who received non-conforming products (N=110 3L+ FL subjects; 107 subjects who received liso-cel within the approved range of 44 to 120 x 10⁶ CAR positive viable T cells and 3 subjects who were leukapheresed but not infused) showed an ORR of 93.6% (87.3-97.4), a CRR of 90.9% (83.9-95.6).

The median DOR per IRC assessment in subjects with CR or PR was not reached (NA, 95% CI: 30.85, NA).

Time to Next Treatment

In the liso-cel-treated Efficacy Analysis Set (N = 103, 3L+ FL subjects) and with a median follow up time of 29.31 months (at the time of the data cutoff date of 10-Jan-2024), the median time to next therapy was not reached. Twelve (11.7%) subjects (11 relapsed after achieving response, 1 progressed without achieving response) received subsequent anticancer therapy (SACT) with time to next therapy ranging from 3.7 to 37.2 months.

Five of the 12 3L+ FL subjects who received SACT, had tumour samples collected at time of relapse, which were evaluable for CD19 testing. Per protocol, tumour biopsy had to be performed if clinically feasible as soon as possible after disease progression/relapse or failure to respond. If a tumour biopsy sample was available at relapse/progression it was tested for CD19 expression using a validated research-use-only immunohistochemistry assay. The CD19 H-Score (0-300) was used to report CD19 tumour expression levels.

Health-related Quality of Life

The PRO Analysis Set consisted of 116 (95.1%) subjects, 122 (100%) subjects, and 115 (94.3%) subjects for the EORTC QLQ-C30 questionnaire, FACT-LymS questionnaire, and EQ-5D Utility Index and VAS of the Liso-cel-treated Analysis Set, respectively.

Completion Rates Across all Questionnaires

Completion rate is defined as the number of subjects submitting a valid PRO assessment at a given timepoint over the number of subjects who are still expected to provide PRO assessment at that time point. Compliance was high at baseline at 95.1% and remained > 70% through Day 545 in 3L+ FL subjects. Available data rate was defined as the number of subjects submitting a valid PRO assessment at a given timepoint over the number of subjects in the PRO Analysis Set.

- EORTC QLQ-C30 - Mean Change from Baseline - Secondary Endpoint

Liso-cel demonstrated improvements over time in evaluations of group-level mean change from baseline on EORTC QLQ-C30 for the pre-selected domains of interest, including in the 5 of the 6 pre-selected domains among 3L+ subjects.

In 3L+ FL subjects:

- Fatigue worsened between Day 1 to Day 15, before clinically meaningfully improving between Day 15 and Day 60, and remained consistent thereafter.
- GHS/QoL clinically meaningfully improved between Day 1 to Day 60, and remained consistent thereafter.
- Physical functioning clinically meaningfully improved between Day 29 to Day 60, and remained consistent thereafter.
- Cognitive functioning and pain clinically meaningfully improved between Day 1 to Day 29, and remained consistent thereafter.

In individual level analyses, from Day 29 onwards, most subjects (~60% to 95%) experienced either meaningful improvement or no meaningful change across visits, and findings were similar across the remaining EORTC domains.

FACT-LymS - Mean Changes from Baseline - Secondary Endpoint

Across visits most subjects (~60% to 95%) experienced meaningful improvement or no meaningful change on the FACT-LymS. The proportion of subjects with meaningful improvement increased while the proportion of subjects with meaningful worsening decreased from Day 1 to Day 29 and then remained relatively constant.

EQ-5D-5L

Subjects showed improvement in the EQ-5D-5L summary index between Day 1 to Day 29 and remaining consistent thereafter in 3L+ FL subjects, with a similar trend in 4L+ FL subjects. In 2L FL subjects there was a trend towards improvement at Day 15, 60, and 365, whereas other time points were stable compared to baseline. The improvements did not reach the clinically meaningful improvement threshold.

Subjects showed improvement in the EQ-5D-5L VAS between Day 1 to Day 90 and remaining consistent thereafter in 3L+ FL subjects, with similar trends in 4L+ FL subjects and 2L FL subjects. The improvements did not reach the clinically meaningful improvement threshold.

Hospital Resource Utilization

Hospitalization may have been required after treatment with liso-cel to manage any treatment associated toxicities. Administration of liso-cel as inpatient or outpatient setting was determined at the PI's discretion.

Table 41. Liso-cel Administration - Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Liso-cel Administration in the Outpatient Setting - N (%)	6 (10.2)	1 (2.1)	7 (6.5)	1 (4.3)	8 (6.2)
Liso-cel Administration in the Inpatient Setting - N (%)	53 (89.8)	47 (97.9)	100 (93.5)	22 (95.7)	122 (93.8)
Reason for Administration in the Inpatient Setting - N (%)					
Lack of Caregiver Support	1 (1.7)	0	1 (0.9)	1 (4.3)	2 (1.5)
Subject is Staying More Than 60 Minutes From the Clinical Trials Site at the Time of Treatment	7 (11.9)	5 (10.4)	12 (11.2)	4 (17.4)	16 (12.3)
Subject has Disease Characteristics That, in the Investigator's Clinical Judgment, Put the Subject at Higher Risk of Complications	11 (18.6)	2 (4.2)	13 (12.1)	0	13 (10.0)
Other	34 (57.6)	40 (83.3)	74 (69.2)	17 (73.9)	91 (70.0)
Liso-cel Intended to be Monitored in the Outpatient Setting - N (%)	12 (20.3)	2 (4.2)	14 (13.1)	1 (4.3)	15 (11.5)
Liso-cel Intended to be Monitored in the Inpatient Setting - N (%)	47 (79.7)	46 (95.8)	93 (86.9)	22 (95.7)	115 (88.5)
Liso-cel Actually Monitored in the Outpatient Setting - N (%)	12 (20.3)	2 (4.2)	14 (13.1)	1 (4.3)	15 (11.5)

Liso-cel Actually Monitored in the Inpatient Setting - N (%)	47 (79.7)	46 (95.8)	93 (86.9)	22 (95.7)	115 (88.5)
Reason for Monitoring in the Inpatient Setting - N (%)					
Lack of Caregiver Support	1 (1.7)	0	1 (0.9)	1 (4.3)	2 (1.5)
PI Decision	12 (20.3)	10 (20.8)	22 (20.6)	3 (13.0)	25 (19.2)
Disease Characteristics	10 (16.9)	2 (4.2)	12 (11.2)	0	12 (9.2)
Risk of TLS					
Yes	10 (16.9)	2 (4.2)	12 (11.2)	0	12 (9.2)
Risk Of CRS					
Yes	10 (16.9)	2 (4.2)	12 (11.2)	0	12 (9.2)
Transportation	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Other	23 (39.0)	33 (68.8)	56 (52.3)	18 (78.3)	74 (56.9)
Not Reported	1 (1.7)	0	1 (0.9)	0	1 (0.8)

In the 116 (89.2%) subjects who received liso-cel and who were monitored as inpatients, the most common reason for hospitalization during liso-cel infusion was other (prophylaxis for CAR T cell administration) (107 [92.2%] subjects). For these 116 subjects, the median duration of hospitalization from liso-cel administration was 15 days (range, 4 to 41). No subjects were admitted to the ICU during liso-cel administration.

Table 42. Summary of Hospitalizations - Liso-cel-Treated Analysis Set, Subjects with Actual Inpatient Monitoring

	4L+ FL Cohort 1 N = 47 n (%)	3L FL Cohort 2 N = 46 n (%)	3L+ FL Cohorts 1 + 2 N = 93 n (%)	2L FL Cohort 3 N = 22 n (%)	Total 2L+ FL Cohorts 1, 2, 3 N = 115 n (%)
Summary of Hospitalizations During Liso-cel Administration					
Reason for Hospitalization - N (%)					
Adverse Event	1 (2.1)	0	1 (1.1)	0	1 (0.9)
Per Protocol	3 (6.4)	11 (23.9)	14 (15.1)	5 (22.7)	19 (16.5)
Other	43 (91.5)	35 (76.1)	78 (83.9)	17 (77.3)	95 (82.6)
Duration of Hospitalization From Liso-cel Administration (Days) ^a					
N	47	46	93	22	115
Median	15.0	15	15	12	15
Q1, Q3	12.0, 16.0	11.0, 15.0	11.0, 15.0	11.0, 15.0	11.0, 15.0
Min, Max	4, 41	7, 30	4, 41	5, 29	4, 41
Duration of ICU Stay From Liso-cel Administration (Days) ^b					
N	0	0	0	0	0

Duration of Non-ICU Stay From Liso-cel Administration (Days)^c

N	47	46	93	22	115
Median	15.0	15	15	12	15
Q1, Q3	12.0, 16.0	11.0, 15.0	11.0, 15.0	11.0, 15.0	11.0, 15.0
Min, Max	4, 41	7, 30	4, 41	5, 29	4, 41

Summary of Hospitalizations During and Post-Liso-cel Administration

Total Duration of All Hospitalizations From Liso-cel Administration (Days)^d

N	47	46	93	22	115
Median	15.0	15	15	14	15
Q1, Q3	14.0, 23.0	12.0, 17.0	14.0, 20.0	11.0, 16.0	12.0, 18.0
Min, Max	8, 84	7, 46	7, 84	8, 29	7, 84

Total Duration of All ICU Stays From Liso-cel Administration (Days)^d

N	2	0	2	1	3
Median	5		5	6	6
Q1, Q3	3.0, 7.0		3.0, 7.0	6.0, 6.0	3.0, 7.0
Min, Max	3, 7		3, 7	6, 6	3, 7

Total Duration of All Non-ICU Stays From Liso-cel Administration (Days)^d

N	47	46	93	22	115
Median	15.0	15	15	14	15
Q1, Q3	14.0, 23.0	12.0, 17.0	14.0, 18.0	11.0, 16.0	12.0, 18.0
Min, Max	8, 84	7, 46	7, 84	8, 29	7, 84

^a Duration (days) = date of discharge - liso-cel infusion date + 1

^b Duration (days) = date of discharge - date of admission after liso-cel administration + 1. If liso-cel administration took place during ICU stay, then days = date of discharge - liso-cel infusion date + 1.

^c Duration (days) = total days in hospital - ICU days.

^d Sum of all hospitalization/ICU/non-ICU days on or after liso-cel administration for subjects who had multiple hospitalizations, ICU admissions, or non-ICU stays during and post- liso-cel infusion.

Data from subjects who receive subsequent anti-follicular lymphoma therapy are included.

In the 14 (10.7%) subjects who received liso-cel and were monitored as outpatients, 7 (50.0%) subjects were hospitalized after liso-cel administration; 7 (100%) were hospitalized due to an AE. The median time from liso-cel administration to first hospitalization was 7 days (range, 4 to 16). None of these subjects had ICU stays.

Table 43. Summary of Hospitalizations - Liso-cel-Treated Analysis Set, Subjects with Actual Outpatient Monitoring

	4L+ FL Cohort 1 N = 12 n (%)	3L FL Cohort 2 N = 2 n (%)	3L+ FL Cohorts 1 + 2 N = 14 n (%)	2L FL Cohort 3 N = 1 n (%)	Total 2L+ FL Cohorts 1, 2, 3 N = 15 n (%)
Hospitalized After Liso-cel Administration - N (%)					

Yes	4 (33.3)	2 (100.0)	6 (42.9)	1 (100.0)	7 (46.7)
No	8 (66.7)	0	8 (57.1)	0	8 (53.3)

Time From Liso-cel Administration To First Hospitalization (Days)^a

N	4	2	6	1	7
Median	6.5	8.5	7.5	7	7
Q1, Q3	4.0, 12.5	6.0, 11.0	4.0, 11.0	7.0, 7.0	4.0, 11.0
Min, Max	4, 16	6, 11	4, 16	7, 7	4, 16

First Hospitalization Within 4 Days After Liso-cel Administration - N (%)

Yes	2 (50.0)	0	2 (33.3)	0	2 (28.6)
No	2 (50.0)	2 (100.0)	4 (66.7)	1 (100.0)	5 (71.4)

Summary Of Initial Hospitalizations After Liso-cel Administration

Reason For Hospitalization - N (%)

Adverse Event	4 (100.0)	2 (100.0)	6 (100.0)	1 (100.0)	7 (100.0)
---------------	-----------	-----------	-----------	-----------	-----------

Duration Of Initial Hospitalization From Liso-cel Administration (Days) (B)

N	4	2	6	1	7
Median	6	5	6	3	5
Q1, Q3	4.0, 7.5	3.0, 7.0	3.0, 7.0	3.0, 3.0	3.0, 7.0
Min, Max	3, 8	3, 7	3, 8	3, 3	3, 8

Duration Of Initial ICU Stay From Liso-cel Administration (Days)^b

N	0	0	0	0	0
---	---	---	---	---	---

Duration Of Initial Non-ICU Stay From Liso-cel Administration (Days)^c

N	4	2	6	1	7
Median	6	5	6	3	5
Q1, Q3	4.0, 7.5	3.0, 7.0	3.0, 7.0	3.0, 3.0	3.0, 7.0
Min, Max	3, 8	3, 7	3, 8	3, 3	3, 8

Summary Of Hospitalizations Post-Liso-cel Administration

Total Duration Of All Hospitalizations From Liso-cel Administration (Days)^d

N	4	2	6	1	7
Median	6	6.5	6.5	3	6
Q1, Q3	4.0, 7.5	6.0, 7.0	5.0, 7.0	3.0, 3.0	3.0, 7.0
Min, Max	3, 8	6, 7	3, 8	3, 3	3, 8

Total Duration Of All ICU Stays From Liso-cel Administration (Days)^d

N	0	0	0	0	0
---	---	---	---	---	---

Total Duration Of All Non-ICU Stays From Liso-cel Administration (Days)^d

N	4	2	6	1	7
Median	6	6.5	6.5	3	6
Q1, Q3	4.0, 7.5	6.0, 7.0	5.0, 7.0	3.0, 3.0	3.0, 7.0

Min, Max	3, 8	6, 7	3, 8	3, 3	3, 8
----------	------	------	------	------	------

^a Time (days) = date of admission after liso-cel administration - liso-cel infusion date + 1.

^b Duration (days) = date of discharge - date of admission after liso-cel administration + 1.

Supportive studies

The MAH provided three supportive studies to contextualize the effectiveness of Liso-cel in respect to the other existing therapies approved for R/R FL.

Real-world External Control Arm (ECA) Study (Study CA082013)

Study CA08201342 was a non-interventional, retrospective study of R/R FL subjects who received at least one line of systemic therapy including an CD20 antibody and an alkylating agent in the real-world clinical oncology setting and historical clinical trials, conducted to provide comparative effectiveness evidence for Liso-cel versus currently used therapies in the 3L+ R/R FL setting, using propensity score methodologies.

The Liso-cel treated population was comprised of subjects from Study FOL-001. The ECA included:

- observational, real-world, subject-level data from multiple vendors
- clinical trial data from the AUGMENT (CC-5013-NHL-007) and MAGNIFY (CC-5013-NHL-008) studies.

Data from all sources were combined into a single ECA.

Real-world Study Design

The retrospective real-world external control arm did not impose a treatment protocol, any diagnostic/interventional procedure, or a visit schedule.

Study CA082013 includes 3 cohorts of subjects (from real-world and clinical settings) with FL constructed using external data that are similar to those in Study FOL-001 to form the ECA. All clinical data sources used in this study have treatment options that are in the current scope of standard of care and thus contain subjects suitable for the ECA. A propensity score matched cohort was separately created of subjects from respective analysis groups and corresponding external cohort as an external cohort for direct comparison of effectiveness with liso-cel in Study FOL-001.

Qualifying Comparator Cohort

The External Control Arm (ECA) subjects in QCC were identified based on the defined inclusion/exclusion criteria, based on those in Study FOL-001. Subjects in the Qualifying Comparator Cohort (QCC) were matched on baseline characteristics with those in the Study FOL-001 population to construct the ACC and baseline evaluations for Study FOL-001 Cohort were defined in the study protocol as the last available recorded value on or prior to the date of the first dose of treatment (preferably within 7 days) and not more than 4 weeks (28 days). Baseline was defined for ECA subjects as the closest value to onset of the qualifying LOT collected after completion of previous LOT, but no more than 3 months prior to index date (with the exception of molecular result, which can have been performed more than 3 months prior to index date).

Cohorts considered for analysis

Two overlapping cohorts were drawn from the ECA cohort: 1) the Qualifying Comparator Cohort (QCC), who met select eligibility criteria similar to those of Study FOL-001; and 2) the Analytic Comparator Cohort (ACC), comprising a subset of patients from the QCC who were matched with the Study FOL-001 population using IPTW and PS matching. The index dates for the QCC and ACC were the start of the first qualifying LOT after satisfying eligibility criteria in the respective analysis groups.

Two overlapping cohorts were drawn from Study FOL-001: the Liso-cel (JCAR017)-treated Efficacy Analysis Cohort (JTEAC) and the Leukapheresed Cohort (LKC). The JTEAC included all subjects in the Liso-cel-treated Analysis Set (all subjects who received a dose of conforming Liso-cel cell product) who had positive disease present before Liso-cel administration based on IRC assessment (PET-CT for FL subjects). The index date for JTEAC was the date of start of infusion of Liso-cel. The LKC included all subjects who signed informed consent, who met all inclusion/exclusion criteria, and underwent leukapheresis. The index date for the LKC cohort was the date of start of leukapheresis.

Study Objective

The primary endpoint for this study was ORR, defined as the percentage of patients achieving a best response of PR or CR as assessed by the investigator. The following key secondary endpoints were assessed: CRR, PFS, OS, TTNT and DOR.

Sensitivity analyses included an analysis in the LKC cohort along with further analyses for the RW cohort and for subjects with and without bridging therapy in the JTEAC cohort.

Population analyzed

Overall, 103 subjects were included in the JTEAC, 338 were included in the QCC, 114 were included in the LKC, and 107 were included in the RW Cohort. The most common 3L+ treatment regimens in the ECA QCC were lenalidomide + rituximab (N = 195, 57.7%), rituximab (N = 52, 15.4%), bendamustine + rituximab (N = 27, 8.0%), and idelalisib (N = 10, 3.0%) which align with recommended therapies for relapsed or progressed patients in ESMO guidelines. The most common 3L+ treatment regimens in the RW QCC were bendamustine + rituximab (N = 27, 25.2%), lenalidomide + rituximab (N = 14, 13.1%), and idelalisib (N = 10, 9.3%).

Covariate Balancing using Trimmed Stabilized IPTW

Based on a threshold of 0.2 for the standardized mean difference, there were differences in several covariates before balancing between JTEAC and QCC, including months since last therapy completion, geographic location, prior HSCT, refractory to last LOT, PD within 24 months after the start of the first LOT, bulky disease, International Prognostic Index Group, and disease stage. Similarly, differences were observed between QCC and LKC in terms of months from initial diagnosis, months since last therapy completion, geographic location, prior HSCT, refractory to last LOT, PD within 24 months after the start of the first LOT, bulky disease, and International Prognostic Index Group. None of these differences were present after balancing.

Demographic and Other Baseline Characteristics

Baseline demographics in the QCC cohort were similar to both the JTEAC and LKC cohorts in terms of mean age, sex, height, double refractory status and number of prior lines of therapies; in the QCC cohort, a higher proportion of patients had bulky disease and more than 4 extranodal site involvement, as determined by the investigator, compared to the JTEAC and LKC cohorts. The QCC cohort had a lower proportion of patients with prior HSCT, follicular lymphoma grade 2 and 3a, Stage III and Stage IV disease, refractory to the last line of therapy prior to the index line, and POD24 status, compared to the JTEAC and LKC cohorts.

For some characteristics, missing information on baseline disease status was more common in the QCC cohort than in the JTEAC and LKC cohorts. Approximately 17%, 29%, 28% and 3% of patients in the QCC cohort had missing information on bulky disease, Follicular Lymphoma International Prognostic Index, staging information, and double refractory status, respectively, while no subjects in the JTEAC and LKC cohorts had missing information in these categories.

In general, patients in the QCC cohort had a shorter interval time from the initial diagnosis of B-NHL to the initiation of their first treatment compared to subjects in the JTEAC and LKC cohorts. However, they experienced a longer duration from the initial diagnosis to the index therapy, as well as a longer period from the completion of their last therapy to the start of the index therapy, when compared to subjects in the JTEAC and LKC cohorts.

Results

Table 44. Comparison of Efficacy Outcomes Adjusted for Trimmed Stabilized IPTW between JTEAC and QCC, LKC, and RW Cohorts (Study CA082013)

Effect Estimate (95% CI)	JTEAC (N = 103) vs QCC (N = 338)	LKC (N = 114) vs QCC (N = 338)	JTEAC (N = 103) vs RW Cohort (N = 107)
ORR	RR:1.3 (1.2, 1.5)	RR:1.3 (1.2, 1.5)	RR: 1.4 (1.1, 1.7)
CRR	RR:2.1 (1.8, 2.5)	RR:2.2 (1.9, 2.6)	RR:2.1 (1.5, 2.8)
PFS	HR: 0.34 (0.20, 0.58)	HR: 0.32 (0.18, 0.58)	HR: 0.50 (0.26, 0.94)
TTNT	HR: 0.27 (0.14, 0.51)	HR: 0.26 (0.13, 0.54)	HR: 0.27 (0.12, 0.59)
OS	HR: 0.45 (0.19, 1.03)	HR: 0.47 (0.19, 1.17)	HR: 0.12 (0.05, 0.29)
DOR	HR: 0.36 (0.20, 0.64)	-	-

Risk Ratio > 1 and Hazard Ratio < 1 indicates favorable results for liso-cel vs standard of care treatments. Statistically significant results are bolded.

The sensitivity analyses showed consistency with results observed between JTEAC and QCC, supporting the primary analysis. The results remained largely consistent between JTEAC and RW cohort, similar to those observed between JTEAC and QCC. A statistically significant difference in OS was observed in favor of Liso-cel compared to the RW cohort.

Indirect Treatment Comparison (ITC) for lisocabtagene maraleucel in the treatment of 3L or 4L+ relapsed/refractory follicular lymphoma

Study Objectives

Study CA08209243 was a non-interventional MAIC study using indirect treatment comparison methods to estimate the comparative efficacy and safety of liso-cel versus mosunetuzumab (a bispecific CD20-directed CD3 T-cell engager; GO29781 trial), axi-cel (a CD19 directed autologous CAR T cell therapy; ZUMA-5 trial), and tisa-cel (a CD19 directed autologous CAR T cell therapy; ELARA trial) in patients with 3L+ R/R FL. Outcomes included efficacy outcomes (ORR, CRR, PFS, and DOR) and AEs (CRS, NEs, infections, prolonged cytopenia, corticosteroid use for CRS management, and tocilizumab use for CRS management).

Investigational Plan

- To conduct an ITC, the included studies need to be sufficiently similar to allow for adequate analytic alignment to mitigate sources of bias. A thorough qualitative comparison of the pivotal trials for liso-cel (TRANSCEND FL), mosunetuzumab (GO29781), axi-cel (ZUMA-5), and tisa-cel (ELARA) was conducted to assess the feasibility of an ITC in terms of the following components: study design characteristics, including phase, visit schedules, and follow-up time
- Study eligibility criteria, including clinical and diagnostic definitions, and study treatment protocols (such as use of bridging therapy)
- Baseline characteristics, including availability, definitions, and assessment of imbalance
- Outcomes, including availability and definitions

The feasibility assessment was performed using IPD from TRANSCEND FL and published summary level data (SLD) from GO29781, ZUMA-5, and ELARA were used. Analyses of interest included all patients who were enrolled and received treatment (hereafter referred as intention to treat [ITT]) and treated

efficacy set for the comparison of efficacy outcomes and all patients who were randomized and received study treatment (ie, treated set) for the comparison of safety outcomes.

Study design

Overall, the trial designs of TRANSCEND FL, GO29781, ZUMA-5, and ELARA were sufficiently similar to allow for MAICs to be performed, as well as for the study eligibility assessments.

Comparisons of baseline characteristics revealed some differences in the definitions or categorizations of patient characteristics such as high tumor bulk, number of prior LOT and R/R status. This required alignment via redefining and recategorizing the variables using IPD from TRANSCEND FL to facilitate a fairer comparison.

Appropriateness of measurements

By comparing the study design, eligibility criteria, baseline characteristics, and outcomes of TRANSCEND FL, GO29781, ZUMA-5, and ELARA, it was determined that there were significant similarities among these studies to permit indirect comparisons via MAIC. The differences between TRANSCEND FL and the other trials are summarized below:

- GO29781: treatment with mosunetuzumab did not involve leukapheresis or lymphodepletion; patients in TRANSCEND FL also had the option for bridging therapy during the treatment manufacturing process, unlike those in GO29781 who received mosunetuzumab immediately after enrolment, alongside corticosteroid premedication which was prohibited in the TRANSCEND FL trial. Large differences in the definitions or categorizations of patient characteristics were identified between TRANSCEND FL and GO29781 including high tumor bulk, number of lines of prior therapy, and refractory or relapse status. To address this variability, alignments were performed by redefining the variables using TRANSCEND FL IPD to facilitate a fairer comparison.
- ZUMA-5: a notable difference was observed in the use of bridging therapy during treatment manufacturing, with a higher proportion of patients in TRANSCEND FL receiving bridging therapy (37.4%) compared to ZUMA-5 (3.2%). Based on this difference, the efficacy and safety endpoints excluded patients who received bridging therapy prior to liso-cel infusion (treated efficacy set, N = 61; treated set, N = 63). Three primary differences in definitions between TRANSCEND FL and ZUMA-5 were noted, including high tumor bulk (according to GELF criteria), number of prior LOT, and refractory status to the last previous therapy. Based on this difference, alignments were performed by redefining the variables using TRANSCEND FL IPD.
- ELARA: comparable proportion of patients in TRANSCEND FL receiving bridging therapy (37.4%) relative to ELARA (45.0%). Consequently, efficacy endpoints were compared between the treated efficacy set (N = 101) from TRANSCEND FL and the efficacy analysis set from ELARA (N = 94). Although definition for bulky disease were the same between trials, there were limited details on the exact timeframe measurements were taken in the ELARA trial; similarly, a difference in the definition of refractory or relapse status was identified between TRANSCEND FL and ELARA. To make the definitions comparable between trials, alignments were performed by redefining the variables using TRANSCEND FL IPD.

