30 March 2023
EMA/171120/2023
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/0005

Note

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

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List of abbreviations

Abbreviation	Definition
1L	first-line
2L	second-line
3L+	third-line or later
aaIPI	age-adjusted International Prognostic Index
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ANC	absolute neutrophil count
ARs	acceptable ranges
ATA	anti-therapeutic antibodies
AUC(0-28)	area under the blood concentration-time curve from time zero to 28 days after dosing
BCL2	B-cell lymphoma gene 2
BCL6	B-cell lymphoma gene 6
BMS	Bristol-Myers Squibb
BOR	best overall response
BSA	bovine serum albumin
CAR	chimeric antigen receptor
CD	cluster of differentiation
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
CLL	chronic lymphocyctic leukemia
Cmax	maximum observed blood concentration
CMAT	cryopreserved material
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COVID-19	Coronavirus disease 2019
Cox-PH	Cox Proportional-Hazards
CPV	continued process verification
CQAs	critical quality attributes

CR	complete response
CrCl	creatinine clearance
CRP	C-reactive protein
CRR	complete response rate
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTA	clinical trial authorization
CV	coefficient of variation
D	day
DLBCL	diffuse large B-cell lymphoma
ddPCR	droplet digital polymerase chain reaction
DHAP	dexamethasone, high dose cytarabine, and cisplatin
DL1D	Dose level 1 (50×10^6 CAR+ T cells), 2 dose regimen
DL1S	Dose level 1 (50×10^6 CAR+ T cells), single-dose regimen
DL2S	Dose level 2 (100×10^6 CAR+ T cells), single-dose regimen
DL3S	Dose level 3 (150×10^6 CAR+ T cells), single-dose regimen
DoCR	duration of complete response
DoR	duration of response
DP	drug product
DRB	Data Review Board
DS	drug substance
DSMB	Data Safety Monitoring Board
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EGFRt	truncated epidermal growth factor receptor
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	end of study
EU	European Union
FACS	fluorescence activated cell sorting
FBS	foetal bovine serum

FC	flow cytometry
FDA	Food and Drug Administration
FL	follicular lymphoma
FL3B	follicular lymphoma grade 3B
GCP	Good clinical practice
GDP	gemcitabine, dexamethasone, and cisplatin
GLP	Good laboratory practice
GMP	Good manufacturing practice
HD	healthy donor
HDCT	high-dose chemotherapy
HGBCL	high-grade B-cell lymphoma
HR	hazard ratio
HSA	human serum albumin
HSCT	hematopoietic stem cell transplant
HTA	Health Technology Assessment
ICS	integrated control strategy
IFNγ	interferon gamma
IgG	immunoglobulin G
iiNT	investigator-identified neurologic toxicity
IL	interleukin
IPC	in-process controls
IPI	International Prognostic Index
IRC	Independent Review Committee
ITT	intent-to-treat
IV	intravenous
IVIG	intravenous immunoglobulin
JCAR017	lisocabtagene maraleucel (liso-cel)
LBCL	large B-cell lymphoma
LD	lymphodepleting
LDC	lymphodepleting chemotherapy
LDH	lactate dehydrogenase
liso-cel	lisocabtagene maraleucel; JCAR017; BMS-986387
LOD	limit of detection

LOQ	limit of quantitation
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
LVV	lentiviral vector
M	month
MAA	Marketing Authorisation Application
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MOI	multiplicity of infection
MYC	myelocytomatosis oncogene
N/A	not applicable
NCA	National Competent Authority
NCCN	National Comprehensive Cancer Network
NE	not evaluable; not estimable
NHL	non-Hodgkin lymphoma
Non-CPPs	non-critical process parameters
NOS	not otherwise specified
NR	not reached
ORR	overall response rate
OS	overall survival
OSS	out of specification
PC	process Characterisation
PCNSL	primary central nervous system lymphoma
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMBCL	primary mediastinal large B-cell lymphoma
PPQ	process performance qualification
PQ	process qualification
PR	partial response