Overview of statistical analysis

For the MAIC approach, ITCs were formed by “matching” and “adjusting” patients from TRANSCEND FL to match the eligible patient population and marginal distribution (eg, mean and variance) of baseline characteristics in patients who received the comparator intervention. Matching consisted of aligning trials on inclusion/exclusion criteria and is required for the positivity assumption of causal inference to be met. Positivity requires that all patients have a nonzero probability of being assigned to either trial, and violations of positivity can bias estimates of treatment effects and their variance. Adjusting consists of weighing patients in TRANSCEND FL so that they represent a population more similar to that of GO29781,

ZUMA-5, and ELARA. After matching and adjusting patients from TRANSCEND FL, statistical predictions of the outcome of interest are an estimate of the outcome that would have occurred had the comparison population (ie, GO29781, ZUMA-5, ELARA) received liso-cel instead of mosunetuzumab, axi-cel, and tisa-cel. Point estimates representing an ITC for liso-cel versus comparator treatments were derived as the difference between this prediction and the estimated outcome using published SLD from the comparator trial. Given that there is no common comparator arm connecting TRANSCEND FL to any of the three comparator trials, unanchored MAICs were conducted for the efficacy and safety analyses. Patients in the TRANSCEND FL IPD were matched and adjusted to comparator trials, GO29781, ZUMA-5, and ELARA. Generalized linear models (GLM) for binary outcomes (ie, ORR, CRR) were used to estimate odds ratios (ORs) of liso-cel versus mosunetuzumab and to estimate relative response ratios of liso-cel versus axi-cel and liso-cel versus tisa-cel. For time-to-event outcomes (ie, DoR, PFS), Cox proportional hazards (PH) models were used to estimate hazard ratios (HRs) of liso-cel vs. its comparators (ie, mosunetuzumab, axi-cel, and tisa-cel).

For a given set of clinical factors, separate MAICs were conducted sequentially, adjusting for one additional variable at a time in an iterative process; after fitting each model, the performance and suitability of each MAIC model was assessed based on the effective sample size, distribution of patients weights and a summary of statistics for each clinical factor before and after matching and adjusting steps. The primary analysis of the MAIC model was chosen based on achieving a balance between these criteria, while also considering the number of clinical factors included.

For all three comparisons, clinical experts separately identified important prognostic factors to adjust for in each MAIC analyses. For each comparison, factors adjusted for in the primary MAIC scenario were selected based on availability of data between comparator studies, similarity of variable definitions, prognostic strength as determined by clinical expert opinion, and impact of adjustment on ESS.

Results

Table 45. Clinical Summary of MAIC Results for Efficacy Outcomes (Study CA082092)

Effect Estimate (95% CI)	Liso-cel vs Mosunetuzumab		Liso-cel vs Axi-cel		Liso-cel vs Tisa-cel	
	Naïve ^a	Primary ^b	Naïve ^a	Primary ^b	Naïve ^a	Primary ^b
ORR	OR: 3.31 (1.37, 8.03)	OR: 3.78 (1.48, 9.67)	RR: 1.04 (0.98, 1.11)	RR: 1.06 (1.00, 1.12)	RR: 1.14 (1.03, 1.25)	RR: 1.09 (0.95, 1.25)
CRR	OR: 6.24 (2.95, 13.23)	OR: 6.46 (2.85, 14.65)	RR: 1.18 (1.02, 1.37)	RR: 1.25 (1.09, 1.45)	RR: 1.37 (1.13, 1.67)	RR: 1.33 (1.06, 1.68)
PFS	HR: 0.35 (0.21, 0.57)	HR: 0.28 (0.16, 0.49)	HR: 0.85 (0.45, 1.62)	HR: 1.14 (0.47, 2.74)	HR: 0.43 (0.23, 0.78)	HR: 0.62 (0.21, 1.87)
DOR	HR: 0.41 (0.23, 0.72)	HR: 0.34 (0.18, 0.63)	HR: 0.89 (0.45, 1.73)	HR: 1.26 (0.52, 3.05)	HR: 0.54 (0.29, 1.01)	HR: 0.47 (0.14, 1.65)

^a Unadjusted

^b MAIC Scenario

Odd Ratios or Response Ratio > 1 and Hazard Ratio <1 indicates favorable results for liso-cel vs mosunetuzumab / axi-cel / tisa-cel. Statistically significant (nominal p-value) results are **bolded**.

When the “FDA algorithm” was applied for the evaluation of response, a different percentage of response can be noted in ZUMA-5 trial, while in ELARA the “FDA algorithm” was used upfront for the primary analysis. To note, also in ZUMA-5 the evaluation of response was introduced with an amendment during the study.

Table 46. CRR per IRC Charter and FDA Algorithm in Study FOL-001, ZUMA-5, and ELARA

Cell Therapy	Study	CRR per IRC Charter	CRR per FDA algorithm
Liso-cel	JCAR017-FOL-001 Data cutoff 27-Jan-2023 ^a	95/101 94.1%	73/101 72.3%
	JCAR017-FOL-001 Data cutoff 10-Jan-2024 ^b	97/103 94.2%	75/103 72.8%
Axi-cel	ZUMA-5	68/86 79.1%	49/81 60.5%
Tisa-cel	ELARA	Not reported	65/94 69.1%

Systematic literature review of clinical evidence of third line and later (3L+) treatments for follicular lymphoma in adult patients

The objective of this systematic literature review (SLR) was to systematically identify all relevant clinical evidence for therapies used in the treatment of adult patients with R/R FL (grade 1-3A) in the 3L+ and 4L+ setting. Additionally, studies investigating outcomes in 2L+ POD24 patients were included.

The secondary objectives were to assess the feasibility of conducting meta-analyses of key efficacy outcomes reported across studies included in the SLR for each population of interest and to conduct meta-analyses for each of the outcome/population combinations deemed feasible.

Methodology

Database searches was conducted in Ovid MEDLINE®, Embase, and the Cochrane Central Register of Controlled Trials using the Ovid® search interface; studies investigating R/R FL (grade 1-3A) patients in the 3L+, 4L+, and 2L+ POD24 setting were considered eligible for the research.

Treatments for FL included systemic induction chemotherapies (ie, chemotherapy, immunotherapy, chemoimmunotherapy) recommended by National Comprehensive Cancer Network (NCCN)/European Society for Medical Oncology (ESMO) and/or treatments deemed relevant to current clinical practice for FL.

The report contains reviews conducted from two searches. The first search was run on 17-Sep-2022 and included studies published between January 1998 and September 2022. The second search was run on 26-Jan-2024 and included studies published between August 2022 and January 2024. The date restriction of 01-Jan-1998 was chosen to align with the introduction of rituximab use for FL, which was considered appropriate for identifying studies of patients receiving relevant therapies for R/R FL. Bibliographies of identified relevant SLRs and key conference websites were manually searched. Study eligibility was assessed according to pre-specified Population, Intervention, Comparator, Outcome, Study design (PICOS) criteria and was performed in duplicate for database searches and by a single reviewer for manual searches. Studies were eligible if they were in the English language and enrolled R/R FL (grade 1-3A) in the 3L+, 4L+, and 2L+ POD24 setting. Outcomes of interest were OS, progression-free survival (PFS), disease-free survival (DFS), overall response rate (ORR), complete response (CR), partial response (PR), duration of response (DoR), time to next treatment (TTNT), and adverse events (AEs). Data from included records (study design characteristics, patient characteristics, and study findings) were collected using standardized data extraction templates. Data extraction was performed by one reviewer and validated by a second independent reviewer to verify data accuracy and completeness. All conflicts were resolved by consensus or third independent reviewer. Quality assessment of included

citations was performed using the National Institute for Health and Care Excellence (NICE) checklists by a single reviewer and validated by a second reviewer.

Statistical considerations

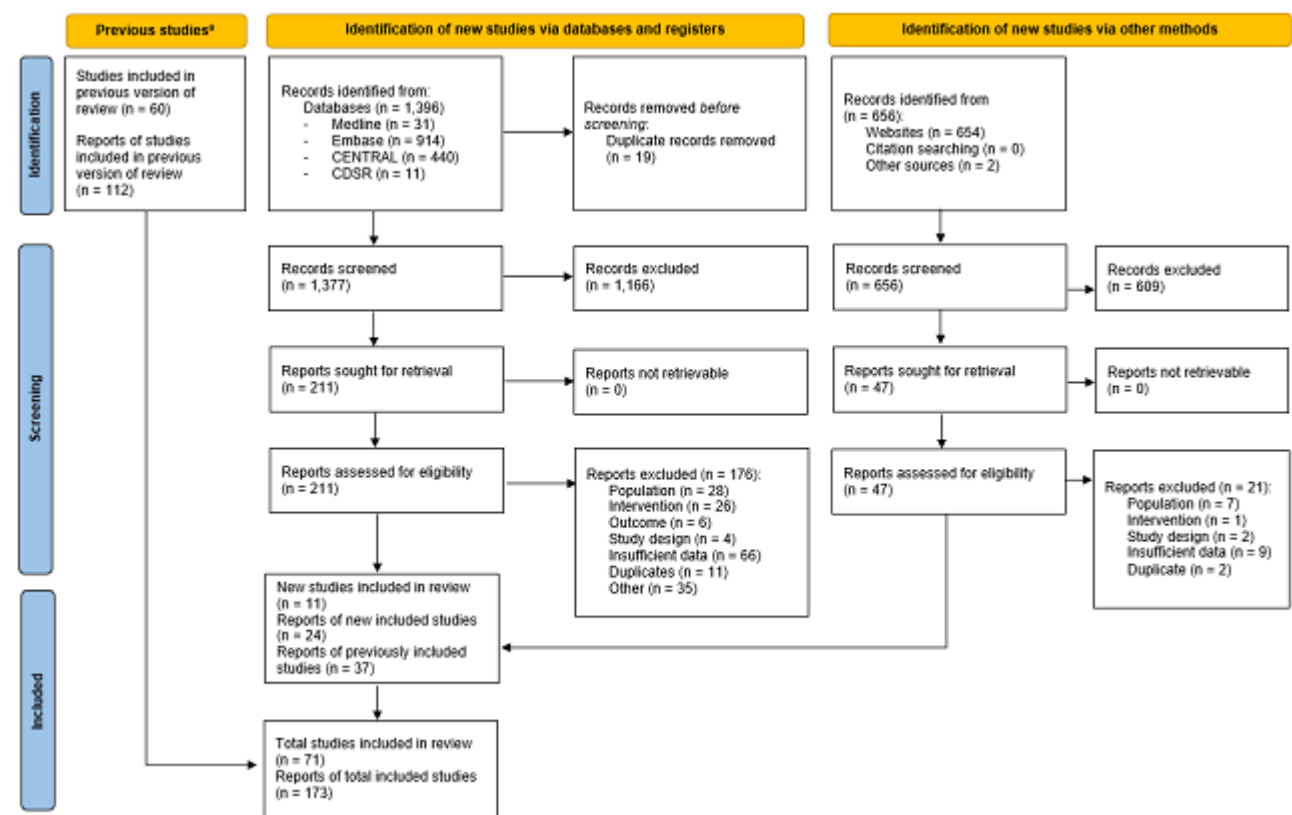
Meta-analysis feasibility assessments were conducted for included studies that reported ORR, CR rate, OS, and/or PFS outcomes for each of 3L+, 4L+, and 2L+ POD24 patient populations. Feasibility was determined based on a qualitative assessment of heterogeneity in study characteristics and clinically significant patient baseline characteristics. When deemed feasible, meta-analyses (both random and fixed effects) were conducted to derive pooled effect estimates for each outcome/population combination.

Results

Literature Search Results

Two searches have informed the current report: (1) the original 2L+ FL search (17-Sep-2022) and (2) an update to the original search (26-Jan-2024).

Figure 10. PRISMA flow diagram



Study Characteristics

In total, 173 reports covering 71 unique studies were included in this review as reported in the diagram below: four RCTs (one of which only reported induction phase, single-arm data), 27 one non-randomized clinical trial, 26 single-arm trials, two prospective observational studies, and 38 retrospective observational studies. Most studies reported data on 3L+ populations or subgroups (n = 60 studies, 85%) while data on 4L+ and 2L+ POD24 populations or subgroups were reported in 18 studies (25%) and 20 studies (28%), respectively. The total number of studies reported exceeds 71 as some studies reported outcomes for multiple line of treatment (LOT) groups (ie, 3L+, 4L+, 2L+ POD24).

Three single-arm Phase 2 clinical trials investigated CAR T-cell therapies: TRANSCEND FL, ZUMA-5 and the ELARA trial; in addition to that, one observational study investigated axicabtagene ciloleucel alone and another observational study investigated both axicabtagene ciloleucel and tisagenlecleucel.

Seven clinical trials investigated T-cell engagers: two single arm trials investigated mosunetuzumab (one single-arm phase 2 and one single-arm Phase 1b/2), two single-arm epcoritamab, two trials investigated odronextamab monotherapy while one nonrandomized trial investigated glofitamab.

Fifty-nine (83%) studies investigated other therapies (PI3K therapies, tazemetostat and other chemotherapy regimens), including 32 studies (54%) that only investigated HSCT (both autologous and allogenic).

Patient Characteristics

The studies varied in terms of eligible population sample size with four studies ranging from 2 to 9 patients and the remaining 67 studies from 11 to 1,842 patients, median length of follow-up (4.2 months to 13.5 years) and investigated therapies. Additionally, there was significant heterogeneity in terms of patient populations and baseline characteristics across the studies. Most of the studies reported findings for 3L+ FL patients, while there was limited evidence for 4L+ and 2L+ POD24 patients.

Median patient age ranged from 43 to 73 years,³⁶ 40 and the proportion of females ranged from 27% to 88%, although two studies with less than five patients did not include female patients. Nineteen studies (27%) reported median time since diagnosis, which ranged from 19.2 months to 11.4 years. Twenty-seven studies (38%) reported median prior lines of therapy, which ranged from 2 to 4.5 median prior lines. Eastern Cooperative Oncology Group performance scores, disease stage, and Follicular Lymphoma International Prognostic Index (FLIPI) scores were reported in 32%, 39%, and 31% of studies, respectively.

Response Outcomes

Response outcomes (ORR, CR, PR, DoR) were reported in 39 studies (55%), and survival outcomes (OS, PFS, DFS) were reported in 53 studies (75%). Among conventional therapies in 3L+, ORR ranged from 37% to 84%. Overall survival data was often reported for 3L+ studies, but follow up time for OS varied, making it difficult to compare evidence across studies. In 3L+ patients, the highest ORRs were seen for CAR T-cell therapies (86% to 97%), with lisocabtagene maraleucel having the highest ORR, and among T-cell engagers (78% to 90%), with epcoritamab having the highest ORR. In patients who were treated with lisocabtagene maraleucel, median OS was not reached after a median follow-up of 18.9 months. In the patients who were treated with axicabtagene ciloleucel, median OS was not reached after a median follow-up of 53.7 months; in patients who were treated with tisagenlecleucel, median OS was not reached at a median follow-up of 40.6 months. Among T-cell engagers, median OS rates were not reached for patients treated with epcoritamab, mosunetuzumab, or odronextamab, after median follow-up times of 17 months, 37.4 months and 26.6 months, respectively. Although availability of studies in 4L+ was limited, ORR ranged from 33% to 100% in patients who received either conventional therapies, HSCT, or tazemetostat. With respect to novel agents, ORR ranged from 77% to 78% for T-cell engagers and from 88% to 93% for CAR T-cell therapies. Conventional therapies in 2L+ POD24 had ORRs ranging from 47% to 75%, whereas the highest ORRs (80% or 100%) were observed among patients who received treatment with CAR T-cell therapies (82% to 92%) or T-cell engagers (68% to 100%), respectively. Safety outcomes were sparsely reported for the populations of interest, and most safety data pertained to the 3L+ population. Adverse events in patients receiving newer treatment options such as T-cell engagers and CAR T-cell therapies were common, including neutropenia, neurotoxicity, and CRS.

Meta-analysis outcome

Various meta-analyses were deemed feasible for 3L+ (ORR, CR rate, 2- and 3-year OS rate, 2- and 3-year PFS rate), 4L+ (ORR and CR rate), and 2L+ POD24 (ORR and CR rate).

The results of the meta-analyses in the 3L+ setting provided pooled estimates of ORR (74% [95% confidence interval [CI]: 66%-81%]), CR Rate (55% [95% CI: 45%- 65%]), 2-year OS rate (69% [95% CI: 59%-80%]), 3-year OS rate (78% [95% CI: 74%-82%]), 2-year PFS rate (45% [95% CI: 33%-57%]) and 3-year PFS rate (54% [95% CI: 41%-67%]). Sensitivity analyses in 3L+ demonstrated a reduction in ORR, CR rate, and 2-year OS rates when CAR T-cell therapies, T-cell engagers, and HSCT were excluded, with values of 62% (95% CI: 53%-72%), 28% (95% CI: 21%-35%), and 67% (95% CI: 50%-85%), respectively. In the 4L+ setting, the meta-analysis provided a pooled ORR estimate of 68% (95% CI: 56%-80%) and a pooled CR rate estimate of 55% (95% CI: 36%-74%). A sensitivity analysis in 4L+ demonstrated a reduction in ORR when CAR Tcell therapies, T-cell engagers, and HSCT were excluded, with a value of 52% (95% CI: 42%-62%). In the 2L+ POD24 setting, the meta-analyses provided a pooled ORR estimate of 78% (95% CI: 68%-87%) and a pooled CR rate estimate of 56% (95% CI: 44%-68%). A sensitivity analysis in 2L+ POD24 demonstrated a reduction in ORR when CAR Tcell therapies and T-cell engagers were excluded, with a value of 64% (95% CI: 58%-70%).

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 47. Summary of Efficacy Results Per IRC charter (Study FOL-001 - 3L+ FL)

	Liso-cel-treated Analysis Set			Leukapheresed Set
	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2	3L+ FL
Primary Endpoint				
ORR^a	N = 55	N = 48	N = 103	N = 114
n (%)	53 (96.4)	47 (97.9)	100 (97.1)	106 (93.0)
95% CI ^b	(87.5, 99.6)	(88.9, 99.9)	(91.7, 99.4)	(86.6, 96.9)
Secondary Endpoints				
CRR^c	N = 55	N = 48	N = 103	N = 114
n (%)	51 (92.7)	46 (95.8)	97 (94.2)	103 (90.4)
95% CI ^b	(82.4, 98.0)	(85.7, 99.5)	(87.8, 97.8)	(83.4, 95.1)
PRR				
n (%)	2 (3.6)	1 (2.1)	3 (2.9)	3 (2.6)
95% CI ^b	(0.4, 12.5)	(0.1, 11.1)	(0.6, 8.3)	(0.5, 7.5)
DOR^d, months	N = 53 responders	N = 47 responders	N = 100 responders	N = 106 responders
Median (95% CI) ^e	30.85 (30.85, N.A.)	N.A.	N.A. (30.85, N.A.)	N.A. (30.85, N.A.)
Min, Max ^f	1.9, 35.0+	1.9, 34.5+	1.9, 35.0+	1.9, 35.0+
Probability of Continued Response After Initial Response, % (95% CI) ^g				
6 months	84.9 (72.1, 92.1)	87.2 (73.8, 94.1)	86.0 (77.5, 91.5)	86.8 (78.7, 92.0)
12 months	79.1 (65.5, 87.9)	82.9 (68.6, 91.0)	80.9 (71.7, 87.4)	82.0 (73.2, 88.1)

18 months	75.2 (61.1, 84.8)	76.3 (61.3, 86.1)	75.7 (66.0, 83.0)	76.1 (66.7, 83.2)
24 months	73.1 (58.8, 83.1)	76.3 (61.3, 86.1)	74.6 (64.8, 82.1)	75.1 (65.6, 82.3)
30 months	73.1 (58.8, 83.1)	76.3 (61.3, 86.1)	74.6 (64.8, 82.1)	75.1 (65.6, 82.3)
DOR if BOR is CR^h, months	N = 53 responders	N = 47 responders	N = 100 responders	N = 103 responders
Median (95% CI) ^e	N.A. (30.85, N.A.)	N.A.	N.A. (30.85, N.A.)	N.A. (30.85, N.A.)
Min, Max ^f	2.1, 35.0+	1.9, 34.5+	1.9, 35.0+	1.9, 35.0+
Probability of Continued Response After Initial Response, % (95% CI) ^g				
6 months	88.2 (75.7, 94.5)	89.1 (75.8, 95.3)	88.7 (80.5, 93.6)	89.3 (81.5, 93.9)
12 months	82.2 (68.6, 90.3)	84.7 (70.5, 92.4)	83.4 (74.3, 89.5)	84.4 (75.8, 90.1)
18 months	78.1 (63.9, 87.2)	78 (62.9, 87.5)	78 (68.3, 85.1)	78.3 (69.0, 85.2)
24 months	75.9 (61.5, 85.6)	78 (62.9, 87.5)	76.9 (67.1, 84.2)	77.3 (67.8, 84.3)
30 months	75.9 (61.5, 85.6)	78 (62.9, 87.5)	76.9 (67.1, 84.2)	77.3 (67.8, 84.3)
PFSⁱ	N = 55	N = 48	N = 103	N = 114
Events, n (%)	17 (30.9)	12 (25.0)	29 (28.2)	33 (28.9)
Median (95% CI) ^e , months	31.77 (31.77, N.A.)	N.A.	N.A. (31.77, N.A.)	33.45 (30.55, N.A.)
Min, Max ^f , months	1.0, 35.9+	2.8, 35.5+	1.0, 35.9+	0.0+, 37.2+
PFS rate (95% CI) ^g , %				
6 months	83.6 (70.9, 91.1)	93.8 (81.9, 97.9)	88.3 (80.4, 93.2)	92.9 (86.2, 96.4)
12 months	78.1 (64.7, 86.9)	81.1 (66.9, 89.7)	79.6 (70.4, 86.2)	83.0 (74.7, 88.8)
18 months	74.4 (60.6, 84.0)	74.7 (59.8, 84.8)	74.5 (64.9, 81.9)	77.5 (68.6, 84.2)
24 months	70.5 (56.3, 80.8)	74.7 (59.8, 84.8)	72.5 (62.7, 80.1)	72.9 (63.5, 80.2)
30 months	70.5 (56.3, 80.8)	74.7 (59.8, 84.8)	72.5 (62.7, 80.1)	71.7 (62.2, 79.2)
OS^{j,k}	N = 55	N = 48	N = 103	N = 114
Events, n (%)	7 (12.7)	5 (10.4)	12 (11.7)	15 (13.2)
Median (95% CI) ^e , months	N.A.	N.A.	N.A.	N.A.
Min, Max ^f , months	3.7, 37.2+	5.6, 35.7+	3.7, 37.2+	0.0+, 38.5+
OS rate (95% CI) ^g , %				
6 months	94.5 (84.0, 98.2)	97.9 (86.1, 99.7)	96.1 (90.0, 98.5)	98.2 (93.1, 99.6)
12 months	90.9 (79.5, 96.1)	93.7 (81.7, 97.9)	92.2 (85.0, 96.0)	92.9 (86.3, 96.4)
18 months	89.1 (77.3, 94.9)	93.7 (81.7, 97.9)	91.2 (83.8, 95.3)	90.2 (83.1, 94.5)
24 months	87.2 (75.1, 93.7)	89.3 (76.2, 95.4)	88.2 (80.1, 93.1)	87.5 (79.7, 92.4)
30 months	87.2 (75.1, 93.7)	89.3 (76.2, 95.4)	88.2 (80.1, 93.1)	87.5 (79.7, 92.4)

^a ORR is defined as the proportion of subjects with an objective response of PR or CR according to the Lugano Classification 2014.

^b Two-sided 95% CI based on exact Clopper-Pearson method.

^c CRR is the proportion of subjects with a BOR of CR.

- ^d DOR is defined as the interval from the first documentation of response to progressive disease or death from any cause, whichever occurs first.
- ^e Median estimated from KM product-limit estimates.
- ^f Symbol + indicates a censored value.
- ^g Based on KM estimates.
- ^h Per protocol, DOR if BOR is CR is defined as the time from first response (CR or PR) to disease progression or death from any cause up to 60 months after liso-cel infusion (EOS). Per SAP, DOR if BOR is CR is defined as the time from first complete response to disease progression or death from any cause up to 60 months after liso-cel infusion. DOR if BOR is CR results per the SAP definition.
- ⁱ PFS is defined as the interval from the date of liso-cel infusion to progressive disease or death due to any cause, whichever occurs first.
- ^j OS is defined as the interval from the date of liso-cel infusion to the date of death due to any reason.
- ^k The OS analysis includes all available OS information from both the FOL-001 and GC-LTFU-001 studies.

2.5.3. Discussion on clinical efficacy

The sought indication is for “*the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy*”; the FOL-001 trial included three cohorts of patients with r/r FL from the second line onwards, although the large majority (107/130 patients) of them were on their 3L+ line of treatment. Data from the remaining 23 second line (2L) patients were only considered as proof of concept of the efficacy of liso-cel in FL.

Based on the study population, the wording of indication is considered appropriate.

Design and conduct of the clinical study

FOL-001 was a global, Phase 2, open-label, single-arm, multicohort and multicentre study, whose design is in line with other registrational CAR-T trials (i.e. three distinct phases: pretreatment, treatment and post-treatment, follow-up and possibility to participate in a LTFU study). In general, the study schedules and duration of follow-up are deemed appropriate. No specific formal dose response studies in FL were conducted, since the single target dose of 100×10^6 CAR+ T cells was ultimately chosen as the dose and regimen across all the liso-cel development program in B-cell malignancies in adults. Overall, based on the available efficacy and safety data with the proposed cell dose in study FOL-001, this is acceptable.

From a regulatory point of view, the single arm nature of FOL-001 has intrinsic limitations, mostly related to the absence of a direct comparison with other approved therapies. Despite the limits, however, 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 CAR-Ts in similar clinical settings.

To support the data from the pivotal single arm trial, the effects of liso-cel have been contextualised through indirect comparisons, including a Real-World External Arm Study, an Indirect Treatment Comparison and a Systematic Literature Review. It should be noted, however, that FL presents with significant biological and clinical heterogeneity (see e.g. Krull JE et al, Cell Rep Med 2024), and a recent evidence based systematic literature and medical review identified more than 20 prognostic factors for R/R FL, including patient demographics and clinical characteristics, disease and treatment characteristics, and laboratory data (see Ubieto Aj et al, Blood 2023 142 (Supplement 1): 7261). Indirect comparison methods require that all factors with a possible prognostic impact on the target outcome are accounted for in the analysis, since all the residual variability is attributed to the intervention. Further uncertainties are introduced by the limited sample size of the studies included in the indirect comparison exercises. Overall, the reliability of the proposed indirect comparisons is considered limited.

In study FOL-001 all patients were required to be either refractory or to have relapsed after their last therapy and no specific time limits after the completion of the previous treatments were requested for the inclusion in the trial. Previous exposure to systemic therapy based on an anti-CD20 antibody and an alkylating agent was considered mandatory for the eligibility: this is supported considering that the use of the combination anti-CD20/alkylating agent is the standard of care for the first- and second-line treatment of patients. Patients may have been exposed also to autologous HSCT as a part of the previous treatment regimens.

Treatment eligibility was defined according to what is reported in the principal guidelines for the treatment of FL (NCCN 2019), which require the presence of at least one of the modified GELF criteria or the presence of rapid progression (i.e. POD24). The use of the latest version of the ("modified") GELF criteria is justified, considering that their use was recommended by the NCCN 2019 guidelines, and it is still considered in line with the current management landscape of r/r FL.

Efficacy was assessed by radiographic tumour evaluation by diagnostic quality computed tomography (CT)/magnetic resonance imaging (MRI) scans (chest, neck, abdomen and pelvis) and/or positron emission tomography (PET) scans and were reviewed by an independent review committee (IRC). For the assessment of response, a modified version of "Modified Lugano Classification Criteria" was applied. Overall, the rate of failure in central pathology assessment observed in study FOL-001 (8%) is considered in line with the known risk of failure for this procedure and did not significantly affect the integrity of the trial.

Regarding the methodology applied to the assessment of response, the evaluation of bone marrow involvement by lymphoma at screening was done by TC/PET and Bone Marrow Biopsy (BMB) was not routinely performed: confirmatory BMBs were conducted as soon as logistically feasible after initial PET CR in all FL subjects who did not have a negative BMB between their most recent disease progression prior to screening and initiation of lymphodepleting chemotherapy. In the current response criteria for lymphoproliferative diseases (Cheson et al, JCO 2014) specific indications about the possibility of omission of the BM assessment were reported only for Hodgkin Lymphoma and DLBCL. For other NHL histologies, the authors concluded that data were insufficient to change the standard practice, and unilateral BMB is still recommended, along with immunohistochemistry and flow cytometry. Therefore, by applying the modified criteria of Lugano without BMB at baseline, it can be postulated that a percentage of patients with bone marrow involvement at baseline was not diagnosed, but this potential bias was covered by the execution of BMB in all patients who reported a CR at the TC-PET assessment of response.

The introduction of immunologic therapies in the treatment of neoplastic diseases (including lymphomas) created a new category of response defined Indeterminate Response (IR), which is determined by signs suggestive of persistence of disease that are actually determined by a flare reaction. The evaluation protocol for IR reported in FOL-001 was in line with standard guidelines and no cases of IR were reported in the pivotal 3L+ cohort.

Overall, the choice of the endpoint reflects the aim of the study, and ORR has been accepted before as primary evidence of anti-tumoral activity of new drugs in the absence of controls, since spontaneous regression is considered unlikely in such advanced disease settings. Significant and clinically relevant improvements in terms of PFS/OS have been usually accepted as adequate basis to inform B/R decisions in NHLs, however the interpretation of time-to-event endpoints in the absence of controls is complicated, since it is impossible to disentangle the impact of the intervention from the effect of heterogeneity e.g. in tumour growth rates. In this regard, it is recognised that, in the absence of controlled evidence, measures of anti-tumour activity and depth of response (in terms of ORR/CR rates), along with clinically relevant results in terms of response duration (DOR per IRC) can provide sufficient basis to support the benefit risk evaluations, especially in presence of outstanding efficacy and high unmet medical need.

The MAH integrated the scientific advice provided by the CHMP in terms of change of the primary endpoint from CRR to ORR (both revised from an Independent Review Committee-IRC). Although the change in the primary endpoint was implemented with Amendment 1 (July 2021) when 116/188 (61.7%) patients were already enrolled in the protocol, the Statistical Analysis Plan was not considered to be severely affected by this decision, especially when the similarly high ORR/CCR observed in study FOL-001 are taken into account. Overall, the two amendments applied to the protocol did not affect the integrity of the trial.

The global incidence of protocol deviations was similar between the overall population of FL (84.2%) and the population of 3L+ patients for which the extension of indication was claimed (83.3%). Although the global rate of deviations was high, the incidence of important protocol deviation was low therefore the effect on the integrity of the trial is not considered relevant.

The study was conducted during the COVID-19 pandemic; overall, based on the number and types of protocol deviations (less than 2% of more than 2 deviations were recorded during the trial), it can be assumed that the conduct of the study was not substantially impacted by COVID-19.

The statistical assumptions are considered in line with the expectation of a single arm trial in the setting of r/r FL.

Notably, the statistical hypothesis for the definition of the primary endpoint was set on literature data about the efficacy of PI3K inhibitors. This assumption can be deemed acceptable considering the time in which the protocol was drawn, although it is not completely adherent to the current therapeutic landscape in r/r FL after at least 2 lines of therapy, especially when the recent approval of anti-CD19 CAR T cell and bispecific monoclonal antibody T cell engagers is taken into account. Nevertheless, in the absence of controls, B/R evaluations are based on the totality of evidence and the actual relevance of the selected efficacy threshold beyond futility is limited.

Regarding the efficacy analysis sets, the Applicant proposed a modified version of the ITT population defined as all subjects who have signed informed consent and underwent leukapheresis (Leukapheresed Set). To note, this "Leukapheresed Set" definition is not perfectly in line with the regulatory definition of ITT, which should include all patients providing informed consent to the trial. Nevertheless, it can be recognised that the production process of a CAR-T can justify a different approach to ITT and, therefore, the proposed modified ITT set can be considered acceptable.

Similarly to other trials in FL involving CAR-Ts, the investigators were allowed to prescribe antineoplastic bridging therapies to stabilize the disease while waiting for liso-cel infusion. The bridging therapy was selected based on the investigators choice and included the current approved therapies for r/r FL; it should be noted that, theoretically, the use of a bridging therapy may induce the CR and, in that case, treatment with liso-cel could be more similar to consolidation rather than salvage therapy. It is noted, however, that the MAH excluded from the Primary Efficacy Set all patients with absence of active disease before liso-cel administration or without a pre-infusion disease evaluation which could confirm the presence of active disease.

Efficacy data and additional analyses

Study population

The primary efficacy set was defined by the all leukapheresed patients who received a conforming product in presence of active disease before liso-cel infusion. The enrolled population could be considered reflective of R/R FL disease condition; although a limited number of patients in 2L disease were enrolled, a significant amount of POD24 patients were included in that cohort.

As of the data cutoff date (10-Jan-2024), all FL cohorts (Cohorts 1, 2, and 3) had been enrolled. All but one subject in the 3L+ FL group (Cohorts 1 and 2) completed the treatment period (Days 1 to 29). As of the data cutoff date, the median follow-up was 29.96 (24.67, 32.76) months, with the majority (82.2%) of 3L+ FL subjects still ongoing in the post-treatment follow-up period (Day 30 to Month 60). The median duration of follow up is considered acceptable in terms of study design, considering that the statistical hypotheses were set on the efficacy of PI3K, which showed a median duration of response of 12 months. Nevertheless, given the indolent nature of the FL, a longer follow up of the efficacy is being expected in the data collected in the agreed studies mentioned in the RMP (version 5.1).

Given that the large majority of patients enrolled in the general population was represented by patients in the 3L+ setting, the clinical features at the diagnosis did not substantially differ between the whole population (i.e. including also 2L patients) and the one for which the approval is sought (3L+ group); and only minor differences can be noted.

In particular, in the 3L+ more than half patients presented with double refractory status (64,5%), which resulted slightly higher than what reported in the general FL population (61.5%). The high incidence of double refractory status is expected in later phases of disease, in line with the higher unmet medical need for new therapies in this setting. The median time from initial diagnosis to liso-cel infusion was 4.71 years (range, 0.70 to 35.27 years); the proportion of subjects in the 2L and 3L+ with Ann Arbor Stage IV disease (47.8% and 52.3%) and Grade 3A FL (26.1% and 23.4%) at screening were similar. Subjects in the 2L cohort had a lower median age (53 vs 62 years), a higher proportion of Grade 1 FL (26.1% vs 8.4%), a higher proportion of subjects that had a low-risk FLIPI score at screening (47.8% vs 11.2%), a lower proportion of subjects with CRP ≥ 20 mg/L at baseline (17.4% vs 30.8%), and a lower proportion of subjects with LDH $>ULN$ at baseline (26.1% vs 43.9%) compared to the 3L+ subjects. However, the 2L cohort had a numerically greater proportion of subjects meeting modified GELF criteria at time of most recent relapse compared to 3L+ subjects (69.6% vs 53.3%), and higher proportion of subjects meeting GELF criteria of symptoms attributable to FL (26.1% vs 12.1%) and threatened end-organ function/cytopenia/bulky disease (30.4% vs 22.4%).

In the 3L+ group (Cohort 1 and Cohort 2), the main reason for treatment eligibility was the fulfilment of at least 1 of the modified GELF criteria (53.3%, the majority of them with "Threatened End-Organ Function/ Cytopenia Secondary to Lymphoma/ Bulky Disease" [22.4%]); patients with POD 24 status accounted for the 43% of patients. Interestingly, more than half of POD24 patients (54.2%) presented this status after the first line therapy with anti-CD20 and an alkylating agent. The presence of other high-risk factors was well represented in the whole enrolled population, which is expected in later lines of therapy for FL; in 3L+ patients high-risk FLIPI and increased LDH accounted for the 57% and 43.9%, respectively. About 1/3 of patients (32.7%) were highly pre-treated, with a previous exposure to 4 or more different lines.

The median number and characteristic of prior systemic therapies is in line with a R/R population set. Given the large variability in the number of previous therapy lines (2-10), patients were exposed to a variety of treatments: as expected, the most commonly used were chemotherapy agents and anti-CD20 monoclonal antibodies.

The use of bridging therapy in the interval time from Leukapheresis and Liso-cel infusion was permitted in order to ensure a better disease control; the use was not mandatory but based on the investigators' decision. In general, the indolent behaviour of FL can explain the reduced need of bridging therapy for disease control (i.e. 37.7% of patients); similarly, the median time between leukapheresis and infusion was acceptable and similar between the whole enrolled population.

No significant impact from deviations in the lymphodepleting therapy were noted.

The median number of total (CD8+ and CD4+) liso-cel administered dose cell counts infused in the 3L+ Liso-cel-treated Analysis Set was 100.02×10^6 CAR+ T cells (range: 93.4 to 109.2×10^6), which is in line with the dose used in the DLBCL.

In respect to the median time from leukapheresis to liso-cel availability, the reported value was similar between the whole population and the 3L+ patients (29 days); similarly, the median time from leukapheresis to liso-cel infusion was superimposable between the two settings (50 and 49 days, respectively). The peculiarity of few cases requiring longer time as described in the section above does not significantly impact on the integrity of the population enrolled.

Primary and Key Secondary Endpoints

The results obtained in terms of ORR (97.1%) can be considered indicative of clinically relevant efficacy in the setting of interest; the percentage of response was homogeneous among the different lines of therapy and substantially consistent also in terms of sensitivity analyses in the Leukapheresed (93%) and Per Investigator set (98.1%). Moreover, the reported ORR was significantly higher compared to the statistical assumption (77%) to refuse the null hypothesis.

The reported CRR rate was also compelling across the different lines of therapy and higher (94.3%) than the statistical assumption threshold for efficacy (48%). Responses were rapidly induced and deep, with a median time to first response (CR or PR) and median time to first CR of 0.95 months (range: 0.6 to 3.3 months). To note, all sensitivity analyses applied to this key secondary endpoint confirmed the validity of the primary analysis (Leukapheresed set: 90.4%, Per Investigator: 94.2%) except when the FDA algorithm was used. In this regard, despite a similar ORR, in 3L+ subjects the proportion of CRR using the "FDA algorithm" was lower (72.3%, 95% CI: 62.5, 80.7) and the proportion of PR higher (25%, 95% CI: 16.4-33.7) compared to the primary analysis. The FDA algorithm differed from the "modified Lugano criteria" used for the primary analysis of study FOL-001 in terms of the mandatory requirement of BMB for the evaluation of response, regardless of the presence of a CR; in general, the FDA approach can be considered more in line with the Lugano recommendations for evaluation of response in PET/TC era (see e.g. Cheson et al, JCO 2014). The FDA algorithm was introduced with Amendment 1, when 84 out of 114 subjects had been already enrolled in the 3L+ FL population. Applying the FDA algorithm, 22 subjects were downgraded from CR to PR: CR could not be confirmed in 19/22 because they did not have BMB available, 2 subjects had BMB yet with unknown result, and 1 subject had evidence of lymphomatous BM involvement. A post-hoc subgroup analysis of time-to-event efficacy outcomes for the 22 subjects with a BOR of CR per IRC charter but with a BOR of PR when the FDA algorithm was used suggested a trend towards reduced DOR (expected 24 months DOR: 58% [34.6-75.5]) and PFS (expected 24 months PFS: 58% [34.6-75.5]) when compared with those reported for patients with a confirmed CR using the FDA algorithm (expected 24 months DOR: 76.9% [67.1-84.2]; expected 24 months PFS: 77% [67.2-84.2]). This finding suggests that some CR in the primary analysis could have been more correctly classified as PR yet results from such post-hoc subgroup analysis should be interpreted with caution because of the limited sample size and broad confidence intervals. Therefore, the general considerations about efficacy of liso-cel are not affected by these results.

Results from an additional non-prespecified sensitivity analysis, including all patients who underwent leukaphereses and excluding subjects who received non-conforming products, were also overall consistent with the primary analysis.

Liso-cel demonstrated a homogeneous effect in respect to the pre-specified subgroups, although in some cases (e.g. patients aged >75: 9 patients, low FLIPI score: 10 patients) the small number of patients increased the uncertainties of effect.

At the DCO of January 2024 and with a median follow-up for the 3L+ patients of 29.96 months (24.67, 32.76), the Time To Event endpoints of DOR, PFS, OS did not reach the median value: although the available follow-up can be considered adequate to weigh the clinical benefit of liso-cel in the context of the current therapeutic landscape of FL, further data with longer follow-up are needed to thoroughly characterise its long-term efficacy. Data are expected to be provided post approval as per the studies included in the RMP version 5.1.

Given the design and the aim of the single arm trial FOL-001, DOR per IRC assumes a value for the isolation of the antitumoral effect of the drug and for its clinical relevance. The median value of DOR was not reached with a median follow-up of 23.13 months (22.93, 23.26) and this result was confirmed also by all sensitivity analyses with the exception of the analysis Per Investigator, which showed a median

DOR of 34.76 months (30.85, N.A.). Similar results were reported for DOR if BOR is CR, as expected considering that most of the obtained responses were CR.

With a median follow-up of 23.98 months (95% CI: 23.82, 24.15), the median PFS per IRC was not reached, but it can be noted that in the sensitivity analyses (Leukapheresed set, Per Investigator), the median PFS was 33.45 months (30.55, N.A.) and 36.14 months (31.77, N.A.), respectively.

The median OS was not reached at the time of the data DCO (median follow-up of 29.47 months [95% CI: 26.51, 29.93]) as well: 12 deaths had occurred in the study, with an estimated probability of survival of 88.2% (80.1, 93.1) at Month 24. Same value can be noted at the last time point reported at 36 months.

Data about Time to Next Treatment (TTNT) were considered in line with what expected with the setting of R/R FL: 12 patients needed further therapy after liso-cel because of relapse (11 subjects) and progressive disease (1 subject); the median TTNT was not reached at a median follow up of 29.31 months, with a range between 3.7 to 37.2 months. Disease status was not available for 3 patients; in the other cases, 2 deaths were recorded, 1 out of 2 attributable to disease progression. The type of subsequent treatments were in line with the therapeutic landscape of R/R FL. The analysis of CD19 status at relapse/progression was missing for 7/12 patients; in the remaining cases, the H-score for CD19 expression varied from 1 to 180. Therefore, no conclusions could be drawn regarding CD19 expression and risk of relapse/progression.

Patient Reported Outcomes (PROs) were assessed with three different questionnaires (EORTC QLQ-C30 questionnaire, FACT-LymS questionnaire, and EQ-5D Utility Index VAS) which all showed very similar results. Nevertheless, despite the linear improvement of symptoms and QoL reported in questionnaires, the level of the evidence obtained in absence of a comparison arm is deemed low due to lack of controls and blinding, and its supportive role for the global definition of efficacy of liso-cel is limited.

Overall, the evidence from FOL-001 is considered supportive of the extension of indication for liso-cel for the treatment of 3L+ FL. Although efficacy data came from a limited set of patients and the long-term benefit with liso-cel is not completely characterised at present, the available data are still considered adequate to inform Benefit/Risk decisions. Longer-term data from a broader population are still needed, however, to thoroughly characterise the efficacy profile of liso-cel. In this regard, the MAH has committed to provide additional efficacy data in R/R FL from the ongoing long-term follow-up study GM-LTFU-001, from the US-based, non-interventional RW registry study CA082-1175 of patients treated with liso-cel for 3L+ R/R FL in the post-marketing setting, and from the ongoing registry study JCAR017-BCM-005 that also includes EU subjects who receive liso-cel post-approval.

Real World Studies

In order to contextualize the results of this single arm trial, the MAH reported the results of three supportive studies (see sections above for details) which indirectly compared the results of Liso-cel to other approved therapies.

- *Real World external control arm study*

As a general comment, data from this external control arm helped in contextualizing the effect of liso-cel compared to common treatments used for the third line therapy. However, considering the large predominance of patients treated with lenalidomide and rituximab, the extrapolation of data is mainly related to this kind of therapy and to other common immune-chemotherapy regimens, while the level of evidence with respect to other therapies like PI3Kis should be considered low.

- *Indirect Treatment Comparison (ITC) for lisocabtagene maraleucel in the treatment of 3L or 4L+ relapsed/refractory follicular lymphoma*

In an indirect comparison (ITC) with mosunetuzumab, axi-cel and tisa-cel, the effects of liso-cel appeared to be superior in respect to mosunetuzumab and similar to other CAR-Ts. Overall, the strength of evidence is necessarily reduced by the intrinsic limitations related to the methodology, the limited sample size of the data sets, the high clinical and biological heterogeneity of FL and uncertainties in CR assessment across studies.

- *Systematic literature review of clinical evidence of third line and later (3L+) treatments for follicular lymphoma in adult patients*

The results of the meta-analyses described a homogeneous scenario in which the reported outcomes in terms of ORR, CR rate OS and PFS were significantly reduced when CARTs therapies, T-cell engagers, and HSCT are excluded, confirming the evidence of superior outcomes with novel immunotherapy approaches (both humoral and cell mediated) compared to standard chemo-immunotherapy regimens.

Overall, the results obtained with these indirect comparisons studies were considered informative and supported the contextualisation of efficacy outcomes from study FOL-001. However, in a regulatory perspective, their role to support B/R evaluations is limited, mainly because of the intrinsic methodological limitations and the high clinical and biological heterogeneity of FL which reduces the strength of evidence, even in case of application of standardization techniques like propensity score methodologies and Matched Adjusted Indirect Comparison (MAIC) analyses.

2.5.4. Conclusions on the clinical efficacy

Results from the FOL-001 showed that treatment with liso-cel in subjects with 3L+ R/R FL resulted in clinically relevant rates of deep and durable responses.

With all the limits intrinsic in such methodologies, results from the provided indirect comparison exercises also suggested that liso-cel treatment could result in clinically relevant efficacy in the target indication, which is at least in line with what observed with other T cell engaging immunotherapies in the claimed indication.

Longer-term efficacy data from a larger population of patients with R/R FL will be provided post-approval from the ongoing long-term follow-up study GM-LTFU-001, from the US-based, non-interventional RW registry study CA082-1175 of patients treated with liso-cel for 3L+ R/R FL in the post-marketing setting (category 3 studies in the RMP), and from the ongoing registry-based study JCAR017-BCM-005 that also include EU subjects who receive liso-cel in the post-approval setting (Category 1 study in the annex II and the RMP).

2.6. Clinical safety

Introduction

For this proposed indication, the safety evaluation is primarily based on the safety data from Study **JCAR017-FOL-001** (TRANSCEND FL).

An overview of safety data from liso-cel treated subjects with R/R FL (n= 130) enrolled in Cohort 1 (4L+ FL), Cohort 2 (3L FL), and Cohort 3 (2L FL) of Study FOL-001 is presented.

A safety analysis of liso-cel in FL by study cohort (i.e., by line of therapy; Cohort 1, Cohort 2, and Cohort 3) and groups (Cohorts 1 + 2 and Cohorts 1 + 2 + 3) is presented.

Additionally, safety data are included from 3L+ FL subjects (proposed indication, from Cohorts 1 and 2 of Study FOL 001; n= 107) presented side-by-side with the pooled safety data for liso-cel monotherapy treated subjects with 2L and 3L+ LBCL (n= 608) in the existing EU-approved indications.

Finally, a safety summary of 2L+ FL subjects (from Cohorts 1, 2, and 3 of Study FOL-001; n= 130) is presented side-by-side with the pooled safety data for 2L/3L+ LBCL. Together, these analyses allow for comparison of the safety profile of liso-cel in 3L+ FL (proposed indication) and 2L+ FL, respectively, to the known safety profile of liso-cel in the approved SmPC.

Patient exposure

In Study FOL-001 Cohorts 1, 2, and 3, 154 subjects were screened and 139 subjects underwent leukapheresis as of the cut-off date of 10-Jan-2024. Of these, 130 (93.5%) subjects received LDC and liso-cel infusion and comprised the Liso-cel treated Analysis Set.

In the Liso-cel-treated Analysis Set (n= 130), 128 (98.5%) subjects completed treatment period and continued to post-treatment follow-up period. Two (1.5%) discontinuations during the treatment period were either due to AE (n= 1 subject in Cohort 3) or subject withdrawal (n= 1 subject in Cohort 2).

In the Leukapheresed (ITT) Set (n= 139), 5 (3.6%) subjects were treated with nonconforming product.

As of the cutoff date of 10-Jan-2024, the median study follow-up was 29.72 months (min, max: 0.3, 39.6 months) for all FL subjects.

Demographic and baseline characteristics

Disease characteristics were reflective of subjects with R/R FL. The key demographic and baseline characteristics were generally similar between the 2L+ FL and 3L+ FL cohorts, with the exception of a higher proportion of 2L+ FL subjects who had a low-risk FLIPI at screening (18.5% vs 11.2%) compared to 3L+ FL subjects.

The median time from start of last systemic regimen prior to liso-cel infusion was 1.35 years (range: 0.2, 13.1); 25.4% (n= 33/130) of subjects received prior autologous HSCT, and the median number of prior systemic therapies was 2 (range: 1, 10). The most commonly used last lines of systemic therapies prior to liso-cel administration were rituximab (54.6% of subjects), cyclophosphamide (27.7% of subjects), and prednisone (20.8% of subjects).

The median time from initial diagnosis to liso-cel infusion was 4.71 years (range, 0.70 to 35.27 years). Anticancer therapy for disease control was permitted between apheresis and lymphodepletion. 37.7% of subjects received bridging therapy for disease control during the liso-cel manufacturing period (33.8% received systemic treatment only and 3.8% received radiotherapy only); the most commonly received bridging therapies were rituximab (15.4% of subjects) and cyclophosphamide (13.1% of subjects).