PT	preferred term
PV	process validation
R	randomization
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-DHAP	rituximab, dexamethasone, cytarabine, cisplatin
R-GDP	rituximab, gemcitabine, dexamethasone, cisplatin
R-ICE	rituximab, ifosfamide, carboplatin, etoposide
R/R	relapsed or refractory
RPSFT	Rank-Preserving Structural Failure Time
sAAIPI	second-line age-adjusted International Prognostic Index
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
scFv	single chain variable fragment
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	stable disease
SE	standard error
SLL	small lymphocyctic lymphoma
SmPC	Summary of Product Characteristics
SOC	standard of care
SPD	sum of the products of the perpendicular diameters
TE	transplant-eligible
TEAE	treatment-emergent adverse event
TI	transplant-intended or tolerance interval, as appropriate
TLS	tumor lysis syndrome
Tmax	time of maximum observed blood concentration
TNE	transplant-noneligible
TNI	transplant not-intended
UK	United Kingdom
US	United States
USM	Urgent Safety Measure
v1	version 1

v2	version 2
v3	version 3
v4	version 4
VCC	viable cell count
VCN	vector copy number
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 26 May 2022 an application for the following variation:

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

Extension of indication to include treatment of adult patients with Second-line (2L) Transplant Intended (TI) Large B-Cell Lymphoma (LBCL) for BREYANZI, based on interim analyses from pivotal study JCAR017-BCM-003; this is a global randomized multicentre Phase III Trial to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell Non-Hodgkin Lymphomas (TRANSFORM); 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 2.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and 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/0558/2021on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received Scientific advice from the CAT/CHMP on the design of the registrational Phase 3 Study BCM-003 (EMA/CHMP/SAWP/807614/2017).

1.2. Steps taken for the assessment of the product

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

Rapporteur: Concetta Quintarelli Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	26 May 2022
Start of procedure	18 June 2022
CAT Rapporteur's preliminary assessment report circulated on	12 August 2022
PRAC Rapporteur's preliminary assessment report circulated on	19 August 2022
PRAC Rapporteur's updated assessment report circulated on	25 August 2022
PRAC RMP advice and assessment overview adopted by PRAC on	1 September 2022
CAT Rapporteur's updated assessment report circulated on	5 September 2022
Request for supplementary information adopted by the CAT on	9 September 2022
MAH's responses submitted on	16 December 2022
CAT Rapporteur's preliminary assessment report on the MAH's responses circulated on	27 January 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	26 January 2023
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on	2 February 2023
PRAC RMP advice and assessment overview adopted by PRAC on	9 February 2023
CAT Rapporteur's updated assessment report on the MAH's responses circulated on	14 February 2023
2nd Request for supplementary information adopted by the CAT on	17 February 2023
MAH's responses submitted on	23 February 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	14 March 2023
CAT Rapporteur's preliminary assessment report on the MAH's responses circulated on	15 March 2023
PRAC RMP advice and assessment overview adopted by PRAC on	16 March 2023
CAT Rapporteur's updated assessment report on the MAH's responses circulated on	21 March 2023
CAT opinion adopted on	23 March 2023
CHMP Opinion adopted on	30 March 2023
The CAT adopted a report on similarity of Breyanzi with Yescarta, Kymriah, Minjuvi, Polivy, Gazyvaro and Lunsumio on	23 March 2023
The CHMP adopted a report on similarity of Breyanzi with Yescarta, Kymriah, Minjuvi, Polivy Gazyvaro and Lunsumio on	30 March 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Large B-cell lymphomas (LBCLs) are a heterogeneous group of aggressive non-Hodgkin lymphomas (NHLs) (Pinkerton et al, 2012; Swerdlow et al, 2016) characterised by the accumulation of malignant large B-cells in nodal and extranodal tissues. Different subtypes are characterised based on morphology, immunophenotypic features, and clinical presentation.

State the claimed therapeutic indication

Breyanzi is indicated 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 are refractory or have relapsed:

• *within 12 months of initial therapy and are candidates for autologous haematopoietic stem cell transplant (HSCT), or*

• *after two or more lines of systemic therapy.*

Epidemiology and risk factors, screening tools/prevention

Non-Hodgkin lymphomas (NHLs) can be classified based on cell of origin (B, T, or NK) and differentiation status (Swerdlow et al, 2016). In the EU, 80% to 90% of NHL cases are B-cell lymphomas (Pinkerton et al, 2012), and diffuse large B-cell lymphoma (DLBCL) is the single most common form of NHL, accounting for 30% to 40% of all NHL cases (NCCN Clinical Practice Guidelines in Oncology for B-Cell Lymphomas V.3.2022).