For additional details on demographic and baseline characteristics of Study FOL-001 Population, please refer to Clinical Efficacy part.

Liso-cel Product, Dose, and Administration

Administration of liso-cel is preceded by LDC with fludarabine (30 mg/m²/day) plus cyclophosphamide (300 mg/m²/day) (flu/cy) for 3 days to increase the expansion, persistence, and anti-tumor activity of the CAR+ T cells.

The target dose of liso-cel is single infusion containing 100×10^6 CAR+ viable T cells consisting of 1:1 CAR+ CD8+ T cells and CAR+ CD4+ T cells supplied separately in one to four single-dose vials.

In the Liso-cel-treated Analysis Set, the median numbers of total (CD8+ and CD4+) liso-cel administered dose cell counts infused by cohort were as follows:

- Cohort 1: 100.13×10^6 CAR+ T cells (range: 93.4×10^6 to 109.2×10^6)
- Cohort 2: 99.73×10^6 CAR+ T cells (range: 96.6×10^6 to 101.8×10^6)
- Cohort 3: 99.92×10^6 CAR+ T cells (range: 97.4×10^6 to 102.9×10^6)
- Cohorts 1 + 2 (3L+ FL): 100.02×10^6 CAR+ T cells (range: 93.4×10^6 to 109.2×10^6)
- Cohorts 1 + 2 + 3 (2L+ FL): 100.02×10^6 CAR+ T cells (range: 93.4×10^6 to 109.2×10^6).

Adverse events

Overall Safety Summary

Table 48. Overall Summary of Safety in Study FOL-001

Safety Parameter	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1, 2	2L FL Cohort 3	2L+ FL Cohorts 1, 2, 3
Leukapheresed Set	N = 65	N = 49	N = 114	N = 25	N = 139
Deaths^a	9 (13.8)	6 (12.2)	15 (13.2)	1 (4.0)	16 (11.5)
Cause of Death					
PD	4 (6.2)	3 (6.1)	7 (6.1)	0	7 (5.0)
Death from AE (Not Otherwise Specified) ^b	3 (4.6)	0	3 (2.6)	1 (4.0)	4 (2.9)
Death from Cardiac Event	1 (1.5)	0	1 (0.9)	0	1 (0.7)
Death from Other Cause ^c	0	3 (6.1)	3 (2.6)	0	3 (2.2)
Death from New Malignancy, or Complication from New Malignancy	1 (1.5)	0	1 (0.9)	0	1 (0.7)
Liso-cel Analysis Set	N = 59	N = 48	N = 107	N = 23	N = 130
Subjects with any TEAE^d	58 (98.3)	48 (100.0)	106 (99.1)	23 (100.0)	129 (99.2)
Grade $\geq$ 3	47 (79.7)	39 (81.3)	86 (80.4)	14 (60.9)	100 (76.9)
Grade 5	0	0	0	1 (4.3)	1 (0.8)
Serious	15 (25.4)	12 (25.0)	27 (25.2)	4 (17.4)	31 (23.8)
Liso-cel-related	54 (91.5)	42 (87.5)	96 (89.7)	19 (82.6)	115 (88.5)
Liso-cel-related Grade $\geq$ 3	34 (57.6)	34 (70.8)	68 (63.6)	13 (56.5)	81 (62.3)
Liso-cel-related Grade 5	0	0	0	1 (4.3)	1 (0.8)
Liso-cel-related serious TEAE	13 (22.0)	8 (16.7)	21 (19.6)	3 (13.0)	24 (18.5)
LDC-related	49 (83.1)	32 (66.7)	81 (75.7)	17 (73.9)	98 (75.4)
Subjects with any AESI	40 (67.8)	32 (66.7)	72 (67.3)	15 (65.2)	87 (66.9)
CRS ^e	35 (59.3)	28 (58.3)	63 (58.9)	12 (52.2)	75 (57.7)
iiNT ^f	9 (15.3)	8 (16.7)	17 (15.9)	4 (17.4)	21 (16.2)
IRR	0	0	0	0	0
MAS ^g	0	0	0	1 (4.3)	1 (0.8)
TLS	0	0	0	0	0
Hypogammaglobulinemia	3 (5.1)	3 (6.3)	6 (5.6)	1 (4.3)	7 (5.4)
Grade $\geq$ 3 infections	3 (5.1)	4 (8.3)	7 (6.5)	0	7 (5.4)
SPM	4 (6.8)	3 (6.3)	7 (6.5)	2 (8.7)	9 (6.9)
Autoimmune disorders	0	0	0	0	0
Prolonged cytopenia ^h	14 (23.7)	12 (25.0)	26 (24.3)	3 (13.0)	29 (22.3)

^a Deaths from Study GC-LTFU-001 are included.

^b Death from AE (NOS) included: Cohort 1: acute respiratory failure hypoxic (LDC-infusion), acute myeloid leukemia (from Day 91 after infusion), progressive multifocal leukoencephalopathy (from Day 91 after infusion), and Cohort 3: HLH (Day 1-30).

^c Death from other cause included: Cohort 2: 2 cases of COVID-19 and erythema multiforme.

^d A TEAE was defined as an AE that started any time from initiation of liso-cel administration through and including 90 days following liso-cel administration.

Treatment Emergent Adverse Events (TEAEs)

The frequency of TEAEs was consistent across all cohorts (lines of therapy) and groups.

Table 49. TEAEs by SOC and PT Reported in $\geq$ 5% by PT in Any Cohort - Liso-cel-treated Analysis Set

System Organ Class Preferred Term (A)	4L+ FL N = 59 n (%)	3L FL N = 48 n (%)	3L+ FL N = 107 n (%)	2L FL N = 23 n (%)	2L+ FL N = 130 n (%)
SUBJECTS WITH AT LEAST ONE TEAE	58 (98.3)	48 (100.0)	106 (99.1)	23 (100.0)	129 (99.2)
Blood and lymphatic system disorders	46 (78.0)	38 (79.2)	84 (78.5)	16 (69.6)	100 (76.9)
Neutropenia	39 (66.1)	35 (72.9)	74 (69.2)	14 (60.9)	88 (67.7)
Anaemia	26 (44.1)	21 (43.8)	47 (43.9)	5 (21.7)	52 (40.0)
Thrombocytopenia	22 (37.3)	13 (27.1)	35 (32.7)	3 (13.0)	38 (29.2)
Leukopenia	8 (13.6)	6 (12.5)	14 (13.1)	4 (17.4)	18 (13.8)
Lymphopenia	8 (13.6)	6 (12.5)	14 (13.1)	5 (21.7)	19 (14.6)
Febrile neutropenia	2 (3.4)	4 (8.3)	6 (5.6)	1 (4.3)	7 (5.4)
Immune system disorders	35 (59.3)	29 (60.4)	64 (59.8)	13 (56.5)	77 (59.2)
Cytokine release syndrome	35 (59.3)	28 (58.3)	63 (58.9)	12 (52.2)	75 (57.7)

System Organ Class Preferred Term (A)	4L+ FL N = 59 n (%)	3L FL N = 48 n (%)	3L+ FL N = 107 n (%)	2L FL N = 23 n (%)	2L+ FL N = 130 n (%)
Gastrointestinal disorders	28 (47.5)	21 (43.8)	49 (45.8)	12 (52.2)	61 (46.9)
Constipation	14 (23.7)	9 (18.8)	23 (21.5)	4 (17.4)	27 (20.8)
Diarrhoea	9 (15.3)	7 (14.6)	16 (15.0)	6 (26.1)	22 (16.9)
Nausea	7 (11.9)	3 (6.3)	10 (9.3)	2 (8.7)	12 (9.2)
Abdominal pain	0	4 (8.3)	4 (3.7)	5 (21.7)	9 (6.9)
General disorders and administration site conditions	27 (45.8)	17 (35.4)	44 (41.1)	14 (60.9)	58 (44.6)
Fatigue	10 (16.9)	3 (6.3)	13 (12.1)	7 (30.4)	20 (15.4)
Asthenia	9 (15.3)	5 (10.4)	14 (13.1)	2 (8.7)	16 (12.3)
Pyrexia	9 (15.3)	10 (20.8)	19 (17.8)	2 (8.7)	21 (16.2)
Non-cardiac chest pain	3 (5.1)	0	4 (3.7)	0	3 (2.3)
Oedema peripheral	2 (3.4)	2 (4.2)	4 (3.7)	2 (8.7)	6 (4.6)
Nervous system disorders	26 (44.1)	20 (41.7)	46 (43.0)	10 (43.5)	56 (43.1)
Headache	19 (32.2)	11 (22.9)	30 (28.0)	8 (34.8)	38 (29.2)
Tremor	9 (15.3)	8 (16.7)	17 (15.9)	2 (8.7)	19 (14.6)
Aphasia	6 (10.2)	1 (2.1)	7 (6.5)	2 (8.7)	9 (6.9)
Dizziness	2 (3.4)	1 (2.1)	3 (2.8)	3 (13.0)	6 (4.6)
Dysgraphia	1 (1.7)	3 (6.3)	4 (3.7)	0	4 (3.1)
Musculoskeletal and connective tissue disorders	22 (37.3)	11 (22.9)	33 (30.8)	7 (30.4)	40 (30.8)
Back pain	5 (8.5)	0	5 (4.7)	4 (17.4)	9 (6.9)
Arthralgia	4 (6.8)	6 (12.5)	10 (9.3)	1 (4.3)	11 (8.5)
Myalgia	4 (6.8)	1 (2.1)	5 (4.7)	2 (8.7)	7 (5.4)
Investigations	13 (22.0)	13 (27.1)	26 (24.3)	6 (26.1)	32 (24.6)
Alanine aminotransferase increased	4 (6.8)	4 (8.3)	8 (7.5)	2 (8.7)	10 (7.7)
Aspartate aminotransferase increased	4 (6.8)	2 (4.2)	6 (5.6)	2 (8.7)	8 (6.2)
Neutrophil count decreased	3 (5.1)	3 (6.3)	6 (5.6)	0	6 (4.6)
Blood alkaline phosphatase increased	1 (1.7)	0	1 (0.9)	2 (8.7)	3 (2.3)
Blood creatinine increased	1 (1.7)	2 (4.2)	3 (2.8)	3 (13.0)	6 (4.6)
Metabolism and nutrition disorders	13 (22.0)	12 (25.0)	25 (23.4)	7 (30.4)	32 (24.6)
Hypokalaemia	7 (11.9)	1 (2.1)	8 (7.5)	1 (4.3)	9 (6.9)
Decreased appetite	4 (6.8)	2 (4.2)	6 (5.6)	1 (4.3)	7 (5.4)
Hyponatraemia	0	3 (6.3)	3 (2.8)	1 (4.3)	4 (3.1)
Skin and subcutaneous tissue disorders	12 (20.3)	5 (10.4)	17 (15.9)	3 (13.0)	20 (15.4)
Rash	4 (6.8)	1 (2.1)	5 (4.7)	2 (8.7)	7 (5.4)
Pruritus	1 (1.7)	3 (6.3)	4 (3.7)	1 (4.3)	5 (3.8)

System Organ Class Preferred Term (A)	4L+ FL N = 59 n (%)	3L FL N = 48 n (%)	3L+ FL N = 107 n (%)	2L FL N = 23 n (%)	2L+ FL N = 130 n (%)
Vascular disorders	12 (20.3)	6 (12.5)	18 (16.8)	4 (17.4)	22 (16.9)
Hypotension	6 (10.2)	3 (6.3)	9 (8.4)	1 (4.3)	10 (7.7)
Hypertension	3 (5.1)	2 (4.2)	5 (4.7)	1 (4.3)	6 (4.6)
Respiratory, thoracic and mediastinal disorders	10 (16.9)	7 (14.6)	17 (15.9)	4 (17.4)	21 (16.2)
Cough	6 (10.2)	1 (2.1)	7 (6.5)	2 (8.7)	9 (6.9)
Pleural effusion	0	0	0	2 (8.7)	2 (1.5)
Psychiatric disorders	9 (15.3)	7 (14.6)	16 (15.0)	3 (13.0)	19 (14.6)
Insomnia	4 (6.8)	1 (2.1)	5 (4.7)	2 (8.7)	7 (5.4)
Confusional state	3 (5.1)	0	3 (2.8)	0	3 (2.3)
Cardiac disorders	3 (5.1)	3 (6.3)	6 (5.6)	3 (13.0)	9 (6.9)
Sinus tachycardia	0	1 (2.1)	1 (0.9)	2 (8.7)	3 (2.3)

A TEAE was defined as any AE that occurred from start of liso-cel infusion and up to 90 days after liso-cel infusion. Any AE occurring after the initiation of another anti-FL treatment was not considered a TEAE.

AEs were coded using MedDRA version 26.0.

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

Source: Table 8.2-1 of Study FOL-001 Addendum 01 CSR¹

Grade 3 and Higher TEAEs

Table 50. Grade 3 or Higher TEAEs by SOC and PT Reported in ≥ 5% by PT in Any Cohort - Liso-cel-treated Analysis Set

System Organ Class Preferred Term (A)	4L+ FL N = 59 n (%)	3L FL N = 48 n (%)	3L+ FL N = 107 n (%)	2L FL N = 23 n (%)	2L+ FL N = 130 n (%)
SUBJECTS WITH AT LEAST ONE GRADE $\geq$ 3 TEAE (B)	47 (79.7)	39 (81.3)	86 (80.4)	14 (60.9)	100 (76.9)
Blood and lymphatic system disorders	42 (71.2)	35 (72.9)	77 (72.0)	14 (60.9)	91 (70.0)
Neutropenia	36 (61.0)	31 (64.6)	67 (62.6)	12 (52.2)	79 (60.8)
Leukopenia	7 (11.9)	4 (8.3)	11 (10.3)	4 (17.4)	15 (11.5)
Lymphopenia	7 (11.9)	5 (10.4)	12 (11.2)	4 (17.4)	16 (12.3)
Anaemia	6 (10.2)	6 (12.5)	12 (11.2)	1 (4.3)	13 (10.0)
Thrombocytopenia	6 (10.2)	8 (16.7)	14 (13.1)	1 (4.3)	15 (11.5)
Febrile neutropenia	2 (3.4)	4 (8.3)	6 (5.6)	1 (4.3)	7 (5.4)
Investigations	4 (6.8)	5 (10.4)	9 (8.4)	1 (4.3)	10 (7.7)
Neutrophil count decreased	3 (5.1)	3 (6.3)	6 (5.6)	0	6 (4.6)

A TEAE was defined as any AE that occurred from start of liso-cel infusion and up to 90 days after liso-cel infusion. Any AE occurring after the initiation of another anti-FL treatment was not considered a TEAE.

AEs were coded using MedDRA version 26.0.

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

Source: Table 8.2.1-1 of Study FOL-001 Addendum 01 CSR.¹

TEAEs Related to LDC or Liso-cel

LDC-related TEAEs occurred in 75.4% of subjects overall; the frequency of LDC-related TEAEs was similar in 3L+ FL and 2L FL subjects (Table 1).

Liso-cel-related Grade $\geq$ 3 TEAEs occurred in 81 (62.3%) subjects and the most frequently reported Grade $\geq$ 3 TEAEs ($\geq$ 10% subjects) were neutropenia (47.7%) and lymphopenia (11.5%) (Table 14.3.1.1.10.1). Of note, most subjects experienced either LDC- or liso-cel-related neutropenia.

Table 51. Liso-cel-related TEAEs by SOC and PT ($\geq$ 10% Subjects) - Liso cel treated Analysis Set

System Organ Class Preferred Term ^a	4L+ FL Cohort 1 N = 59 n (%)	3L FL Cohort 2 N = 48 n (%)	3L+ FL Cohorts 1 + 2 N = 107 n (%)	2L FL Cohort 3 N = 23 n (%)	Total 2L+ FL Cohorts 1, 2, 3 N = 130 n (%)
Subjects With at Least One Liso-cel-Related TEAE	54 (91.5)	42 (87.5)	96 (89.7)	19 (82.6)	115 (88.5)
Immune system disorders	35 (59.3)	29 (60.4)	64 (59.8)	13 (56.5)	77 (59.2)
Cytokine release syndrome	35 (59.3)	28 (58.3)	63 (58.9)	12 (52.2)	75 (57.7)
Blood and lymphatic system disorders	33 (55.9)	34 (70.8)	67 (62.6)	13 (56.5)	80 (61.5)
Neutropenia	27 (45.8)	31 (64.6)	58 (54.2)	12 (52.2)	70 (53.8)
Anaemia	16 (27.1)	17 (35.4)	33 (30.8)	5 (21.7)	38 (29.2)
Thrombocytopenia	15 (25.4)	10 (20.8)	25 (23.4)	2 (8.7)	27 (20.8)
Lymphopenia	8 (13.6)	6 (12.5)	14 (13.1)	3 (13.0)	17 (13.1)
General disorders and administration site conditions	17 (28.8)	14 (29.2)	31 (29.0)	10 (43.5)	41 (31.5)
Fatigue	9 (15.3)	3 (6.3)	12 (11.2)	5 (21.7)	17 (13.1)
Pyrexia	7 (11.9)	8 (16.7)	15 (14.0)	2 (8.7)	17 (13.1)
Nervous system disorders	13 (22.0)	12 (25.0)	25 (23.4)	4 (17.4)	29 (22.3)
Tremor	6 (10.2)	6 (12.5)	12 (11.2)	2 (8.7)	14 (10.8)
Headache	4 (6.8)	7 (14.6)	11 (10.3)	2 (8.7)	13 (10.0)

Graded using NCI CTCAE version 5.0. CRS is graded according to a system based on modified criteria (Lee, 2014)⁵.

Frequencies are listed in descending order of the frequency of system organ class and preferred term within the system organ class based on Analysis Group 1 (4L+ FL). A Liso-cel TEAE is defined as any AE that occurs from start of Liso-cel infusion and up to 90 days after Liso-cel infusion. Any AE occurring after the initiation of another anti-follicular lymphoma treatment is not considered a TEAE. Related AEs are those for which the Investigator selects 'Related' to Liso-cel on the AE CRF. Missing relationship is considered as Related.

^a Coded using MedDRA version 25.1. A subject is counted only once for multiple events within preferred term/system organ class.

Source: Table 14.3.1.1.9.1

Adverse Events by Time Period

Most subjects experienced an AE during the Treatment Period. AEs in the post-treatment emergent period (≥ 91 days after liso-cel infusion) were infrequent (data not shown).

Serious adverse event/deaths/other significant events

Deaths

Table 52. Summary of Deaths and Causes - Leukapheresed Set

Primary Cause	4L+ FL N = 65 n (%)	3L FL N = 49 n (%)	3L+ FL N = 114 n (%)	2L FL N = 25 n (%)	2L+ FL N = 139 n (%)
OVERALL NUMBER OF DEATHS	9 (13.8)	6 (12.2)	15 (13.2)	1 (4.0)	16 (11.5)
CAUSE OF DEATH					
DEATH FROM MALIGNANT DISEASE UNDER STUDY, OR COMPLICATION DUE TO MALIGNANT DISEASE UNDER STUDY	4 (6.2)	3 (6.1)	7 (6.1)	0	7 (5.0)
DEATH FROM ADVERSE EVENT (NOT OTHERWISE SPECIFIED)	3 (4.6)	0	3 (2.6)	1 (4.0)	4 (2.9)
DEATH FROM CARDIAC EVENT	1 (1.5)	0	1 (0.9)	0	1 (0.7)
DEATH FROM OTHER CAUSE	0	3 (6.1)	3 (2.6)	0	3 (2.2)
DEATH FROM NEW MALIGNANCY, OR COMPLICATION FROM NEW MALIGNANCY	1 (1.5)	0	1 (0.9)	0	1 (0.7)
DEATH					
BETWEEN LEUKAPHERESIS AND LYMPHODEPLETING CHEMOTHERAPY START (A)	0	0	0	0	0
BETWEEN LYMPHODEPLETING CHEMOTHERAPY AND INFUSION (B)	1 (1.5)	0	1 (0.9)	0	1 (0.7)
DEATH FROM ADVERSE EVENT (NOT OTHERWISE SPECIFIED)	1 (1.5)	0	1 (0.9)	0	1 (0.7)
INFUSION, DAY 1- 30 (C)	0	0	0	1 (4.0)	1 (0.7)
DEATH FROM ADVERSE EVENT (NOT OTHERWISE SPECIFIED)	0	0	0	1 (4.0)	1 (0.7)
INFUSION, DAY 31- 90 (D)	0	0	0	0	0
FROM INFUSION, DAY 91 (E)	8 (12.3)	6 (12.2)	14 (12.3)	0	14 (10.1)
DEATH FROM MALIGNANT DISEASE UNDER STUDY, OR COMPLICATION DUE TO MALIGNANT DISEASE UNDER STUDY	4 (6.2)	3 (6.1)	7 (6.1)	0	7 (5.0)
DEATH FROM ADVERSE EVENT (NOT OTHERWISE SPECIFIED)	2 (3.1)	0	2 (1.8)	0	2 (1.4)
DEATH FROM CARDIAC EVENT	1 (1.5)	0	1 (0.9)	0	1 (0.7)
DEATH FROM OTHER CAUSE	0	3 (6.1)	3 (2.6)	0	3 (2.2)
DEATH FROM NEW MALIGNANCY, OR COMPLICATION FROM NEW MALIGNANCY	1 (1.5)	0	1 (0.9)	0	1 (0.7)

(A) If LDC start date was not available, death is included in this section.

(B) If LDC start date was available and infusion date was not available, death is included in this section.

(C) This period is defined from the first day of infusion until Day 30 after infusion.

(D) This period is defined from Day 31 until Day 90 after infusion.

(E) This period is defined from Day 91 after infusion.

Deaths from GC-LTFU-001 study are included.

Death from AE (Not Otherwise Specified) included: Cohort 1: acute respiratory failure hypoxic (LDC-infusion), AML (from Day 91 after infusion), PML (from Day 91 after infusion), and Cohort 3: HLH (Day 1-30).

Death from other cause included: Cohort 2: 2 cases of COVID-19 and erythema multiform.

Source: Table 8.3-1 of Study FOL-001 Addendum 01 CSR.¹

Treatment-emergent Serious Adverse Events

Twenty-four (18.5%) of all FL subjects (n= 130) experienced at least one liso-cel-related serious TEAEs.

Table 53. Treatment-emergent SAEs by SOC and PT Reported in ≥ 2% by PT in Any Cohort - Liso-cel-treated Analysis Set

System Organ Class Preferred Term (A)	4L+ FL N = 59 n (%)	3L FL N = 48 n (%)	3L+ FL N = 107 n (%)	2L FL N = 23 n (%)	2L+ FL N = 130 n (%)
SUBJECTS WITH AT LEAST ONE SERIOUS TEAE	15 (25.4)	12 (25.0)	27 (25.2)	4 (17.4)	31 (23.8)
Immune system disorders	7 (11.9)	4 (8.3)	11 (10.3)	2 (8.7)	13 (10.0)
Cytokine release syndrome	7 (11.9)	4 (8.3)	11 (10.3)	1 (4.3)	12 (9.2)
Allergy to immunoglobulin therapy	0	0	0	1 (4.3)	1 (0.8)
Haemophagocytic lymphohistiocytosis	0	0	0	1 (4.3)	1 (0.8)
Nervous system disorders	4 (6.8)	2 (4.2)	6 (5.6)	1 (4.3)	7 (5.4)
Aphasia	4 (6.8)	0	4 (3.7)	1 (4.3)	5 (3.8)
Tremor	2 (3.4)	1 (2.1)	3 (2.8)	0	3 (2.3)
Dyscalculia	1 (1.7)	1 (2.1)	2 (1.9)	0	2 (1.5)
Dysgraphia	1 (1.7)	1 (2.1)	2 (1.9)	0	2 (1.5)
Depressed level of consciousness	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Fine motor skill dysfunction	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Speech disorder	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Psychiatric disorders	4 (6.8)	1 (2.1)	5 (4.7)	0	5 (3.8)
Confusional state	2 (3.4)	0	2 (1.9)	0	2 (1.5)
Irritability	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Blood and lymphatic system disorders	3 (5.1)	2 (4.2)	5 (4.7)	0	5 (3.8)
Febrile neutropenia	2 (3.4)	2 (4.2)	4 (3.7)	0	4 (3.1)
Infections and infestations	3 (5.1)	4 (8.3)	7 (6.5)	0	7 (5.4)
COVID-19 pneumonia	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Cellulitis	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Device related bacteraemia	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Pyelonephritis	0	1 (2.1)	1 (0.9)	0	1 (0.8)

System Organ Class Preferred Term (A)	4L+ FL N = 59 n (%)	3L FL N = 48 n (%)	3L+ FL N = 107 n (%)	2L FL N = 23 n (%)	2L+ FL N = 130 n (%)
Cardiac disorders	1 (1.7)	1 (2.1)	2 (1.9)	0	2 (1.5)
Atrioventricular block	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Bradycardia	0	1 (2.1)	1 (0.9)	0	1 (0.8)
General disorders and administration site conditions	1 (1.7)	2 (4.2)	3 (2.8)	1 (4.3)	4 (3.1)
Pyrexia	1 (1.7)	2 (4.2)	3 (2.8)	0	3 (2.3)
Feeling abnormal	0	0	0	1 (4.3)	1 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.7)	0	1 (0.9)	1 (4.3)	2 (1.5)
Adenocarcinoma of colon	0	0	0	1 (4.3)	1 (0.8)
Gastrointestinal disorders	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Large intestinal obstruction	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Chylothorax	0	1 (2.1)	1 (0.9)	0	1 (0.8)

A TEAE was defined as any AE that occurred from start of liso-cel infusion and up to 90 days after liso-cel infusion. Any AE occurring after the initiation of another anti-FL treatment was not considered a TEAE.

AEs were coded using MedDRA version 26.0.

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

Source: Table 14.3.2.2.1.1 of Study FOL-001 Addendum 01 CSR.¹

Other Significant Adverse Events of Special Interest

The frequency of AESIs was consistent across cohorts (lines of therapy) and groups. There were no AESIs in the IRR, TLS, and autoimmune disorder categories.

Table 54. Overall Summary of AESIs - Liso-cel-treated Analysis Set

	4L+ FL N = 59 n (%)	3L FL N = 48 n (%)	3L+ FL N = 107 n (%)	2L FL N = 23 n (%)	2L+ FL N = 130 n (%)
ANY AESI	40 (67.8)	32 (66.7)	72 (67.3)	15 (65.2)	87 (66.9)
CYTOKINE RELEASE SYNDROME (CRS)	35 (59.3)	28 (58.3)	63 (58.9)	12 (52.2)	75 (57.7)
INVESTIGATOR-IDENTIFIED NEUROLOGICAL TOXICITY (iint)	9 (15.3)	8 (16.7)	17 (15.9)	4 (17.4)	21 (16.2)
INFUSION RELATED REACTION (IRR)	0	0	0	0	0
MACROPHAGE ACTIVATION SYNDROME (MAS)	0	0	0	1 (4.3)	1 (0.8)
TUMOR LYSIS SYNDROME (TLS)	0	0	0	0	0
HYPOGAMMAGLOBULINAEMIA	3 (5.1)	3 (6.3)	6 (5.6)	1 (4.3)	7 (5.4)
INFECTIONS GRADE $\geq$ 3	3 (5.1)	4 (8.3)	7 (6.5)	0	7 (5.4)
SECOND PRIMARY MALIGNANCY (SEM)	4 (6.8)	3 (6.3)	7 (6.5)	2 (8.7)	9 (6.9)
AUTOIMMUNE DISORDERS	0	0	0	0	0
PROLONGED CYTOPENIA	14 (23.7)	12 (25.0)	26 (24.3)	3 (13.0)	29 (22.3)

Related AEs were those for which the Investigator selects 'Related' to liso-cel or LDC on the AE CRF. Missing relationship was considered as Related.

Cytokine Release Syndrome

The frequency of CRS was consistent across cohorts (lines of therapy) and groups. The most common symptoms of CRS ($\geq 10\%$) included pyrexia (56.9%) and hypotension (13.8%). The median time of CRS onset from the time of liso-cel infusion was 6 days (range: 1 to 17 days). CRS resolved in all subjects; the median time to resolution was 3 days (range: 1 to 10 days). Of the subjects treated with concomitant medications for CRS, 18 (13.8%) subjects received tocilizumab only (median 1 dose [range, 1 to 3]), no subjects received corticosteroids only, 15 (11.5%) subjects received both tocilizumab and corticosteroids, and 2 (1.5%) subjects received vasopressors (Table 14.1.5.8 and Table 14.1.5.11 of Study FOL-001 Addendum 01 CSR1).

Table 55. Summary of CRS - Liso-cel treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Subjects With at Least One CRS	35 (59.3)	28 (58.3)	63 (58.9)	12 (52.2)	75 (57.7)
Overall Duration Of CRS (Days) ^a					
N	35	28	63	12	75
Median	3	4	4	3	3
Q1, Q3	2.0, 4.0	3.0, 5.0	2.0, 5.0	2.0, 6.0	2.0, 5.0
Min, Max	1, 9	1, 10	1, 10	2, 7	1, 10
Maximum Toxicity Grade					
Grade 1	28 (47.5)	20 (41.7)	48 (44.9)	7 (30.4)	55 (42.3)
Grade 2	6 (10.2)	8 (16.7)	14 (13.1)	5 (21.7)	19 (14.6)

Grade 3	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Grade $\leq$ 2	34 (57.6)	28 (58.3)	62 (57.9)	12 (52.2)	74 (56.9)
Grade $\geq$ 3	1 (1.7)	0	1 (0.9)	0	1 (0.8)

Events that stop/start within 7 days will be considered as a single episode.

^a Duration of event is based on event start and stop dates ([stop/cut-off date - start date] + 1).

Source: [Table 14.3.2.4.21](#)

Neurological Toxicity

The frequency of iiNT was consistent across cohorts (lines of therapy) and groups. The most common iiNTs by PT ($\geq 5\%$ of subjects) were tremor (7.7%) and aphasia (6.9%). The median time to iiNT onset from the time of liso-cel infusion was 8 days (range: 4 to 16 days). iiNT resolved in all subjects; the median time to resolution was 4 days (range: 1 to 17 days). Of the subjects treated with concomitant medications for iiNT, no subjects received tocilizumab only, 9 (6.9%) subjects received corticosteroids only, no subjects received both tocilizumab and corticosteroids, no subjects received vasopressors. The selected AE category of iiNT was used to report the CAR T cell-associated signs and symptoms suggestive of neurotoxicity, which include ICANS, as enrolment for Study FOL 001 began prior to 2019 (before ASTCT consensus 2019 for ICANS).

Table 56. Summary of iiNT - Liso cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Subjects With at Least One iiNT	9 (15.3)	8 (16.7)	17 (15.9)	4 (17.4)	21 (16.2)
Overall Duration of iiNT (Days) ^a					
N	9	8	17	4	21
Median	5	3	4	2.5	4
Q1, Q3	3.0, 7.0	2.0, 5.5	2.0, 6.0	1.5, 3.5	2.0, 5.0
Min, Max	1, 17	2, 8	1, 17	1, 4	1, 17
Maximum Toxicity Grade					
Grade 1	6 (10.2)	6 (12.5)	12 (11.2)	3 (13.0)	15 (11.5)
Grade 2	2 (3.4)	0	2 (1.9)	0	2 (1.5)
Grade 3	1 (1.7)	2 (4.2)	3 (2.8)	1 (4.3)	4 (3.1)
Grade ≤ 2	8 (13.6)	6 (12.5)	14 (13.1)	3 (13.0)	17 (13.1)
Grade ≥ 3	1 (1.7)	2 (4.2) ^b	3 (2.8)	1 (4.3)	4 (3.1)

Events that stop/start within 7 days will be considered as a single episode.

iiNT was captured using the preferred term Neurotoxicity and graded using CTCAE v.5.0 on the basis of the highest individual symptom grade.

^a Duration of event is based on event start and stop dates ([stop/cut-off date - start date] + 1).

^b After the 10-Jan-2024 data cut-off date, the relation of Grade 3 iiNT (agitation) was re-evaluated by the investigator and updated as not related to liso-cel/LDC/study procedure and not considered as an iiNT event.

Source: Table 14.3.2.4.21

Prolonged cytopenia

In the Liso-cel-treated Analysis Set, prolonged cytopenia, defined as Grade ≥3 cytopenia at the Day 29 (± 2 days) visit based on local laboratory assessments of neutropenia, thrombocytopenia, or anemia, occurred in 29 (22.3%) subjects (see Table below). Data were consistent across cohorts.

Table 57. Summary of Prolonged Cytopenia - Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59 n (%)	3L FL Cohort 2 N = 48 n (%)	3L+ FL Cohorts 1 + 2 N = 107 n (%)	2L FL Cohort 3 N = 23 n (%)	Total 2L+ FL Cohorts 1, 2, 3 N = 130 n (%)
Grade $\geq$ 3 Cytopenia ^a From Day 1 Through Day 29 Visit ^b	50 (84.7)	37 (77.1)	87 (81.3)	16 (69.6)	103 (79.2)
Grade $\geq$ 3 At Day 29 Visit	14 (23.7)	12 (25.0)	26 (24.3)	3 (13.0)	29 (22.3)
Grade $\leq$ 2 At Day 29 Visit	34 (57.6)	20 (41.7)	54 (50.5)	10 (43.5)	64 (49.2)
	4L+ FL Cohort 1 N = 59 n (%)	3L FL Cohort 2 N = 48 n (%)	3L+ FL Cohorts 1 + 2 N = 107 n (%)	2L FL Cohort 3 N = 23 n (%)	Total 2L+ FL Cohorts 1, 2, 3 N = 130 n (%)
Unknown At Day 29 Visit	2 (3.4)	5 (10.4)	7 (6.5)	3 (13.0)	10 (7.7)
Grade $\geq$ 3 Hemoglobin From Day 1 Through Day 29 Visit	12 (20.3)	6 (12.5)	18 (16.8)	4 (17.4)	22 (16.9)
Grade $\geq$ 3 At Day 29 Visit	4 (6.8)	2 (4.2)	6 (5.6)	0	6 (4.6)
Grade $\leq$ 2 At Day 29 Visit	8 (13.6)	3 (6.3)	11 (10.3)	4 (17.4)	15 (11.5)
Unknown At Day 29 Visit	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Grade $\geq$ 3 Platelets From Day 1 Through Day 29 Visit	12 (20.3)	10 (20.8)	22 (20.6)	2 (8.7)	24 (18.5)
Grade $\geq$ 3 At Day 29 Visit	10 (16.9)	8 (16.7)	18 (16.8)	1 (4.3)	19 (14.6)
Grade $\leq$ 2 At Day 29 Visit	2 (3.4)	0	2 (1.9)	1 (4.3)	3 (2.3)
Unknown At Day 29 Visit	0	2 (4.2)	2 (1.9)	0	2 (1.5)
Grade $\geq$ 3 Neutrophils From Day 1 Through Day 29 Visit	49 (83.1)	37 (77.1)	86 (80.4)	16 (69.6)	102 (78.5)
Grade $\geq$ 3 At Day 29 Visit	8 (13.6)	10 (20.8)	18 (16.8)	2 (8.7)	20 (15.4)
Grade $\leq$ 2 At Day 29 Visit	38 (64.4)	22 (45.8)	60 (56.1)	11 (47.8)	71 (54.6)
Unknown At Day 29 Visit	3 (5.1)	5 (10.4)	8 (7.5)	3 (13.0)	11 (8.5)

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

Laboratory results after the initiation of subsequent anti-follicular lymphoma therapy are excluded.

^a Grade $\geq$ 3 Cytopenia includes any Grade $\geq$ 3 decreased hemoglobin, decreased neutrophil count, or decreased platelet count.

^b Protocol defined window for Day 29 Visit is 29 $\pm$ 2 days after liso-cel infusion.

Source: Table 14.3.2.4.10

Second Primary Malignancy

In the Liso-cel-treated Analysis Set, SPM was reported in 9 (6.9%) subjects. 12 SPM events were reported in 9 subjects: melanoma (Grade 2), colorectal cancer (Grade 3), mucoepidermoid carcinoma (Grade 2), MDS (Grade 4), basal cell carcinoma (Grade 1), SCC/Bowen's disease (Grade 2), AML (2 Grade 4 events and 2 Grade 5 events), rectal cancer (Grade 3), and colon adenocarcinoma (Grade 3). No events of T-cell malignancies were reported.

Cardiac Events

9 subjects with 2L+ FL experienced TEAEs with SOC of Cardiac disorder, including PT of tachycardia (n=3; Grade 1), sinus tachycardia (n=3; Grade 1/2), palpitations (n=1; Grade 3), bradycardia (n=1; Grade 3), atrioventricular block (n=1; Grade 3). There were no Cardiac disorder AEs reported beyond 90 days after liso-cel infusion. All cardiac TEAEs resolved by Day 33 post liso-cel infusion. No subsequent cardiac events were reported for these patients.

Among the 9 subjects with cardiac TEAEs, 5 subjects developed cardiac TEAE during or approximately 1 to 2 days prior or after the CRS event, and 2 subjects developed cardiac TEAE at least 2 weeks after resolutions of CRS; 2 subjects never experienced CRS. Two subjects with cardiac TEAE experienced death not related to cardiac events; one died on Day 29 due to Grade 5 HLH and the other died on Day 169 due to COVID-19.

In addition to the above Cardiac disorder TEAEs, one death was reported on Day 171 after liso-cel infusion due to cardiac event of heart failure. The subject was reported to have history of Grade 1 cardiomyopathy. Screening echocardiogram prior to the study treatment showed LVEF of 45%, and screening ECG was interpreted as abnormal but without clinical significance. No acute cardiac events or CRS were reported for this subject during TEAE or post TEAE periods. This death of Cardiac event of heart failure was not reported as AE related to liso-cel.

Laboratory findings

Hematology

In the Liso-cel-treated Analysis 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 (data not shown).

Serum Chemistry

In the Liso-cel-treated Analysis Set, most serum chemistry parameters remained stable over time (data not shown).

Persistence of Viral Vector Sequence Monitoring

Vector ISA was performed if persistence of CAR vector sequence was detected in $\geq 1\%$ of nucleated blood cells at any time point ≥ 12 months after the liso-cel infusion.

In the Liso-cel-treated Analysis Set, 2 subjects met the criteria for ISA: for one subject, the transgene percentage was 11.4% at Month 12, and for the other subject it was 3.5% at Month 24. ISA was performed on both samples. Results for the subject with 11.4% transgene at Month 12 showed the sample was polyclonal without evidence of a monoclonal outgrowth. Results for the subject with 3.5% transgene at Month 24 were pending as of the data cutoff date of 10-Jan-2024.

Replication-competent Lentivirus by Visit

No RCL was detected in the 464 samples tested from the Liso-cel-treated Analysis Set.

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 Liso-cel-treated Analysis Set.

Safety in Outpatient Setting

Administration of liso-cel as inpatient or outpatient was determined at the PI's discretion.

In the Liso-cel-treated Analysis Set, 14 (10.8%) subjects were monitored as outpatients (13 3L+ FL subjects and 1 2L FL subject):

- TEAEs occurred in 14 (100%) subjects overall, 8 (57.1%) experienced Grade ≥ 3 TEAEs, and 7 (50.0%) SAEs.
- AESI occurred in 8 (57.1%) subjects overall, most commonly, CRS (6 [42.9%] subjects) and iiNT (2 [14.3%] subjects).

50.0% of these subjects were hospitalized after liso-cel administration due to an AE. The median time from liso-cel administration to first hospitalization was 7 days (range, 4 to 16). None of these subjects had ICU stays.

Pooled Analyses of Safety

Liso-cel pooled safety analyses included side-by-side comparison of each Liso-cel Treated Set in 3L+ FL and 2L+ FL subjects from Study FOL-001 with 2L/3L+ LBCL subjects in EU-approved indications.

Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

Subject Disposition

154 subjects were screened in Study FOL-001 and all 139 subjects (including 114 subjects with 3L+ FL) who met the inclusion/exclusion criteria underwent leukapheresis as of the data cut-off date of 10-Jan-2024. Of the 114 3L+ FL subjects, 107 (93.9%) received LDC and liso-cel infusion and comprised the 3L+ FL Liso cel Treated Set. 18 out of 107 (16.8%) subjects discontinued the study; the most common reasons for study discontinuation were death and consent withdrawal (see Table below).

Table 58. Subject Disposition - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

	3L+ FL (FOL-001 Cohorts 1, 2) N = 107	2L/3L+ LBCL Total N = 608	Overall Total N = 715
STUDY STATUS			
ONGOING	88 (82.2)	151 (24.8)	239 (33.4)
COMPLETED STUDY	1 (0.9)	154 (25.3)	155 (21.7)
DISCONTINUED FROM STUDY	18 (16.8)	303 (49.8)	321 (44.9)
ADVERSE EVENT	0	0	0
DEATH	7 (6.5)	237 (39.0)	244 (34.1)
LOST TO FOLLOW-UP	1 (0.9)	5 (0.8)	6 (0.8)
OTHER (A)	3 (2.8)	23 (3.8)	26 (3.6)
STUDY TERMINATION BY SPONSOR	0	0	0
SUBJECT WITHDREW CONSENT	7 (6.5)	38 (6.3)	45 (6.3)
CONSENTED TO THE LONG-TERM FOLLOW UP STUDY	1 (0.9)	111 (18.3)	112 (15.7)
SUBJECTS RECEIVED RETREATMENT	0	19 (3.1)	19 (2.7)

(A) Refer to Listing 2.1.1 of Appendix 2 for details.

Study Duration

Table 59. Study Duration - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

	3L+ FL (FOL-001 Cohorts 1, 2) N = 107	2L/3L+ LBCL Total N = 608	Overall Total N = 715
ON-STUDY FOLLOW-UP TIME			
(MONTHS) (A)			
N	107	608	715
MEAN	25.38	14.06	15.76
SD	7.291	9.241	9.839
MEDIAN	27.24	12.39	16.16
Q1 , Q3	23.75 , 30.03	5.54 , 23.74	6.21 , 24.15
MIN , MAX	3.7 , 37.2	0.2 , 45.2	0.2 , 45.2
DURATION OF ON-STUDY FOLLOW-UP			
>= 1 DAY, N (%)	107 (100.0)	608 (100.0)	715 (100.0)
>= 29 DAYS, N (%)	107 (100.0)	595 (97.9)	702 (98.2)
>= 2 MONTHS, N (%)	107 (100.0)	559 (91.9)	666 (93.1)
>= 3 MONTHS, N (%)	107 (100.0)	533 (87.7)	640 (89.5)
>= 6 MONTHS, N (%)	103 (96.3)	442 (72.7)	545 (76.2)
>= 9 MONTHS, N (%)	98 (91.6)	372 (61.2)	470 (65.7)
>= 12 MONTHS, N (%)	98 (91.6)	319 (52.5)	417 (58.3)
>= 18 MONTHS, N (%)	95 (88.8)	231 (38.0)	326 (45.6)
>= 24 MONTHS, N (%)	75 (70.1)	128 (21.1)	203 (28.4)
TOTAL ON-STUDY FOLLOW-UP TIME	226.3	712.6	938.8
(YEARS)			

(A) The follow-up time was (EOS date - first liso-cel dose date + 1)/30.4375 for subjects who did not enroll in the LTFU study. If a subject was ongoing in the study, the earliest of the last known alive date or data cut-off date) was used to impute the EOS date for the purpose of the calculation. For subjects who enrolled in the LTFU study, the follow-up time was (min [last known alive date, death date, data cut-off date] - first dose date + 1)/30.4375.

Source: Table 2.3.1.1 of Appendix 2.

Lymphodepleting Chemotherapy and Liso-cel Dose

A low-intensity LDC regimen of fludarabine IV (30 mg/m²/day for 3 days) and cyclophosphamide IV (300 mg/m²/day for 3 days) was administered prior to liso-cel administration. The majority of Liso-cel Treated Set subjects with 3L+ FL (n= 96/107, 89.7%) and 2L/3L+ LBCL (n= 504/608, 82.9%) received the specified dose of fludarabine and cyclophosphamide with no missing doses. The Liso-cel Treated Set subjects with 3L+ FL received a median total liso-cel dose of 100.0 × 10⁶ CAR+ T cells (49.8 × 10⁶ CD8+ and 50.0 × 10⁶ CD4+ CAR+ T cells), which was similar to the dose received by subjects with 2L/3L+ LBCL.

Demographic and Other Characteristics of 3L+ FL and 2L/3L+ LBCL Populations

The demographics and baseline disease characteristics in the Liso-cel Treated Set subjects with 3L+ FL and 2L/3L+ LBCL were representative of FL and LBCL populations, respectively. In 3L+ FL, 60.7% of subjects had an ECOG PS score of 0 and 43.9% of subjects had LDH ≥ ULN at baseline. The median SPD was 19.89 cm² for subjects with 3L+ FL indicating similar burden of disease compared to subjects with 2L/3L+ LBCL (20.91 cm²). Despite similar burden of disease based on SPD, a lower proportion of Liso-cel Treated Set subjects with 3L+ FL received anticancer therapy for disease control than subjects with 2L/3L+ LBCL (41.1% vs 60.9%), possibly reflective of a population with less rapidly progressive disease in the 3L+ FL.

Adverse Events in 3L+ FL and 2L/3L+ LBCL

Table 60. Overview of TEAEs - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

	3L+ FL (FOL-001 Cohorts 1, 2) N = 107	2L/3L+ LBCL Total N = 608	Overall Total N = 715
DURATION OF PERIOD (DAYS), MEDIAN (RANGE)	90.0 (90-90)	90.0 (7-218)	90.0 (7-218)
SUBJECTS WITH ANY TEAE	106 (99.1)	602 (99.0)	708 (99.0)
SUBJECTS WITH ANY GRADE 3-4 TEAE	86 (80.4)	482 (79.3)	568 (79.4)
SUBJECTS WITH ANY GRADE 3-5 TEAE	86 (80.4)	497 (81.7)	583 (81.5)
SUBJECTS WITH ANY GRADE 5 TEAE	0	15 (2.5)	15 (2.1)
SUBJECTS WITH ANY SERIOUS TEAE	27 (25.2)	260 (42.8)	287 (40.1)
SUBJECTS WITH ANY LDC-RELATED TEAE	81 (75.7)	498 (81.9)	579 (81.0)
SUBJECTS WITH ANY LDC-RELATED GRADE 3-4 TEAE	68 (63.6)	419 (68.9)	487 (68.1)
SUBJECTS WITH ANY LDC-RELATED GRADE 3-5 TEAE	68 (63.6)	427 (70.2)	495 (69.2)
SUBJECTS WITH ANY LDC-RELATED GRADE 5 TEAE	0	8 (1.3)	8 (1.1)
SUBJECTS WITH ANY LDC-RELATED SERIOUS TEAE	8 (7.5)	67 (11.0)	75 (10.5)
SUBJECTS WITH ANY JCAR017-RELATED TEAE	96 (89.7)	486 (79.9)	582 (81.4)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 3-4 TEAE	68 (63.6)	277 (45.6)	345 (48.3)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 3-5 TEAE	68 (63.6)	285 (46.9)	353 (49.4)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 5 TEAE	0	8 (1.3)	8 (1.1)
SUBJECTS WITH ANY JCAR017-RELATED SERIOUS TEAE	21 (19.6)	181 (29.8)	202 (28.3)

CRS was graded based on the Lee criteria.³ Other AEs were graded using CTCAE version 5.0 for Study FOL-001 and version 4.03 for all other studies.

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

TEAE was defined as an AE that started any time from initiation of liso-cel administration through and including 90 days following the final dose of liso-cel. Any AE occurring after the initiation of subsequent anticancer therapy or liso-cel retreatment or start of combination therapy (BCM-002) was not considered as a TEAE.

Source: Table 3.1.1.1 of Appendix 2.

Treatment-emergent Adverse Events

Table 61. TEAEs by SOC and PT Reported in ≥ 10% of FL or LBCL Subjects - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ FL (FOL-001 Cohorts 1, 2) N = 107 n (%)	2L/3L+ LBCL Total N = 608 n (%)	Overall Total N = 715 n (%)
SUBJECTS WITH ANY TEAE	106 (99.1)	602 (99.0)	708 (99.0)
Blood and lymphatic system disorders	84 (78.5)	494 (81.3)	578 (80.8)
Neutropenia	74 (69.2)	409 (67.3)	483 (67.6)
Anaemia	47 (43.9)	275 (45.2)	322 (45.0)
Thrombocytopenia	35 (32.7)	228 (37.5)	263 (36.8)
Leukopenia	14 (13.1)	140 (23.0)	154 (21.5)
Lymphopenia	14 (13.1)	69 (11.3)	83 (11.6)
General disorders and administration site conditions	44 (41.1)	386 (63.5)	430 (60.1)
Fatigue	13 (12.1)	205 (33.7)	218 (30.5)
Pyrexia	19 (17.8)	120 (19.7)	139 (19.4)
Oedema peripheral	4 (3.7)	76 (12.5)	80 (11.2)
Asthenia	14 (13.1)	49 (8.1)	63 (8.8)

System Organ Class Preferred Term	3L+ FL (FOL-001 Cohorts 1, 2) N = 107 n (%)	2L/3L+ LBCL Total N = 608 n (%)	Overall Total N = 715 n (%)
Gastrointestinal disorders	49 (45.8)	378 (62.2)	427 (59.7)
Nausea	10 (9.3)	164 (27.0)	174 (24.3)
Constipation	23 (21.5)	121 (19.9)	144 (20.1)
Diarrhoea	16 (15.0)	127 (20.9)	143 (20.0)
Vomiting	4 (3.7)	88 (14.5)	92 (12.9)
Abdominal pain	4 (3.7)	70 (11.5)	74 (10.3)
Nervous system disorders	46 (43.0)	352 (57.9)	398 (55.7)
Headache	30 (28.0)	154 (25.3)	184 (25.7)
Dizziness	3 (2.8)	101 (16.6)	104 (14.5)
Tremor	17 (15.9)	82 (13.5)	99 (13.8)
Immune system disorders	64 (59.8)	283 (46.5)	347 (48.5)
Cytokine release syndrome	63 (58.9)	254 (41.8)	317 (44.3)
Hypogammaglobulinaemia	2 (1.9)	61 (10.0)	63 (8.8)
Metabolism and nutrition disorders	25 (23.4)	292 (48.0)	317 (44.3)
Decreased appetite	6 (5.6)	124 (20.4)	130 (18.2)
Hypokalaemia	8 (7.5)	100 (16.4)	108 (15.1)
Hypomagnesaemia	4 (3.7)	86 (14.1)	90 (12.6)
Musculoskeletal and connective tissue disorders	33 (30.8)	244 (40.1)	277 (38.7)
Arthralgia	10 (9.3)	66 (10.9)	76 (10.6)
Back pain	5 (4.7)	65 (10.7)	70 (9.8)
Respiratory, thoracic and mediastinal disorders	17 (15.9)	233 (38.3)	250 (35.0)
Cough	7 (6.5)	91 (15.0)	98 (13.7)
Infections and infestations	24 (22.4)	208 (34.2)	232 (32.4)
Psychiatric disorders	16 (15.0)	187 (30.8)	203 (28.4)
Insomnia	5 (4.7)	67 (11.0)	72 (10.1)
Confusional state	3 (2.8)	66 (10.9)	69 (9.7)
Vascular disorders	18 (16.8)	184 (30.3)	202 (28.3)
Hypotension	9 (8.4)	97 (16.0)	106 (14.8)
Skin and subcutaneous tissue disorders	17 (15.9)	154 (25.3)	171 (23.9)
Investigations	26 (24.3)	134 (22.0)	160 (22.4)

System Organ Class Preferred Term	3L+ FL (FOL-001 Cohorts 1, 2) N = 107 n (%)	2L/3L+ LBCL Total N = 608 n (%)	Overall Total N = 715 n (%)
Cardiac disorders	6 (5.6)	129 (21.2)	135 (18.9)
Renal and urinary disorders	4 (3.7)	94 (15.5)	98 (13.7)
Injury, poisoning and procedural complications	3 (2.8)	83 (13.7)	86 (12.0)
Eye disorders	4 (3.7)	67 (11.0)	71 (9.9)

CRS was graded based on the Lee criteria.³ Other AEs were graded using CTCAE version 5.0 for Study FOL-001 and version 4.03 for all other studies.