The incidence of DLBCL in Europe is approximately 4.92 cases per 100.000 persons per year (Sant M et al, 2010). A slight male predominance is observed, with approximately 55% of cases occurring in men. Incidence is known to increase with age, with a median age at presentation of approximately 65 years (Morton LM et al, 2006). Although the vast majority of cases are sporadic, familial aggregation has been reported, with close relatives of probands being at higher risk (~3.5-fold) of developing DLBCL or other B-cell NHLs compared to the general population (Goldin LR et al, 2005).

High-grade B-cell lymphoma (HGBCL) is a very aggressive form of large B-cell lymphoma that has been recently introduced in the 2016 revision of the WHO classification of lymphoid neoplasms. Most HGBCL cases harbour the dual rearrangement of MYC and BCL2 and/or BCL6 genes, accounting for 5% to 7% of all DLBCLs (Riedell PA et al, 2018).

Primary mediastinal large B-cell lymphoma (PMBCL) is a rare form of large B-cell lymphoma (2.4% of all NHLs) characterised by female predominance, younger age at diagnosis (onset in the third to fourth decade), and primary mediastinal involvement (Nguyen LN et al, 2000).

Follicular lymphoma grade 3B (FL3B) is a rarer subtype of follicular lymphoma (FL) that shares biologic similarities to DLBCL and, compared to low-grade FL, is characterised by an aggressive clinical behaviour.

Aetiology and pathogenesis

Environmental and genetic factors are known to contribute to the development of NHLs (Araujo LH et al, 2008) with higher incidence rates observed in subjects with chronic inflammatory diseases (e.g. Sjögren syndrome, celiac disease or rheumatoid arthritis) and congenital immunodeficiency disorders. In DLBCL, factors such as ultraviolet radiation, pesticides, and hair dye have also been potentially associated with higher risk. In addition, immunosuppression and infectious agents have also been related to the pathogenesis of DLBCL, especially HIV and EBV (Rodrigues Gouveia G et al, 2012).

The pathogenesis of DLBCL is complex and consists of a multistep process resulting in the transformation and expansion of rapidly proliferating clonal B-cells of germinal or post-germinal origin. Most DLBCLs not of germinal centre origin are categorised as "activated B cell (ABC) type", due to gene expression similarities to normal activated B cells. Although some steps in the pathway to malignant transformation have been characterised, most aspects remain unknown. Acquired genetic lesions (e.g., rearrangements of BCL6, BCL2, MYC and inactivation of p53) are commonly observed in DLBCL and may reflect the biological background of evolution from lower grade lymphomas or pre-malignant clonal expansions (see e.g. Rao PH et al, Blood 1998, Pasqualucci L et al, Nat Genet 2011).

Clinical presentation, diagnosis and prognosis

Patients with DLBCL usually present with rapidly enlarging masses, in most cases arising from lymph nodes in the neck, abdomen or mediastinum (the latter especially in PMBCL). Extranodal involvement is not uncommon, with the bone marrow involved in up to 30% of cases. Other sites that might be involved by extranodal disease include (but are not limited to) the gastrointestinal tract, the testis, bone, salivary glands, tonsil, skin, liver, breast, nasal cavity, ocular adnexa, paranasal sinuses, and central nervous system (CNS). Approximately 60 percent of patients present with advanced stage DLBCL.

Local symptoms at presentation depend on the pattern of organ involvement, while systemic "B" symptoms (i.e., fever, weight loss, drenching night sweats) have been reported in approximately 30% percent of patients.

Clinical guidelines (Tilly H et al, *Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*, 2015 and NCCN Clinical practice guidelines for B-Cell Lymphomas, v. 5.2022) recommend that the diagnosis of LBCLs should be based on surgical excision biopsy to allow for the assessment of nodal architecture and for phenotypic/molecular studies.