AEs were coded using MedDRA version 26.0.

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

TEAE was defined as an AE that started any time from initiation of liso-cel administration through and including 90 days following the final dose of liso-cel. Any AE occurring after the initiation of subsequent anticancer therapy or liso-cel retreatment or start of combination therapy (BCM-002) was not considered as a TEAE.

Source: Table 3.2.1.1 of Appendix 2.

Grade 3 or Higher Treatment-emergent Adverse Events

Table 62. Grade 3 or Higher TEAEs by SOC and PT Reported in ≥ 10% of FL or LBCL Subjects - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ FL (FOL-001 Cohorts 1, 2) N = 107 n (%)	2L/3L+ LBCL Total N = 608 n (%)	Overall Total N = 715 n (%)
SUBJECTS WITH ANY GRADE 3 OR HIGHER TEAE	86 (80.4)	497 (81.7)	583 (81.5)
Blood and lymphatic system disorders	77 (72.0)	460 (75.7)	537 (75.1)
Neutropenia	67 (62.6)	388 (63.8)	455 (63.6)
Anaemia	12 (11.2)	203 (33.4)	215 (30.1)
Thrombocytopenia	14 (13.1)	177 (29.1)	191 (26.7)
Leukopenia	11 (10.3)	127 (20.9)	138 (19.3)
Lymphopenia	12 (11.2)	63 (10.4)	75 (10.5)
Metabolism and nutrition disorders	2 (1.9)	80 (13.2)	82 (11.5)
Infections and infestations	7 (6.5)	73 (12.0)	80 (11.2)
Nervous system disorders	3 (2.8)	62 (10.2)	65 (9.1)

AEs were graded using CTCAE version 5.0 for Study FOL-001 and version 4.03 for all other studies. AEs were coded using MedDRA version 26.0.

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

Treatment-emergent Adverse Events Related to Liso-cel

Table 63. Liso-cel-Related TEAEs by SOC and PT Reported in ≥ 10% of FL or LBCL Subjects - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ FL (FOL-001 Cohorts 1, 2) N = 107 n (%)	2L/3L+ LBCL Total N = 608 n (%)	Overall Total N = 715 n (%)
SUBJECTS WITH ANY LISO-CEL RELATED TEAE	96 (89.7)	486 (79.9)	582 (81.4)
Immune system disorders	64 (59.8)	274 (45.1)	338 (47.3)
Cytokine release syndrome	63 (58.9)	254 (41.8)	317 (44.3)
Blood and lymphatic system disorders	67 (62.6)	264 (43.4)	331 (46.3)
Neutropenia	58 (54.2)	193 (31.7)	251 (35.1)
Anaemia	33 (30.8)	124 (20.4)	157 (22.0)
Thrombocytopenia	25 (23.4)	122 (20.1)	147 (20.6)
Leukopenia	7 (6.5)	68 (11.2)	75 (10.5)
Lymphopenia	14 (13.1)	41 (6.7)	55 (7.7)
General disorders and administration site conditions	31 (29.0)	198 (32.6)	229 (32.0)
Fatigue	12 (11.2)	96 (15.8)	108 (15.1)
Pyrexia	15 (14.0)	76 (12.5)	91 (12.7)
Nervous system disorders	25 (23.4)	197 (32.4)	222 (31.0)
Headache	11 (10.3)	64 (10.5)	75 (10.5)
Tremor	12 (11.2)	60 (9.9)	72 (10.1)
Gastrointestinal disorders	12 (11.2)	83 (13.7)	95 (13.3)
Psychiatric disorders	10 (9.3)	84 (13.8)	94 (13.1)
Metabolism and nutrition disorders	12 (11.2)	54 (8.9)	66 (9.2)
Investigations	16 (15.0)	45 (7.4)	61 (8.5)

CRS was graded based on the Lee criteria.³ Other AEs were graded using CTCAE version 5.0 for Study FOL-001 and version 4.03 for all other studies.

AEs were coded using MedDRA version 26.0.

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

TEAE was defined as an AE that started any time from initiation of liso-cel administration through and including 90 days following the final dose of liso-cel. Any AE occurring after the initiation of subsequent anticancer therapy or liso-cel retreatment or start of combination therapy (BCM-002) was not considered as a TEAE.

Source: Table 3.10.1.1 of Appendix 2.

Post Treatment-emergent Period Adverse Events

Table 64. Liso-cel-Related Grade 3 or Higher TEAEs by SOC and PT Reported in ≥ 10% of FL or LBCL Subjects - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ FL (FOL-001 Cohorts 1, 2) N = 107 n (%)	2L/3L+ LBCL Total N = 608 n (%)	Overall Total N = 715 n (%)
SUBJECTS WITH ANY LISO-CEL RELATED GRADE 3 OR HIGHER TEAE	68 (63.6)	285 (46.9)	353 (49.4)
Blood and lymphatic system disorders	61 (57.0)	240 (39.5)	301 (42.1)
Neutropenia	52 (48.6)	181 (29.8)	233 (32.6)
Thrombocytopenia	10 (9.3)	96 (15.8)	106 (14.8)
Anaemia	9 (8.4)	87 (14.3)	96 (13.4)
Lymphopenia	12 (11.2)	35 (5.8)	47 (6.6)

AEs (except CRS) were graded using CTCAE version 5.0 for Study FOL-001 and version 4.03 for all other studies.

AEs were coded using MedDRA version 26.0.

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

TEAE was defined as an AE that started any time from initiation of liso-cel administration through and including 90 days following the final dose of liso-cel. Any AE occurring after the initiation of subsequent anticancer therapy or liso-cel retreatment or start of combination therapy (BCM-002) was not considered as a TEAE.

Source: Table 3.10.1.2 of Appendix 2.

Table 65. Overview of AEs - Post-treatment Emergent Period - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

	3L+ FL (FOL-001 Cohorts 1, 2) N = 107	2L/3L+ LBCL Total N = 559	Overall Total N = 666
DURATION OF PERIOD (DAYS), MEDIAN (RANGE)	740.0 (25-1042)	359.0 (2-1287)	452.0 (2-1287)
SUBJECTS WITH ANY AE	37 (34.6)	254 (45.4)	291 (43.7)
SUBJECTS WITH ANY GRADE 3-4 AE	18 (16.8)	124 (22.2)	142 (21.3)
SUBJECTS WITH ANY GRADE 3-5 AE	21 (19.6)	143 (25.6)	164 (24.6)
SUBJECTS WITH ANY GRADE 5 AE	3 (2.8)	19 (3.4)	22 (3.3)
SUBJECTS WITH ANY SERIOUS AE	17 (15.9)	85 (15.2)	102 (15.3)
SUBJECTS WITH ANY LDC-RELATED AE	11 (10.3)	89 (15.9)	100 (15.0)
SUBJECTS WITH ANY LDC-RELATED GRADE 3-4 AE	4 (3.7)	51 (9.1)	55 (8.3)
SUBJECTS WITH ANY LDC-RELATED GRADE 3-5 AE	5 (4.7)	56 (10.0)	61 (9.2)
SUBJECTS WITH ANY LDC-RELATED GRADE 5 AE	1 (0.9)	5 (0.9)	6 (0.9)
SUBJECTS WITH ANY LDC-RELATED SERIOUS AE	3 (2.8)	25 (4.5)	28 (4.2)
SUBJECTS WITH ANY JCAR017-RELATED AE	26 (24.3)	111 (19.9)	137 (20.6)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 3-4 AE	13 (12.1)	56 (10.0)	69 (10.4)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 3-5 AE	14 (13.1)	60 (10.7)	74 (11.1)
SUBJECTS WITH ANY JCAR017-RELATED GRADE 5 AE	1 (0.9)	4 (0.7)	5 (0.8)
SUBJECTS WITH ANY JCAR017-RELATED SERIOUS AE	9 (8.4)	22 (3.9)	31 (4.7)

AEs (except CRS) were graded using CTCAE version 5.0 for Study FOL-001 and version 4.03 for all other studies.

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.

Source: [Table 3.1.3.1 of Appendix 2](#).

Table 66. AEs by SOC and PT Reported in ≥ 10% of FL or LBCL Subjects - Post-treatment Emergent Period - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ FL (FOL-001 Cohorts 1, 2) N = 107 n (%)	2L/3L+ LBCL Total N = 559 n (%)	Overall Total N = 666 n (%)
SUBJECTS WITH ANY AE POST TREATMENT-EMERGENT PERIOD	37 (34.6)	254 (45.4)	291 (43.7)
Blood and lymphatic system disorders	16 (15.0)	133 (23.8)	149 (22.4)
Neutropenia	12 (11.2)	66 (11.8)	78 (11.7)
Infections and infestations	15 (14.0)	61 (10.9)	76 (11.4)

AEs were coded using MedDRA version 26.0.

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

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.

Source: [Table 3.7.1.1 of Appendix 2](#).

Table 67. Grade 3 or Higher AEs by SOC and PT Reported in ≥ 10% of FL or LBCL Subjects - Post-treatment Emergent Period - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ FL (FOL-001 Cohorts 1, 2) N = 107 n (%)	2L/3L+ LBCL Total N = 559 n (%)	Overall Total N = 666 n (%)
SUBJECTS WITH ANY GRADE 3 OR HIGHER AE POST TREATMENT-EMERGENT PERIOD	21 (19.6)	143 (25.6)	164 (24.6)
Blood and lymphatic system disorders	10 (9.3)	97 (17.4)	107 (16.1)

AEs were coded using MedDRA version 26.0.

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

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.

Source: [Table 3.8.1.1 of Appendix 2](#).

Deaths

Table 68. Summary of Deaths - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

	3L+ FL (FOL-001 Cohorts 1, 2) N = 107	2L/3L+ LBCL Total N = 608	Overall Total N = 715
DEATHS OCCURRED AFTER FIRST LISO-CEL INFUSION	12 (11.2)	258 (42.4)	270 (37.8)
PRIMARY CAUSE OF DEATH			
DISEASE PROGRESSION	7 (6.5)	206 (33.9)	213 (29.8)
ADVERSE EVENT	2 (1.9)	23 (3.8)	25 (3.5)
COVID-19	2 (1.9)	9 (1.5)	11 (1.5)
UNKNOWN	0	6 (1.0)	6 (0.8)
OTHER (A)	1 (0.9)	14 (2.3)	15 (2.1)
DEATHS OCCURRED AFTER FIRST LISO-CEL INFUSION AND WITHIN 30 DAYS POST LISO-CEL INFUSION	0	12 (2.0)	12 (1.7)
PRIMARY CAUSE OF DEATH			
DISEASE PROGRESSION	0	7 (1.2)	7 (1.0)
ADVERSE EVENT	0	5 (0.8)	5 (0.7)
COVID-19	0	0	0
UNKNOWN	0	0	0
OTHER (A)	0	0	0
DEATHS OCCURRED BETWEEN 31 AND 90 DAYS POST LISO-CEL INFUSION	0	45 (7.4)	45 (6.3)
PRIMARY CAUSE OF DEATH			
DISEASE PROGRESSION	0	31 (5.1)	31 (4.3)
ADVERSE EVENT	0	9 (1.5)	9 (1.3)
COVID-19	0	2 (0.3)	2 (0.3)
UNKNOWN	0	2 (0.3)	2 (0.3)
OTHER (A)	0	1 (0.2)	1 (0.1)
DEATHS OCCURRED FROM 91 DAYS POST LISO-CEL INFUSION UNTIL THE END OF STUDY	12 (11.2)	201 (33.1)	213 (29.8)
PRIMARY CAUSE OF DEATH			
DISEASE PROGRESSION	7 (6.5)	168 (27.6)	175 (24.5)
ADVERSE EVENT	2 (1.9)	9 (1.5)	11 (1.5)
COVID-19	2 (1.9)	7 (1.2)	9 (1.3)
UNKNOWN	0	4 (0.7)	4 (0.6)
OTHER (A)	1 (0.9)	13 (2.1)	14 (2.0)

Treatment-emergent Serious Adverse Events

The most commonly reported treatment-emergent SAEs were consistent in Liso-cel Treated Set subjects with 3L+ FL and 2L/3L+ LBCL; the frequency of treatment-emergent SAEs was lower in 3L+ FL than 2L/3L+ LBCL (see Table below).

Table 69. Treatment-emergent SAEs by SOC and PT Reported in ≥ 2% of FL or LBCL Subjects - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

System Organ Class Preferred Term	3L+ FL (FOL-001 Cohorts 1, 2) N = 107 n (%)	2L/3L+ LBCL Total N = 608 n (%)	Overall Total N = 715 n (%)
SUBJECTS WITH ANY SERIOUS TEAE	27 (25.2)	260 (42.8)	287 (40.1)
Immune system disorders	11 (10.3)	101 (16.6)	112 (15.7)
Cytokine release syndrome	11 (10.3)	100 (16.4)	111 (15.5)
Nervous system disorders	6 (5.6)	78 (12.8)	84 (11.7)
Aphasia	4 (3.7)	17 (2.8)	21 (2.9)
Encephalopathy	0	20 (3.3)	20 (2.8)
Tremor	3 (2.8)	14 (2.3)	17 (2.4)
Infections and infestations	7 (6.5)	61 (10.0)	68 (9.5)
Pneumonia	1 (0.9)	13 (2.1)	14 (2.0)
Blood and lymphatic system disorders	5 (4.7)	48 (7.9)	53 (7.4)
Febrile neutropenia	4 (3.7)	22 (3.6)	26 (3.6)
Neutropenia	1 (0.9)	19 (3.1)	20 (2.8)
Thrombocytopenia	0	17 (2.8)	17 (2.4)
Psychiatric disorders	5 (4.7)	39 (6.4)	44 (6.2)
Confusional state	2 (1.9)	19 (3.1)	21 (2.9)
General disorders and administration site conditions	3 (2.8)	29 (4.8)	32 (4.5)
Pyrexia	3 (2.8)	21 (3.5)	24 (3.4)
Gastrointestinal disorders	1 (0.9)	28 (4.6)	29 (4.1)
Respiratory, thoracic and mediastinal disorders	1 (0.9)	19 (3.1)	20 (2.8)
Cardiac disorders	2 (1.9)	15 (2.5)	17 (2.4)
Musculoskeletal and connective tissue disorders	0	15 (2.5)	15 (2.1)
Vascular disorders	0	15 (2.5)	15 (2.1)
Metabolism and nutrition disorders	0	12 (2.0)	12 (1.7)

CRS was graded based on the Lee criteria.³ Other AEs were graded using CTCAE version 5.0 for Study FOL-001 and version 4.03 for all other studies.

AEs were coded using MedDRA version 26.0.

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

TEAE was defined as an AE that started any time from initiation of liso-cel administration through and including 90 days following the final dose of liso-cel. Any AE occurring after the initiation of subsequent anticancer therapy or liso-cel retreatment or start of combination therapy (BCM-002) was not considered as a TEAE.

Source: Table 3.6.1.1 of Appendix 2.

Other Significant Adverse Events of Special Interest

In Liso-cel Treated Set subjects with 3L+ FL, the most frequently occurring AESIs known to be associated with the therapeutic class of CAR T-cell therapies were CRS (58.9% vs. 41.8% in 2L/3L+ LBCL) and NT (15.9% vs. 24.8% in 2L/3L+ LBCL). Most CRS and NT AESIs were mild to moderate in severity (Grade 1-2); no Grade 5 incidences of either AESI were reported. No subjects had AESIs of IRR, MAS, or TLS. Most AESIs were assessed as liso-cel-related by the investigator.

In Liso-cel Treated Set subjects with 3L+ FL, the incidences of Grade $\geq$ 3 SPM and hypogammaglobulinemia reported were 0.9% (vs. 0.7% in 2L/3L+ LBCL) and 0% (vs. 0.2% in 2L/3L+ LBCL), respectively, for the treatment-emergent period and 4.7% (vs. 3.4% in 2L/3L+ LBCL) and 0.9% (vs. 0% in 2L/3L+ LBCL), respectively, for the post-treatment-emergent period.

No incidence of autoimmune disorders was reported in 3L+ FL during treatment-emergent or post-treatment-emergent periods.

The frequency of Grade 3-4 infections and infestations was lower in Liso-cel Treated Set subjects with 3L+ FL compared with 2L/3L+ LBCL (6.5% vs 12%). In 3L+ FL, the most common Grade 3-4 infection and infestation was infections - pathogen unspecified (4.7% subjects); there were no Grade 5 infections and infestations TEAEs.

The rate of prolonged cytopenia at Day 29 was lower in Liso-cel Treated Set subjects with 3L+ FL compared with 2L/3L+ LBCL (24.3% vs 35.7%, respectively).

Clinical Laboratory Evaluations in 3L+ FL and 2L/3L+ LBCL

Hematology

In Liso-cel Treated Set subjects with 3L+ FL, the 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.

Table 70. New or Worsening Laboratory Abnormalities by Laboratory Shift Treatment-emergent Hematology Laboratory Results - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

	Subjects with Baseline Result, n	Subjects with Baseline and at least one Post-baseline Result, n	Maximum Post-baseline Treatment-emergent Laboratory Abnormality			
			All Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3-4 n (%)
3L+ FL FOL-001 Cohorts 1, 2						
NEUTROPHIL COUNT DECREASED	107	107	81 (75.7)	17 (15.9)	50 (46.7)	67 (62.6)
WHITE BLOOD CELL DECREASED	107	107	64 (59.8)	21 (19.6)	27 (25.2)	48 (44.9)
ANEMIA	107	107	48 (44.9)	10 (9.3)	0	10 (9.3)
PLATELET COUNT DECREASED	107	107	43 (40.2)	4 (3.7)	10 (9.3)	14 (13.1)
LYMPHOCYTE COUNT DECREASED	107	107	8 (7.5)	4 (3.7)	2 (1.9)	6 (5.6)
LYMPHOCYTE COUNT INCREASED	107	107	0	0	0	0
2L/3L+ LBCL Total						
NEUTROPHIL COUNT DECREASED	608	608	483 (79.4)	146 (24.0)	294 (48.4)	440 (72.4)
PLATELET COUNT DECREASED	608	608	401 (66.0)	88 (14.5)	130 (21.4)	218 (35.9)
WHITE BLOOD CELL DECREASED	608	608	362 (59.5)	132 (21.7)	199 (32.7)	331 (54.4)
ANEMIA	608	608	313 (51.5)	137 (22.5)	0	137 (22.5)
LYMPHOCYTE COUNT DECREASED	594	592	26 (4.4)	6 (1.0)	20 (3.4)	26 (4.4)
LYMPHOCYTE COUNT INCREASED	594	592	12 (2.0)	0	0	0
Overall Total						
NEUTROPHIL COUNT DECREASED	715	715	564 (78.9)	163 (22.8)	344 (48.1)	507 (70.9)
PLATELET COUNT DECREASED	715	715	444 (62.1)	92 (12.9)	140 (19.6)	232 (32.4)
WHITE BLOOD CELL DECREASED	715	715	426 (59.6)	153 (21.4)	226 (31.6)	379 (53.0)
ANEMIA	715	715	361 (50.5)	147 (20.6)	0	147 (20.6)
LYMPHOCYTE COUNT DECREASED	701	699	34 (4.9)	10 (1.4)	22 (3.1)	32 (4.6)
LYMPHOCYTE COUNT INCREASED	701	699	12 (1.7)	0	0	0

Baseline was the last observation collected prior to or on the date of product infusion.

A treatment-emergent laboratory abnormality was defined as an abnormality that, compared to baseline, worsened by ≥ 1 grade after product infusion and up to 90 days post product infusion. Any laboratory abnormality occurring after the initiation of subsequent anticancer therapy or retreatment were not considered as treatment-emergent.

Toxicity grade was determined based on CTCAE version 5.0 for Study FOL-001 and version 4.03 for all other studies.

The percentage was calculated based on the number of subjects with baseline and at least one post-baseline result.

Source: [Table 5.2.1.1 of Appendix 2](#).

Clinical Chemistry

In Liso-cel Treated Set subjects with 3L+ FL, most chemistry parameters remained stable over time. Grade 3-4 clinical chemistry laboratory abnormalities were generally lower in the 3L+ FL than 2L/3L+ LBCL. The most frequent Grade 3-4 new or worsening chemistry laboratory abnormality in subjects with FL was increased blood bilirubin in 2 (1.9%) subjects (see Table below). The frequency of new or worsening abnormalities in fibrinogen (decreases) was lower in Liso-cel Treated Set subjects with 3L+ FL than in subjects with 2L/3L+ LBCL (all grade 16.3% vs 47%, respectively).

Table 71. New or Worsening Laboratory Abnormalities by Laboratory Shift Treatment-emergent Chemistry Laboratory Results - Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL

	Subjects with Baseline Result, n	Subjects with Baseline and at least one Post-baseline Result, n	Maximum Post-baseline Treatment-emergent Laboratory Abnormality			
			All Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3-4 n (%)
3L+ FL FOL-001 Cohorts 1, 2						
ALANINE AMINOTRANSFERASE INCREASED	107	107	37 (34.6)	0	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	107	107	30 (28.0)	0	0	0
BLOOD BILIRUBIN INCREASED	107	107	25 (23.4)	2 (1.9)	0	2 (1.9)
HYPONATREMIA	107	107	22 (20.6)	0	0	0
CREATININE INCREASED	107	107	19 (17.8)	0	0	0
HYPOALBUMINEMIA	107	107	17 (15.9)	0	0	0
HYPOKALEMIA	107	107	16 (15.0)	1 (0.9)	0	1 (0.9)
HYPOMAGNESEMIA	107	105	15 (14.3)	0	0	0
HYPERKALEMIA	107	107	7 (6.5)	0	0	0
HYPERNATREMIA	107	107	5 (4.7)	0	0	0
HYPERMAGNESEMIA	107	105	4 (3.8)	1 (1.0)	0	1 (1.0)
HYPERURICEMIA	102	100	N.A.	N.A.	N.A.	N.A.
HYPOPHOSPHATEMIA	105	105	N.A.	N.A.	N.A.	N.A.
2L/3L+ LBCL Total						
HYPOPHOSPHATEMIA	608	608	189 (31.1)	60 (9.9)	3 (0.5)	63 (10.4)
HYPONATREMIA	608	608	174 (28.6)	32 (5.3)	0	32 (5.3)
HYPOALBUMINEMIA	608	608	171 (28.1)	12 (2.0)	0	12 (2.0)
ALANINE AMINOTRANSFERASE INCREASED	608	608	156 (25.7)	6 (1.0)	1 (0.2)	7 (1.2)
HYPOKALEMIA	608	608	137 (22.5)	15 (2.5)	0	15 (2.5)
ASPARTATE AMINOTRANSFERASE INCREASED	608	608	135 (22.2)	7 (1.2)	0	7 (1.2)
HYPOMAGNESEMIA	608	608	116 (19.1)	0	0	0
CREATININE INCREASED	608	608	84 (13.8)	1 (0.2)	0	1 (0.2)
HYPERMAGNESEMIA	608	608	52 (8.6)	5 (0.8)	0	5 (0.8)

	Subjects with Baseline Result, n	Subjects with Baseline and at least one Post-baseline Result, n	Maximum Post-baseline Treatment-emergent Laboratory Abnormality			
			All Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3-4 n (%)
BLOOD BILIRUBIN INCREASED	608	608	49 (8.1)	9 (1.5)	1 (0.2)	10 (1.6)
HYPERNATREMIA	608	608	33 (5.4)	0	0	0
HYPERURICEMIA	608	608	17 (2.8)	12 (2.0)	0	12 (2.0)
HYPERKALEMIA	608	608	16 (2.6)	1 (0.2)	2 (0.3)	3 (0.5)
Overall Total						
HYPONATREMIA	715	715	196 (27.4)	32 (4.5)	0	32 (4.5)
ALANINE AMINOTRANSFERASE INCREASED	715	715	193 (27.0)	6 (0.8)	1 (0.1)	7 (1.0)
HYPOPHOSPHATEMIA	713	713	189 (26.5)	60 (8.4)	3 (0.4)	63 (8.8)
HYPOALBUMINEMIA	715	715	188 (26.3)	12 (1.7)	0	12 (1.7)
ASPARTATE AMINOTRANSFERASE INCREASED	715	715	165 (23.1)	7 (1.0)	0	7 (1.0)
HYPOKALEMIA	715	715	153 (21.4)	16 (2.2)	0	16 (2.2)
HYPOMAGNESEMIA	715	713	131 (18.4)	0	0	0
CREATININE INCREASED	715	715	103 (14.4)	1 (0.1)	0	1 (0.1)
BLOOD BILIRUBIN INCREASED	715	715	74 (10.3)	11 (1.5)	1 (0.1)	12 (1.7)
HYPERMAGNESEMIA	715	713	56 (7.9)	6 (0.8)	0	6 (0.8)
HYPERNATREMIA	715	715	38 (5.3)	0	0	0
HYPERKALEMIA	715	715	23 (3.2)	1 (0.1)	2 (0.3)	3 (0.4)
HYPERURICEMIA	710	708	17 (2.4)	12 (1.7)	0	12 (1.7)

Baseline was the last observation collected prior to or on the date of product infusion.

A treatment-emergent laboratory abnormality was defined as an abnormality that, compared to baseline, worsened by ≥ 1 grade after product infusion and up to 90 days post product infusion. Any laboratory abnormality occurring after the initiation of subsequent anticancer therapy or retreatment were not considered as treatment-emergent.

Toxicity grade was determined based on CTCAE version 5.0 for Study FOL-001 and version 4.03 for all other studies.

The percentage was calculated based on the number of subjects with baseline and at least one post-baseline result.

Source: Table 5.2.2.1 of Appendix 2.

Liso-cel Treated Set in 2L+ FL and 2L/3L+ LBCL

Safety data from Cohorts 1, 2, and 3 of Study FOL-001 (2L+ FL subjects; n= 130) were analyzed side-by-side with pooled safety data for liso-cel monotherapy treated subjects with 2L/3L+ LBCL (n= 608) (see Table below):

- 1 (0.8%) death was reported as occurring within 30 days after the first liso-cel infusion in 2L+ FL. Deaths of subjects reported at any time after the first liso-cel infusion were 9.2% in liso-cel Treated Set subjects with 2L+ FL and 42.4% in subjects with 2L/3L+ LBCL and most of the deaths reported after the first liso-cel infusion were due to disease progression in both FL and LBCL.

- The frequency of any grade or Grade 3-4 TEAEs regardless of causality was consistent between subjects with 2L+ FL (99.2% and 76.2%, respectively) and 2L/3L+ LBCL (99.0% and 79.3%, respectively).
- The frequency of all-cause SAEs was lower in subjects with 2L+ FL (23.8%) than 2L/3L+ LBCL (42.8%).
- As for 3L+ FL, the frequency of liso-cel-related any grade and Grade 3-4 TEAEs was higher in subjects with 2L+ FL (88.5% and 61.5%, respectively) than 2L/3L+ LBCL (79.9% and 45.6%, respectively), but the frequency of liso-cel related SAEs was lower in subjects with 2L+ FL (18.5%) than 2L/3L+ LBCL (29.8%).
- As for 3L+ FL, Grade 1-2 CRS was higher in 2L+ FL subjects than 2L/3L+ LBCL (56.9% vs 40.1%, respectively). However, the frequencies of Grade 3-4 AESIs of CRS and iINT were lower in subjects with 2L+ FL (0.8% and 2.3% subjects, respectively) than 2L/3L+ LBCL (1.6% and 8.4% subjects, respectively).

Table 72. Summary of Safety in Pooled Studies - Liso-cel Treated Set in 2L+ FL (FOL-001) and 2L/3L+ LBCL

Safety Parameter	2L+ FL (FOL-001 Cohorts 1, 2, 3) N = 130	2L/3L+ LBCL Total N = 608	Overall Total N = 738
Deaths Occurred After First Liso-cel Infusion	12 (9.2)	258 (42.4)	270 (36.6)
Primary Cause of Death			
PD	6 (4.6)	206 (33.9)	212 (28.7)
AE	3 (2.3)	23 (3.8)	26 (3.5)
COVID-19	2 (1.5)	9 (1.5)	11 (1.5)
Unknown	0	6 (1.0)	6 (0.8)
Other ^a	1 (0.8)	14 (2.3)	15 (2.0)
Subjects with any TEAE	129 (99.2)	602 (99.0)	731 (99.1)
Grade 3-4	99 (76.2)	482 (79.3)	581 (78.7)
Grade ≥ 3	100 (76.9)	497 (81.7)	597 (80.9)
Grade 5	1 (0.8)	15 (2.5)	16 (2.2)
Serious	31 (23.8)	260 (42.8)	291 (39.4)
Subjects with any LDC-related TEAE	98 (75.4)	498 (81.9)	596 (80.8)
LDC-related Grade 3-4	81 (62.3)	419 (68.9)	500 (67.8)
LDC-related Grade ≥ 3	81 (62.3)	427 (70.2)	508 (68.8)
LDC-related Grade 5	0	8 (1.3)	8 (1.1)
LDC-related Serious	8 (6.2)	67 (11.0)	75 (10.2)

Safety Parameter	2L+ FL (FOL-001 Cohorts 1, 2, 3) N = 130	2L/3L+ LBCL Total N = 608	Overall Total N = 738
Subjects with any Liso-cel-related TEAE	115 (88.5)	486 (79.9)	601 (81.4)
Liso-cel-related Grade 3-4	80 (61.5)	277 (45.6)	357 (48.4)
Liso-cel-related Grade ≥ 3	81 (62.3)	285 (46.9)	366 (49.6)
Liso-cel-related Grade 5	1 (0.8)	8 (1.3)	9 (1.2)
Liso-cel-related Serious	24 (18.5)	181 (29.8)	205 (27.8)
Subjects with any treatment-emergent AESI			
CRS	75 (57.7)	254 (41.8)	329 (44.6)
Grade 1-2	74 (56.9)	244 (40.1)	318 (43.1)
Grade 3-4	1 (0.8)	10 (1.6)	11 (1.5)
iINT	20 (15.4)	151 (24.8)	171 (23.2)
Grade 1-2	17 (13.1)	100 (16.4)	117 (15.9)
Grade 3-4	3 (2.3)	51 (8.4)	54 (7.3)
IRR	0	6 (1.0)	6 (0.8)
MAS	1 (0.8)	4 (0.7)	5 (0.7)
TLS	0	2 (0.3)	2 (0.3)
Grade ≥ 3 infections	7 (5.4)	73 (12.0)	80 (10.8)

^a Refer to Listing 2.7.5 in Appendix 2 of the Module 2.7.4 SCS²⁹ for details.

CRS was graded based on the Lee criteria.⁴⁰

Other AEs were graded using CTCAE version 5.0 for Study FOL-001 and version 4.03 for all other studies.

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

TEAE was defined as an AE that started any time from initiation of liso-cel administration through and including 90 days following the final dose of liso-cel. Any AE occurring after the initiation of subsequent anticancer therapy or liso-cel retreatment or start of combination therapy (BCM-002) was not considered as a TEAE.

Source: Table 6.2-1 of the Module 2.7.4 SCS, Table 3.9.1.2.1, Table 4.1.1.10.1 from Appendix 3 of the Module 2.7.4 SCS

Safety to support the Product Information

The approved dose range of liso-cel in the SmPC is 44 to 120 × 10⁶ CAR+ T cells. Thus, pooled safety analyses were performed for 691 subjects receiving liso-cel dose in the range of 44 to 120 × 10⁶ CAR+ T cells. These analyses included subjects with 2L+ FL (n= 130; from Study FOL-001), 2L LBCL (n= 177; from studies BCM-003 [Arm B], 017006, and BCM-001 [Cohort 2]), and 3L+ LBCL (n= 384; from studies BCM-001 [Cohorts 1, 3, and 7], 017001, 017007, and BCM-002). ADRs represent all reported TEAEs across LBCL disease histologies and are not restricted to AEs deemed related by the investigator. All grouped terms and PTs are reported with a frequency of 1% or greater in the ADR table (see section 4.8 of the SmPC). Other clinically important ADRs that occurred in less than 1% of subjects treated with liso-cel are included in the ADR table as footnotes.

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 FOL-001 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 (EMA/H/C/004731). A Type II variation for extension of indication to include 2L LBCL was approved on 28-Apr-2023. Review of available post-marketing data presented in the most recent Periodic Benefit-Risk Evaluation Report (reporting period 05-Aug-2023 through 04-Feb-2024) did not reveal any significant safety/efficacy concerns that changed the existing benefit-risk profile of liso-cel. The post-marketing data were consistent with the safety profile of liso-cel as previously reported and described in the approved product label.

2.6.1. Discussion on clinical safety

For this proposed indication (R/R FL after 2 or more lines of systemic therapy), the safety evaluation was primarily based on the safety data from the **Study FOL-001** as of data cutoff of 10-Jan-2024.

All the analysis provided and described in the sections above allow for comparison of the safety profile of liso cel in 3L+ FL (proposed indication) and 2L+ FL (overall FL treated subjects) to the known safety profile of liso-cel in the approved SmPC.

In Study FOL-001, the exposure to liso-cel was adequate and in line with EU SmPC recommendations (i.e., 44 to 120 × 10⁶ CAR+ T cells).

As of the data cut-off date of 10-Jan-2024, with a median follow-up of 29.72 (min, max: 0.3, 39.6) months, no new safety concerns with liso-cel were identified in subjects with R/R 2L+ FL.

In the Liso-cel-treated Analysis Set (n= 130), TEAEs occurred in 99.2% of subjects; serious TEAEs occurred in 23.8% of subjects and Grade ≥3 TEAEs occurred in 76.9% of subjects. Most TEAEs were related to liso-cel (115 [88.5%] subjects) or LDC (98 [75.4%] subjects).

Liso-cel safety profile was consistent across all cohorts (lines of therapy), i.e., Cohort 1 (4L+ FL), Cohort 2 (3L FL), and Cohort 3 (2L FL) (with the exception of lower rate of Grade ≥ 3 TEAE and any serious TEAE in 2L FL, 60.9% and 17.4%, respectively) and across all groups, i.e., Cohorts 1 and 2 (3L+ FL) and Cohorts 1, 2, and 3 (2L+ FL). TEAEs that led to death occurred in 1 (0.8%) subject (additional details are reported in "Death" section).

Liso-cel-related TEAEs occurred in 115 (88.5%) subjects overall. In 3L+ FL subjects (n= 107), liso-cel TEAEs occurred in 89.7% of subjects and the most common SOC were blood and lymphatic system disorders (62.6% of subjects), immune system disorders (59.8% of subjects), and general disorders and administration site conditions (29.0% of subjects). These results were consistent with 2L+ FL subjects, and no major differences were observed between 4L+ FL, 3L FL, and 2L subjects.

Liso-cel-related Grade ≥ 3 TEAEs occurred in 81 (62.3%) subjects overall and the most frequently reported Grade ≥ 3 TEAEs ($\geq 10\%$ subjects) were neutropenia (47.7%) and lymphopenia (11.5%).

Deaths were mainly due to disease progression. In the Leukapheresed (ITT) Set (n= 139), 16 (11.5%) subjects died during study: 1 (0.7%) subject from Cohort 1 died after LDC and before liso-cel infusion (due to acute respiratory failure, assessed by the investigator as not related to liso-cel/LDC/study procedure); 1 (0.7%) subject from Cohort 3 died after liso-cel infusion, within 30 days after liso-cel infusion (due to occurrence of HLH assessed as related to liso-cel treatment by the investigator); 14 (10.1%) subjects died after the 90-day post-infusion period (from Day 91 after infusion; mainly due to disease progression). One subject from Cohort 1 died due to PML on Day 190 and this event was considered as related to fludarabine and liso-cel by the investigator. Of note, the subject had undergone four prior lines of systemic therapy, including anti-CD20 antibodies (rituximab and obinutuzumab), which are known to associate with development of PML.

A total of 4 (2.9%) subjects died from AEs, the PTs included: AML, PML, HLH, and acute respiratory failure (hypoxic).

A total of 3 (2.2%) subjects died from other causes, which included: COVID-19, COVID-19 pneumonia, and erythema multiforme.

The **COVID-19** rate and severity were in the expected range for the FL population and overall, the impact of the COVID-19 pandemic on study conduct was limited.

One (0.7%) subject died due to a cardiac event (heart failure, reported as an AE not related to liso-cel). One (0.8%) subject experienced a TEAE that led to death: Hemophagocytic lymphohistiocytosis (HLH) in the 2L FL cohort assessed as related to liso-cel treatment by the investigator. No additional information has been provided on this subject. However, HLH/MAS is adequately reported in the current SmPC (section 4.4) and RMP and no updates to the existing SmPC are required based on this fatal case.

AESIs occurred in 87 (66.9%) subjects with 2L+ FL and 72 (67.3%) subjects with 3L+ FL. The frequency of AESIs was consistent across cohorts (lines of therapy) and groups. There were no AESIs in the IRR, TLS, and autoimmune disorder categories. The majority of AESIs were mild to moderate in severity and manageable with protocol-specified guidelines and/or local standard of care.

Cytokine Release Syndrome (CRS). In the Liso-cel-treated Analysis Set (n= 130), CRS occurred in 75 (57.7%) subjects (58.9% in 3L+ FL subjects), including 1 (0.8%) subject with Grade 3 CRS from Cohort 1 (4L+ FL). There were no subjects with Grade 4 CRS and no subjects with fatal CRS. The frequency of CRS was consistent across cohorts (lines of therapy) and groups. The most common symptoms of CRS ($\geq 10\%$) included pyrexia (56.9%) and hypotension (13.8%). The median time of CRS onset from the time of liso-cel infusion was 6 days (range: 1 to 17 days). CRS resolved in all subjects; the median time to resolution was 3 days (range: 1 to 10 days). Of the subjects who were treated with concomitant medications for CRS, 18 (13.8%) subjects received tocilizumab only (median

1 dose [range, 1 to 3]), no subjects received corticosteroids only, 15 (11.5%) subjects received both tocilizumab and corticosteroids, and 2 (1.5%) subjects received vasopressors.

Neurological Toxicity (including ICANS). iiNT occurred in 21 (16.2%) subjects with 2L+ FL (15.9% in 3L+FL subjects), including 4 (3.1%) subjects with Grade 3 iiNT. There were no subjects with Grade 4 iiNT and no subjects with fatal iiNT. The most common iiNTs by PT were tremor (7.7%) and aphasia (6.9%). The median time to iiNT onset from the time of liso-cel infusion was 8 days (range: 4 to 16 days). iiNT resolved in all subjects; the median time to resolution was 4 days (range: 1 to 17 days). Of the subjects who were treated with concomitant medications for iiNT, no subjects received tocilizumab only, 9 (6.9%) subjects received corticosteroids only, no subjects received both tocilizumab and corticosteroids, no subjects received vasopressors.

Prolonged Cytopenia. In the Liso-cel-treated Analysis Set, prolonged cytopenia, defined as Grade ≥ 3 cytopenia at the Day 29 (± 2 days) visit based on local laboratory assessments of neutropenia, thrombocytopenia, or anemia, occurred in 29 (22.3%) subjects. Based on the data presented, the cytopenias observed after liso-cel infusion seem to be transient.

Second Primary Malignancies (SPMs). In the Liso-cel-treated Analysis Set, a total of 12 SPM events were reported in 9 subjects (6.9%). No events of T-cell malignancies were reported. When a secondary malignancy occurs, a sample of the neoplastic tissue is requested, and if received, submitted to test for the presence of liso-cel transgene using a validated RNAscope ISH test. Of the 12 SPM events, tumor samples from 7 SPM events were received for testing and no samples were available in the remaining 5 SPM events. Of the 7 tumor samples analyzed by ISH, 3 were negative for transgene (AML, mucoepidermoid carcinoma, and adenocarcinoma of colon), 1 failed testing due to insufficient sample quality (MDS), and 3 are pending for ISH results (melanoma, SCC/Bowen's disease, and rectal cancer). In addition to tumor samples, the MAH also requested blood samples at the time of the SPM event for RCL and transgene testing. For the 2 SPM events (AML, and colon adenocarcinoma), where tumor sample tested negative for transgene as described above, blood samples were negative for RCL. No blood samples from the remaining 10 SPM events from 8 subjects (mucoepidermoid carcinoma [1], MDS [1], melanoma [1], SCC/Bowen's disease [1], rectal cancer [1], AML [3], BCC [1], and colorectal cancer [1]) were available for testing. The MAH provided additional data for 5 of the 9 subjects previously reported with SPMs. For one subject (105-1002) with SPM of malignant melanoma, the relationship with liso-cel was updated from not suspected to suspected. The event of malignant melanoma was resolved on Day 751 and no recurrence has been reported at the last clinical data available about a year later. The initial results of the ISH testing (inconclusive), has been repeated, confirming negative transgene. The MAH was reminded to put every effort to comply with the PRAC recommendation to have a process in place to adequately handle collection and further testing of tissue samples from patients for whom a secondary T-cell malignancy has been reported in the post marketing setting. This process should include instructions on prioritization of analyses to be conducted in case of limited availability of tumour tissue sample, bone marrow aspirate, and/or fresh blood from the patient.

Moreover, in the Liso-cel-treated Analysis Set 2 subjects met the criteria for **integration site analysis (ISA)**: for one subject, the transgene percentage was 11.4% at Month 12, and the other subject (250-1006) was 3.5% at Month 24. ISA was performed on both samples. Results for the subject with 11.4% transgene at Month 12 showed the sample was polyclonal without evidence of a monoclonal outgrowth. ISA results for subject 250-1006 were also available, with no evidence of a predominant clone.

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*).

Taking into account all data provided, no correlation was identified between baseline cardiac function (ejection fraction and ECG) prior to liso-cel infusion and cardiac events reported post liso-cel infusion. Moreover, in the majority of these subjects, multiple prior lines of chemotherapy (including alkylating agents) were administered and the cardiotoxicity after CAR-T treatment might also be influenced by previous treatments in these patients. The SmPC covers this safety aspect and for the moment, no additional patient monitoring protocols should be advised before or after liso-cel infusion. However, CAR-T therapies (as well as bispecific T-cell engagers), despite their potential life-saving benefits, have been associated with a significant risk of cardiac toxicity. As reported in initial studies from VigiBase (*Karthikeyan et al. Communications Medicine 2024* <https://doi.org/10.1038/s43856-024-00540-9>), additional analyses are needed to further investigate the cardiovascular profile of CRS occurring in the context of CAR-T therapy. The MAH confirmed that the adverse events of cardiac and vascular disorders are collected through routine pharmacovigilance and data will be presented in upcoming PSURs.

There were no major differences in frequency of TEAEs and Grade ≥ 3 TEAEs across subgroups (age, sex, ethnicity, race, anticancer treatment of disease control status [yes vs no], and region). Some variability was observed, potentially due to the small sample size of some subgroups, but no definitive conclusion can be drawn.

In the Pooled Analyses of Safety regarding *Liso-cel Treated Set in 3L+ FL and 2L/3L+ LBCL* the frequency of **any grade** or **Grade 3-4 TEAEs** regardless of causality was consistent between Liso cel Treated Set subjects with 3L+ FL and 2L/3L+ LBCL.

The most commonly reported **liso-cel-related all-grade TEAEs** were consistent across Liso-cel Treated Set subjects with 3L+ FL and 2L/3L+ LBCL; however, the frequency of all-grade related TEAEs was higher in subjects with FL respect to the subjects with LBCL (89.7% vs. 79.9%). Similarly, the frequency of **Grade ≥ 3 related TEAEs** such as neutropenia and lymphopenia were higher in subjects with FL than LBCL (neutropenia 48.6% vs. 29.8%; lymphopenia 11.2% vs. 5.8%, respectively) whereas thrombocytopenia and anemia were lower in subjects with FL than LBCL (thrombocytopenia 9.3% vs. 15.8%; anemia 8.4% vs. 14.3%, respectively).

Regarding **AESIs**, liso-cel exhibited a manageable safety profile and no new safety concerns emerged. In 3L+ FL subjects compared to 2L/3L+ LBCL, the incidence of CRS, Grade 3-4 CRS, iiNT, and MAS/HLH was 58.9, 0.9%, 15.9%, and 0%, respectively (vs 41.8%, 1.6%, 24.8% and 0.7% in 2L/3L+ LBCL, respectively) and considered manageable using the protocol-specified criteria. The rates of high-grade infections (6.5% vs 12%) and prolonged cytopenia (24.3% vs 35.7%) were considered acceptable, and the reported type and incidence of Grade ≥ 3 SPMs (4.7% vs 3.4% during post treatment-emergent period) was as expected for a heavily pre-treated population.

Higher rates of CRS and some liso-cel-related hematological AEs (i.e., neutropenia and thrombocytopenia) were observed in 3L+ FL compared to 2L/3L+ LBCL. However, the difference in CRS rates was mainly due to higher rate of Grade 1 CRS and the frequency of hematological AEs, regardless of investigator-assessed relatedness, was similar or lower in 3L+ FL than in 2L/3L+ LBCL.

For Liso-cel Treated Set in 2L+ FL and 2L/3L+ LBCL the safety events reported in 2L+ FL subjects from Study FOL-001 were consistent with those previously reported in 2L/3L+ LBCL subjects. As for 3L+ FL, **Grade 1-2 CRS** was higher in 2L+ FL subjects than 2L/3L+ LBCL (56.9% vs 40.1%, respectively). However, the frequencies of Grade 3-4 AESIs of CRS and iiNT were lower in subjects with 2L+ FL (0.8% and 2.3% of subjects, respectively) than 2L/3L+ LBCL (1.6% and 8.4% of subjects, respectively). No new safety signals were identified.

To date, no clinical condition for EGFRt-mediated cell ablation has been identified in the liso-cel development program.

Product Information. Pooled safety analyses were performed for 691 subjects receiving liso-cel dose in the range of 44 to 120 × 10⁶ CAR+ T cells. These analyses included subjects with 2L+ FL (n= 130; from Study FOL-001), 2L LBCL (n= 177; from studies BCM-003 [Arm B], 017006, and BCM-001 [Cohort 2]), and 3L+ LBCL (n= 384; from studies BCM-001 [Cohorts 1, 3, and 7], 017001, 017007, and BCM-002). ADRs represent all reported TEAEs across LBCL disease histologies, with frequency of 1% or greater in the ADR table and are not restricted to AEs deemed related by the investigator. Given the consistency between the safety profiles of 2L+ FL and 3L+ FL, the inclusion of the 2L+ FL dataset in the Product Information to provide a more comprehensive dataset is supported.

2.6.2. Conclusions on clinical safety

The safety database included 130 FL patients treated with liso-cel in the Study FOL-001. Overall, the safety events reported in this study were consistent with those previously observed in the authorised indication of 2L/3L+ LBCL and were manageable. In general, similar rates of CAR T-cell-associated toxicities were observed in this FL population when compared to the 2L/3L+ LBCL population. The data presented in the Summary of Product Characteristics (SmPC) reflect the entire clinical experience at the recommended dose range. With a median follow up of 29.72 (min, max: 0.3, 39.6) months, no new safety concerns with liso-cel were identified in subjects with R/R 2L+ FL. However, while this period would be enough to identify the earlier and immediate AEs, there are certain potential risks for which conclusive data could not be obtained due to the limited sample size and a limited follow-up time, including the long-term safety. The MAH committed to provide additional safety data post-approval from the ongoing long-term follow-up study GM-LTFU-001, from the US-based, non-interventional RW registry study CA082-1175 including patients treated with liso-cel for 3L+ R/R FL in the post-marketing setting (category 3 studies in the RMP), and from the ongoing registry-based study JCAR017-BCM-005 that also include EU subjects who receive liso-cel in the post-approval setting (Category 1 study in the annex II and RMP).

The 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 (5.1) with this application.

The (main) RMP changes were the following:

- Expanded indication for the treatment of adult patients with relapsed or refractory follicular lymphoma (R/R FL) after two or more lines of systemic therapy.
- Updated clinical trial exposure and safety data in line with new DLP.
- Updated existing FL and LBCL epidemiology data.
- Update of post-authorisation exposure information in line with new DLP.
- Addition of Study CA082-1175 as a Category 3 APVA in the PV Plan.

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

The PRAC considered that the risk management plan version 05.1 is acceptable. In addition, revisions were recommended to be taken into account with the next RMP update, as follows:

Inclusion of FL patients in the category 1 study ongoing registry-based study JCAR017-BCM-005 that also include EU subjects who receive liso-cel in the post-approval setting.

The CAT/CHMP endorsed this advice without changes.

The CAT/CHMP endorsed the Risk Management Plan version 05.1 with the following content:

Safety concerns

There are no new safety concerns or reclassification of safety concerns in this updated RMP.

Table 73. Summary of 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
Important potential risks	Autoimmune disorders Aggravation of graft versus host disease Secondary malignancies/insertional oncogenesis 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

No changes were proposed to the pharmacovigilance activities. Current additional pharmacovigilance activities include an imposed category one PASS (JCAR017-BCM-005), a category three LTFU study (GC-LTFU-001), and a transgene assay service for testing of patient samples with secondary malignancies.