The assessment of the presence of MYC rearrangements in combination with BCL2/BCL6 rearrangements, and possibly other genetic abnormalities, is needed to exclude "double-hit" or "triple-hit" HGL: rearrangements of MYC/BCL2/BCL6 should be investigated by interphase FISH techniques in all newly diagnosed and relapsed patients treated with curative intent.

In the last years, genome/histology studies have supported the establishment of several pathologic entities under the umbrella term "DLBCL" that are sufficiently distinct to be considered as separate diagnostic (sub)types (Swerdlow et al, 2016), including:

- T-cell/histiocyte rich large B cell lymphoma (1-3% of all DLBCLs), defined by the presence of fewer than 10% malignant large B-cells in the setting of polyclonal T cells with or without histiocytes.
- Primary mediastinal large B cell lymphoma
- Intravascular large B cell lymphoma
- Lymphomatoid granulomatosis, an EBV-related form of large B-cell lymphoma usually involving extranodal sites (e.g. the lung) and characterised by a scarce infiltrate of EBV-positive B-cells in the midst of reactive T-cells and macrophages that make up the majority of the tumour mass
- EBV-positive DLBCL
- DLBCL associated with IRF4 rearrangements, a subtype that is predominantly seen in children and young adults and frequently involves the structures of the Waldeyer's ring and the gastrointestinal tract
- DLBCL associated with chronic inflammation

The recommended workup for LBCLs at diagnosis and at the time of relapse includes complete blood cell count (CBC), lactate dehydrogenase (LDH) and uric acid levels, a comprehensive metabolic panel, PET/CT scan +/- bone marrow biopsy for staging, echocardiogram or multigated acquisition (MUGA) scan if anthracycline or anthracenedione-based regimens are planned, and lumbar puncture in subjects at higher risk of CNS involvement.

Disease extension is usually assessed using the Ann-Arbor staging system as recently revised (Cheson BD et al, The Lugano classification. 2014), with stage I indicating that the disease is limited to one single node, group of adjacent nodes or extranodal site, and stage IV identifying extensive nodal and extranodal involvement.

Outcome in LBCL is heterogeneous and several prognostic scoring systems have been developed. The most commonly used in clinical practice is the International Prognostic Index (IPI), which includes age, performance status, serum LDH, disease stage, and number of extranodal sites as prognostic variables. The IPI distinguishes two prognostic groups among patients treated with standard immunotherapy (although it defined four groups in the pre-rituximab era). An age-adjusted IPI was developed for patients aged ≤60 years. The revised IPI (R-IPI) uses the same risk factors and scoring system as the IPI, but patients are assigned to three risk groups. The NCCN-IPI also uses the same clinical variables, but age and LDH are considered as continuous variables, rather than dichotomous, and the location of extranodal disease is used rather than the number of extranodal sites.

The cell of origin phenotype by gene expression profiling is also a major prognostic factor in DLBCL, with lymphomas arising from germinal centre faring significantly better than those with an activated B-cell phenotype. Cell of origin can also be determined by IHC but published data on the prognostic effect of immunohistochemical techniques are contradictory, also because of reproducibility issues.

Management

The frontline treatment of advanced stage DLBCL is based on the combination of anthracycline-including polychemotherapy regimens and anti-CD20 monoclonal antibodies. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) for six to eight cycles is the recommended regimen for the initial treatment of DLBCL. In a higher risk population, R-CHP plus polatuzumab has been recently shown to yield higher PFS and EFS rates compared to R-CHOP, although no survival

benefit could be demonstrated (Tilly H et al, 2022). The optimal frontline treatment of other forms of LBCL is currently unknown, and in most cases R-CHOP (or the dose-adjusted R-EPOCH variant) remains the regimen of choice. Involved field radiotherapy is sometimes used as consolidation in the case of residual masses. Approximately 60-80% of patients with DLBCL, PMBCL and FL3B (depending on age and other baseline risk factors) are expected to achieve long-term remission-cure with frontline immunochemotherapy. The outcome of HGBCL with standard immunochemotherapy is less favourable.

Approximately 10-40% of DLBCL patients are refractory (i.e. not able to achieve at least a PR) to frontline immunochemotherapy or experience disease relapse after CR was documented by PET/CT. Most relapses occur in the first two years after completing treatment, but up to one-fifth occur more than five years after treatment (Wang Y et al, 2019).