With the responses to RSI, the MAH submitted an updated RMP Version 5.1 (DLP 04-Feb-2024; sign off 13-Nov-2024). The update included the addition of a category 3 activity: study CA082-1175 collects

efficacy and safety for patients treated for RR follicular lymphoma in the post-marketing setting in the USA based on CIBMTR registry data.

Table 74. Ongoing and Planned Additional Pharmacovigilance Activities

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				
PASS (JCAR017-BCM-005) / Ongoing	<u>Primary Objective:</u>	CRS/MAS ^a /HLH ^a	Protocol Submission to EMA	14-Apr-2022
	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.	NT including ICANS ^b	Date of protocol approval by PRAC	01-Dec-2022
		Infections		
		Hypogammaglobulinaemia		
		TLS		
		Cytopenia, including bone marrow failure	Start of data collection ^c	Q1 2023
	<u>Secondary Objectives:</u>	Secondary malignancies /insertional oncogenesis	Safety reports ^d	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
	To assess long-term effectiveness in patients treated with liso-cel in the postmarketing setting.	Impact on pregnancy and lactation (for pregnancy events)		
	To assess the liso-cel safety and effectiveness profile in certain subgroups including but not limited to:	Long-term safety		
		Aggravation of GvHD ^a		
		Safety in patients ≥ 75 years		
	- By large B-cell lymphoma subtypes (eg, FL3B, PMBCL, DLBCL not otherwise specified, high grade B-cell lymphoma). - According to geographical regions (eg, Europe). - Subjects aged ≥ 75 years. - Subjects with comorbid conditions (eg, renal impairment, reduced cardiac function). - Subjects with secondary CNS involvement. - Subjects with ECOG performance score ≥ 2. - By possible prognostic factors (eg, high-risk IPI). - Subjects previously exposed to anti-CD19 therapy. - Subjects with low pre-leukapheresis absolute		Interim reports ^e	At Year 5, 10, and 15 or when last patient is out of the registry-based study
			Date of Study Completion ^f	Q4 2042
			Date of Final Study Report Submission to EMA	Q4 2043

Table 74. Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
	lymphocyte count ($< 0.3 \times 10^9/L$). 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 to 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 malignancies/insertional oncogenesis 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	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	Start of data collection Progress updates	31-Aug-2024 corresponds to the date from which data extraction starts. Aligned with the reporting period of the PSURs

Table 74. Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
setting (CA082-1175) / Ongoing		Secondary malignancies /insertional oncogenesis	Interim reports	At Year 5 and 10
		Impact on pregnancy and lactation (for pregnancy events)	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.)
		Long-term safety		
		Aggravation of GvHD ^a		
		Safety in patients ≥ 75 years		
			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 malignancies/insertional oncogenesis	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.

Risk minimisation measures

No changes were proposed to the risk minimisation measures as outlined in the RMP previously. Current additional risk minimisation measures include a Controlled Distribution Programme as well as an educational programme for Healthcare Professionals and Patients.

Table 75. Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
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: - Educational programme for HCPs and patients - 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: - Educational programme for HCPs and patients - 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Table 75. Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: PASS (JCAR017-BCM-005) 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)
Important Potential Risks		
Autoimmune disorders	Routine risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Table 75. Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: 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/inser-tional oncogenesis	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) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable
Generation of replication competent lentivirus	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).
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.

Table 75. Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	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 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: 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 Additional risk minimisation measures: • Educational programme for HCPs • Controlled Distribution Programme	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. 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 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (JCAR017-BCM-005) and US registry study (CA082-1175) for pregnancy events LTFU study (GC-LTFU-001).
Long-term safety	Routine risk minimisation measures: None 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)

Table 75. Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Safety in patients < 18 years old	Routine risk minimisation measures: SmPC Section 4.2, PL Section 2 - warnings and advice Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: LTFU study (GC-LTFU-001).
Safety in patients ≥ 75 years	Routine risk minimisation measures: None 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)

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 were updated. The Package Leaflet has also been updated accordingly.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet was submitted by the MAH and found acceptable for the following reasons: the readability of the PL of Breyanzi was assessed during the review of the initial MAA, the current new indication in adults has the same route of administration and a similar safety profile as the previously approved indication, Breyanzi is administered by a health care professional and the instructions for preparation, administration, storage and disposal remain unchanged, the general design and layout of the proposed PL have not changed compared to the tested one.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

3.1.2. Available therapies and unmet medical need

Follicular lymphoma (FL) is the most commonly diagnosed type of indolent non-Hodgkin lymphoma (iNHL), accounting for approximately 35% of all NHLs and 70% of iNHLs in Western Europe and the US; it is a heterogeneous entity that includes tumours derived from germinal centre B cells, both centrocytes and centroblasts. The t(14;18) translocation has been recognized as a genetic hallmark of FL and results in constitutive overexpression of the BCL-2 protein. The disease is characterized by diffuse lymphadenopathy, bone marrow involvement, splenomegaly, and other less common sites of extranodal involvement.

FL is characterised by an indolent, relapsing/remitting clinical behaviour and as a general rule drug resistance increases and clinical benefit is reduced with each subsequent line of therapy.

Current treatment guidelines (2020 ESMO guidelines; NCCN guidelines for classic FL v. 3.2024) recommend that conventional immunochemotherapy is used early in the course of the disease (e.g. at frontline or at first relapse). In later settings of relapse/progression, alternative approaches are usually preferred. Therefore, in the indication claimed for Breyanzi, only a selected group of patients can be reasonably expected to benefit from the use of classic immune-chemotherapy regimens such as bendamustine plus rituximab (BR), R-CHOP/R-CVP, or other similar regimens.

Rituximab, an anti-CD20 monoclonal antibody, is recommended by current guidelines for the treatment of R/R FL in monotherapy or in combination. Rituximab monotherapy is often preferred in older subjects with indolent disease because of its manageable toxicity profile; in the rituximab arm of the Phase III HOMER study (Maloney DG et al, Blood Adv 2020) only subjects with rituximab-sensitive disease could be enrolled, the ORR was 66%, the CRR was 20% and the median PFS was 19.2 months. The SCHOLAR-5, a large observational study investigating the RW outcomes of subjects with R/R NHLs, showed that the ORR and CRR for subjects with R/R FL receiving various rituximab-based salvage treatments in their 3L+ ranged from 43% to 69% and from 20% to 46%, respectively.

The main clinical need in R/R FL patients is represented, however, by the increased rate of resistance to rituximab-based regimens in later lines of therapy, resulting in reduced disease-free intervals between relapses and the accumulation of treatment-related toxicities.

The combination of obinutuzumab (a 2nd generation anti-CD20 mAb) plus bendamustine (BO), followed by obinutuzumab maintenance, is approved for the treatment of subjects who did not respond or progressed during or up to 6 months after treatment with rituximab or rituximab-containing regimens. The results from registrational study GAO4753g/GADOLIN showed that the BOR (CR+PR) in the BO arm was 79.7% and the CRR 15.7%. At the time of approval, the median PFS by IRC in the BO arm was not reached nor the median DoR and OS with a median FU of up to 22 months. Updated results with a median FU of 57.5 months in the BO arm (Sehn LH et al, Blood 2019) showed that the median PFS was 24.1 months, while the median OS was still not reached.

The therapy landscape for these patients has also evolved in recent years, with more chemo-free options becoming available.

Idelalisib and duvelisib are PI3K inhibitors (PI3Kis) approved for the treatment as monotherapy of adult patients with FL that are refractory to two prior therapies. The efficacy outcomes from the registrational studies (single-arm, multicentre study 101-09 and single-arm, multicentre study IPI-145-06, respectively) showed ORRs ranging between 40% and 55.6% and CRRs in the range 0% to 16.7%. Long-term outcomes data showed mDoR, mPFS and mOS ranging between 10-12 months, 8-11 months and 28-61 months, respectively. With respect to safety, long-term treatment with PI3Kis is characterised by significant rates of neutropenia, infection, GI ADRs and rash.

Zanubrutinib (a 2nd generation BTK inhibitor) is approved in combination with obinutuzumab (OZ) for the treatment of adult patients with R/R FL who have received at least two prior systemic therapies. Data from Phase 2, randomised, controlled study ROSEWOOD showed in the OZ arm an ORR of 69% (CRR 39.3%), with a 69% DoR rate at 18 months and a median PFS of approximately 28 months.

Lenalidomide is approved in combination with rituximab (RR) for the treatment of adult patients with previously treated FL. The efficacy and safety of the RR regimen was investigated in a phase 3, multicentre, randomised, double-blind, controlled study (AUGMENT) that compared RR with rituximab plus placebo in patients with R/R indolent NHLs, including FL. With a median follow-up of approximately 28 months, the ORR for FL patients in the RR arm was 80.3%, the CRR 34.7%, the median DoR 36.6 months, the median PFS 39.4 months and the 5-year OS rate was 85.9%.

Mosunetuzumab is an anti-CD20/CD3 T-cell-engaging bispecific mAb approved conditionally for the treatment of adult patients with R/R FL who have received at least two prior systemic therapies. The CMA of Lunsumio was based on the results from a single open-label, multicentre, multi-cohort study (GO29781) in subjects with R/R B-cell NHLs. Efficacy results showed that the ORR was 80%, the CRR 60%, the mDoR 22.8 months, the median PFS 17.9 months and the median OS was not yet reached. Epcoritamab and odronextamab are two additional anti-CD20/CD3 bispecific mABs approved as monotherapy for the treatment of adult patients with R/R FL after two or more lines of systemic therapy that showed similar results to mosunetuzumab.

Tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel) are two anti-CD19 CAR T cell (CARTs) advanced medicinal products (ATMPs). Tisa-cel is approved for the treatment of subjects with R/R FL after two or more lines of systemic therapy. Results from the registrational ELARA trial (a Phase 2, open-label, single-arm study) showed that treatment with tisa-cel resulted in high ORR (86%) and CRR (69%), with a median PFS of 18.4 months and median DoR and OS not yet reached after a median follow-up of 20.8 months.

Axi-cel is approved for treatment of patients with R/R FL after three or more lines of systemic therapy. Supporting efficacy data come from study ZUMA-5, a single-arm Phase 2 trial in subjects with R/R indolent NHLs, and showed that the ORR was 94%, the CRR 78%, the median DoR 38.6 months, the median PFS 39.6 months and the median OS was not yet reached with a median FU of 25.9 months.

The safety profile of T cell engaging immunotherapies (including bispecific mAbs and CARTs) is characterised by CRS, neurotoxicity including ICANS, infections, persisting hypogammaglobulinemia and cytopenias. Rates and severity of AEs vary across different products.

Overall, despite several products approved for the treatment of subjects with 3L+ FL, with CAR-T therapies offering the most compelling efficacy, there is a continuous need for efficacious treatments with better safety profiles to further enhance patient outcomes. FL, in fact, remains largely incurable, and death occurs mainly due to histological transformation to aggressive LBCL, infection, or because FL becomes refractory to the available options. Further, a higher medical need can be recognised for POD24 patients (i.e. subjects with early progression), who are at high risk of poor long-term outcomes, with an estimated 5-year OS 50% (vs. 90% in the absence of early progression).

3.1.3. Main clinical studies

Study FOL-001 was a global Phase 2, open-label, single-arm, multicohort, multicentre study designed to evaluate the efficacy and safety of liso-cel in adult subjects with R/R FL or MZL, with the aim to register an indication for R/R FL subjects after at least 2 previous therapies (3L+). The FOL-001 trial enrolled three distinct patient groups based on the previous number of line therapies (Cohort 1: 4L patients, Cohort 2: 3L patients, Cohort 3: 2L patients); pooled data from Cohort 1 and 2 provided the

main evidence to support this extension of indication application; data from Cohort 3 were only supportive.

No specific dose-response study was conducted for FL, and the single target dose of 100×10^6 CAR+ T cells already approved for LBCLs was eventually selected as recommended dose across the whole liso-cel development program in B-cell malignancies in adults, including FL.

The MAH provided further contextualisation of the results from study FOL-001 through indirect comparisons, including a Real-World External Arm Study (RWEAS), an unanchored MAIC and a Systematic Literature Review (SLR).

Treatment eligibility was defined in accordance with the main clinical guidelines for the treatment of FL (NCCN 2019), which requires the presence of at least one of the modified GELF criteria or the presence of the POD24; efficacy was assessed by radiographic tumour evaluation by diagnostic quality computed tomography (CT)/magnetic resonance imaging (MRI) scans (chest, neck, abdomen and pelvis) and/or positron emission tomography (PET) scans and were reviewed by an independent review committee (IRC), according to a modified version of the "Lugano Response Criteria".

The primary endpoint of study FOL-001 was ORR, while CRR and time to event endpoints like DOR, PFS and OS were analysed as secondary ones.

The number of patients included in the 3L+ liso-cel treated efficacy set was n=107 out of 114 subjects who was leukapheresed in study FOL-001. Four subjects received non-conforming products, 3 were not infused because of AE, failure to meet inclusion/exclusion criteria and "other". Subjects with no PET positive disease before liso-cel infusion or with no pre-infusion PET scan (n=4) were excluded from the liso-cel treated efficacy set. Similarly to other trial in FL involving CAR-T, the investigators were allowed to prescribe antineoplastic bridging therapies to stabilize the disease while waiting for liso-cel infusion. Bridging therapy was selected based on the Investigators choice and included the current approved therapies for r/r FL.

3.2. Favourable effects

Efficacy data from study FOL-001 in a heavily pre-treated population (the median number of prior lines of therapy was n=3 and 64.5% of patients were double-refractory to rituximab and alkylating agents) showed that treatment with liso-cel resulted in high rates of deep and rapidly induced responses: the ORR by IRC was 97.1% (95%CI 91.7, 99.4) and the CRR by IRC 94.3% (95%CI 87.8, 97.8), with a median time to first response/first CR of 0.95 months (range: 0.6 to 3.3 months).

Response rates were consistent in most pre-specified sensitivity analyses (ORR in the Leukapheresed set: 93%, ORR Per Investigator assessment: 98.1%) and subgroup analyses, including patients with high risk factors at baseline like POD24 status, refractoriness to the last line of therapy and high LDH value at baseline.

Responses with liso-cel were generally durable: with a median follow up of 29.96 months (95%CI 24.67, 32.76), median DOR by IRC was not reached (95%CI 30.85 months, NA; range 1.9, 35.0+). Consistent results were observed in the Leukapheresed set (mDoR not reached) and in the analysis by Investigator assessment (median DoR 34.76 months).

With the limits intrinsic in indirect comparisons (ICs) in heterogeneous conditions such as FL, the results from the three IC exercises provided by the MAH are suggestive of an efficacy with liso-cel that is at least similar to that of other T cell engaging immunotherapies, including CARTs.

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.
- At the DCO of January 2024 and with a median follow-up for the 3L+ patients of 29.96 months the DOR, PFS and OS analyses were not sufficiently mature.
- Significant and clinically relevant improvements in terms of PFS/OS have been historically accepted as adequate basis to inform B/R decisions in NHLs; the interpretation of time-to-event endpoints in the absence of controls is complicated, since disentangling e.g. the impact of the intervention from the effect of heterogeneity in tumour growth rate is not possible.
- The sample size and follow-up of study FOL-001 is limited to thoroughly characterise the clinical benefit with liso-cel, especially in terms of long-term efficacy and activity in subgroups of clinical relevance. Additional efficacy data will be provided post-approval from the long-term follow-up study GC-LTFU-00, from the US-based non-interventional, RW study CA082-1175 in 3L+ R/R FL patients treated with liso-cel, and from the registry-based study JCAR017-BCM-005, which also includes EU subjects who receive liso-cel in the post-approval setting.
- The relevance of the efficacy threshold selected to claim efficacy is limited in the current treatment paradigm and contextualisation of the efficacy results for 3L+ subjects with R/R FL relies on unanchored indirect comparisons. FL presents with significant biological and clinical heterogeneity and the reliability of indirect comparison methods is based in the assumption that all factors with prognostic value are accounted for in the analysis. Such assumption is hardly acceptable in FL.
- When the “FDA algorithm” (which requires CR confirmation by bone marrow biopsy) was applied, the proportion of 3L+ subjects who achieved CR was consistently lower compared to the “primary” analysis (72.3% vs. 94.1%, respectively). Subjects with “unconfirmed CR” as per the FDA algorithm showed a trend towards shorter DoR and PFS compared to subjects with “confirmed CR”. Some degree of overestimation in the CR rate observed in the primary analysis of study FOL-001 cannot be excluded.
- Due to lack of blinding and controls, the reliability of the linear improvement in symptoms and QoL reported in study FOL-001 is uncertain.

3.4. Unfavourable effects

- Unfavourable effects of liso-cel in FL are consistent with the generally known identified risks, i.e., CRS, neurotoxicity and prolonged cytopenias.
- The most common adverse reactions of any grade were neutropenia (68%), CRS (58%), anaemia (40%), headache (29%), thrombocytopenia (29%) and constipation (21%).
- The most common serious adverse reactions were CRS (9%), aphasia (4%), febrile neutropenia (3%), pyrexia (2%) and tremor (2%).
- The most common Grade 3 or higher adverse reactions included neutropenia (61%), leukopenia (12%), lymphopenia (12%), thrombocytopenia (12%) and anaemia (10%).
- **CRS** occurred in 57.7% of patients, 0.8% of whom experienced Grade 3 CRS (no fatal events). The median time to onset was 6 days (range: 1 to 17 days) and the median duration of CRS was 3 days (range: 1 to 10 days). The most common manifestations of CRS included pyrexia (56.8%) and hypotension (13.8%). 33 of 130 (25%) patients received tocilizumab and/or a corticosteroid for CRS

after infusion of Breyanzi. Eighteen (13.8%) patients received tocilizumab only, 15 (11.5%) received tocilizumab and a corticosteroid and no patients received corticosteroids only.

- **iiNT including ICANS** occurred in 16.2% of patients receiving Breyanzi, including Grade 3 in 3.1% of patients (no fatal events). The median time to onset of the first event was 8 days (range: 4 to 16 days); 100% of all neurologic toxicities occurred within the first 8 weeks following Breyanzi infusion. The median duration of neurologic toxicities was 3 days (range: 1 to 17 days). The most common neurologic toxicities included tremor (7.7%) and aphasia (6.9%).
- **Grade 3 or higher cytopenias** present at Day 29 following Breyanzi administration, occurred in 22.3% of patients, and included thrombocytopenia (14.6%), neutropenia (15.4%) and anaemia (4.6%).
- **Grade 3 infections** occurred in 5.4% of patients.

3.5. Uncertainties and limitations about unfavourable effects

The safety database included 130 FL patients treated with liso-cel in the Study FOL-001. Generally, the spectrum of the unfavourable effects of liso-cel as a CAR-T cell product is known, and currently no major additional issues seem to arise. With a median follow up of 29.72 (min, max: 0.3, 39.6) months, no new safety concerns with liso-cel were identified in subjects with R/R 2L+ FL. However, while this period would be enough to identify the earlier and immediate AEs, there are certain potential risks for which conclusive data could not be obtained due to the limited sample size and a limited follow-up time, including the long-term safety. Additional safety data will be provided post-approval from the long-term follow-up study GC-LTFU-00, from the US-based non-interventional, RW study CA082-1175 in 3L+ R/R FL patients treated with liso-cel in the post-marketing setting, and from the registry-based study JCAR017-BCM-005, which also includes EU subjects who receive liso-cel in the post-approval setting.

3.6. Effects Table

Table 76. Effects Table for liso-cel in treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. (Data cut-off: 10-Jan-2024)

Effect	Short description	Unit	Treatment	Control (none)	Uncertainties / Strength of evidence	References
Favourable Effects						
Overall Response Rate	Best OR (CR or PR) per IRC charter based on the Lugano classification	%	Efficacy Set: 97.1% ITT Set: 93.0%	N/A	Single arm trial with limited sample size	Study FOL-001
Complete response rate	Best OR of CR per IRC charter based on the Lugano classification	%	Efficacy Set: 94.2% ITT Set: 90.4%	N/A	High rates of deep and durable responses	
Median Duration of response	Time from first response (Complete response, CR or partial	Months	Efficacy Set: N.R. ITT Set: N.R. Efficacy Set: 75.7%	N/A	Consistent results across most sensitivity analysis and pre-specified subgroups	

Effect	Short description	Unit	Treatment	Control (none)	Uncertainties / Strength of evidence	References
% of Response at 18 months	response, PR) to progressive disease or death from any cause (whichever occurs first) per IRC charter		ITT Set: 76.1%			
Unfavourable Effects						
Cytokine release syndrome		N (%)	75/130 (57.7%)	N/A	Safety profile consistent across treatment lines	Study FOL-001*
Investigator identified neurologic toxicity		N (%)	21/130 (16.2%)	N/A		
Prolonged cytopenia	≥ Grade 3	N (%)	29/130 (22.3%)	N/A		
Infections	≥ Grade 3	N (%)	7/130 (5.4%)	N/A		
Second Primary Malignancy	≥ Grade 3	N (%)	9/130 (6.9%)	N/A		
Hypogammaglobulinaemia		N (%)	7/130 (5.4%)			
Deaths	Overall deaths	N (%)	16/139 (11.5%)	N/A		
	Due to PD	N (%)	7/139 (5%)			
	Due to TEAES	N (%)	4/139 (2.9%)			

Notes: * The safety database included 130 FL patients treated with liso-cel in the Study FOL-001.

Abbreviation: N/A= not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

FL is an indolent malignancy characterised by a relapsing/remitting clinical behaviour. Despite several agents/combinations being approved for the treatment of R/R FL, drug resistance increases with each subsequent line of therapy and clinical benefit, especially in terms of long-term disease control, is reduced. Due to progressing disease in the context of widespread refractoriness or to histological transformation to aggressive LBCL, most patients with R/R FL have a reduced life expectancy compared to the general population.

Results from pivotal study FOL-001 showed that treatment with liso-cel provides a consistent and clinically relevant antitumoral effect in a setting of patients in advanced stages of relapse and with high rates of refractoriness. In particular, high rates of rapid, deep and durable responses could be observed (i.e. ORR by IRC 97.1%, CRR by IRC: 94.2%, median DOR by IRC not reached with a median follow-up of 29.96 months). Although CR rate is not a validated surrogate endpoint for long-term clinical benefit in R/R FL, depth of response has been associated with prolonged disease-free intervals in FL (see e.g. Sargent et al, JCO 2015), which are considered of relevance for patients.

The toxicity profile of liso-cel in FL is generally consistent with the known identified risks of CAR T cell therapy, i.e., CRS, neurotoxicity and prolonged cytopenias. The most common adverse reactions reported in study FOL-001 were, in fact, neutropenia (68%), CRS (58%), anaemia (40%), headache (29%), thrombocytopenia (29%) and constipation (21%). CRS and iINT were not uncommon but occurred early after treatment (100% of all neurologic toxicities occurred within the first 8 weeks following liso-cel infusion) and usually resolved within a week. Severe CRS and iINT events were uncommon and no fatal events were reported.

The main clinical uncertainties relate to the lack of control, the limited sample size (which did not allow to characterise rare adverse drug reactions nor the efficacy of liso-cel in clinically relevant subgroups) and the current follow-up that is not sufficient to fully capture the long-term benefit and risks of liso-cel, yet relevant in a chronic condition such as FL; further long-term data are expected in the post approval setting as committed by the MAH in specific safety and efficacy long term follow up studies. Although only subjects with Grade 1-3a FL (i.e. indolent or “classical” FL) could be enrolled in study FOL-001, it is noted that Breyanzi is already approved for the treatment of the more aggressive Grade 3b FL after at least 2 prior lines of therapy.

3.7.2. Balance of benefits and risks

Based on the current evidence, the overall B/R of liso-cel in the claimed indication is considered favourable, since the high rates of deep and durable responses balance the known risks associated with anti-CD19 CAR T cell therapy.

Uncertainties remain, however, due to the limited sample size, short follow-up and the uncontrolled nature of the available evidence.

3.7.3. Additional considerations on the benefit-risk balance

To better characterize the long-term clinical benefit with liso-cel in the claimed indication, and its efficacy and safety in clinically relevant subgroups, additional clinical data will be provided post-approval from the long-term follow-up study GC-LTFU-00, from a US-based non-interventional, RW study CA082-1175 in 3L+ R/R FL patients treated with liso-cel in the post-marketing setting (category 3 study in the RMP), and from the registry-based study JCAR017-BCM-005, which also includes EU subjects who receive liso-cel in the post-approval setting (category 1 study in the RMP and annex II condition).

3.8. Conclusions

The B/R of Breyanzi in the claimed indication is considered 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 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 in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	Type II	None
B.II.d.1.a	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	Type IB	None
B.II.d.1.a	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	Type IB	None
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

A grouped application consisting of:

C.I.6 (Type II): Extension of indication for Breyanzi to include treatment of adult patients with 3rd line + follicular lymphoma (FL) based on final results from the pivotal study JCAR017-FOL-001 (FOL-001, TRANSCEND-FL). This is a phase 2, open-label, single-arm, multicohort, multicenter study to evaluate efficacy and safety of JCAR017 in adult subjects with relapsed or refractory (r/r) follicular Lymphoma (FL) or marginal zone lymphoma (MZL). As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is also updated in accordance. Version 5.1 of the RMP was also submitted.

The group of variations led to amendments of the Summary of Product Characteristics, Package Leaflet and 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 Gazyvaro, Kymriah, Lunsumio and Yescarta within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Additional market protection

During the assessment for the submitted request for additional market protection, the MAH decided to withdraw the claim and this has been acknowledged.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Breyanzi -H-C-004731-II-0043G