Salvage treatment with non-cross resistant chemotherapy followed by autologous hematopoietic stem cell transplant (ASCT) has long been considered the standard of care in this setting and has been associated with long-term survival/cure in approximately half of patients with first relapsed DLBCL. Subjects with DLBCL were prevalent in all studies investigating the efficacy of 2nd line salvage immunochemotherapy strategies: the extent of the efficacy of salvage regimens in LGBL histologies other than DLBCL is, therefore, uncertain, yet in the absence of dedicated options, patients with other LBCL histologies are usually treated according to the DLBCL salvage paradigm.

The role of salvage chemotherapy, usually administered for 2-3 cycles, is to reduce the burden of disease and determine residual chemosensitivity. Only subjects who achieve CR/Deauville 4 PR according to PET/CT are eligible for ASCT, since patients with inadequate response to intensive salvage therapy (i.e. with secondary refractory disease) have been shown not to benefit from transplant consolidation.

Several salvage immunochemotherapy regimens are currently available (e.g. R-DHAP [rituximab, dexamethasone, high dose cytarabine, cisplatin], R-ESHAP [rituximab, etoposide, methylprednisolone, cytarabine, cisplatin] R-GEMOX [rituximab, gemcitabine, oxaliplatin], R-ICE [rituximab, ifosfamide, carboplatin, etoposide], R-GDP [rituximab, gemcitabine, dexamethasone, cisplatin]) and none was demonstrated to be clearly superior to the others.

Tafasitamab (an anti-CD19 antibody used in combination with lenalidomide) and polatuzumab vedotin (an anti-CD79b monoclonal antibody conjugated to monomethyl auristatin E used in combination with bendamustine and rituximab) have received conditional marketing authorisation (CMA) in the EU for the treatment of patients with R/R DLBCL who are not eligible to ASCT, representing possible alternatives in the salvage setting.

Duration of initial remission has been described as a significant prognostic factor in the salvage setting: in the PARMA and CORAL studies (Guglielmi et al, 1998 and Van Den Neste et al, 2016) subjects with refractory DLBCL or early relapse after frontline chemotherapy (e.g. <12 months) showed lower ORR (14-55%) and shorter OS (mOS 4.4 months) with salvage chemotherapy +/- ASCT.

Overall, a medical need for new effective alternatives to the currently available salvage treatments can be recognized, with the aim to improve remission rates and long-term disease control/cure, especially for subjects with primary refractory or early relapsed disease.

2.1.2. About the product

Breyanzi (JCAR017, lisocabtagene maraleucel/lisocabtagene maraleucel, liso-cel ,BMS-986387), is a CD19-directed genetically modified autologous cellular immunotherapy consisting of purified CD8-positive and CD4-positive T cells in a defined (1:1) composition, that have been separately activated

and transduced with a replication incompetent lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR).

The CAR comprises an FMC63 monoclonal antibody-derived single-chain variable fragment (scFv), immunoglobulin G (IgG)4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. In addition, JCAR017 includes a non-functional truncated Epidermal Growth Factor Receptor (EGFRt) that is co-expressed on the cell surface with the CD19-specific CAR.

A single dose of JCAR017 contains a target of 100 x 10^6 (range 44-120 × 10^6) CAR-positive viable T cells consisting of a defined composition of CD8+ and CD4+ cell components:

• CD8+ cell component: Each vial contains 5.1-322 × 10^6 CAR-positive viable T cells in 4.6 mL (1.1-70 × 10^6 CAR-positive viable T cells/mL).

• CD4+ cell component: Each vial contains 5.1-322 × 10^6 CAR-positive viable T cells in 4.6 mL (1.1-70 × 10^6 CAR-positive viable T cells/mL).

More than one vial of each of the CD8+ cell component and CD4+ cell component may be needed to achieve the dose of JCAR017.

Breyanzi is currently indicated in the EU for "the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy".

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

The MAH received Scientific advice from the CAT/CHMP on the design of the registrational Phase 3 Study BCM-003 (EMA/CHMP/SAWP/807614/2017). The CAT/CHMP considered the study design of BCM-003 overall acceptable, recommending that additional subgroup analyses and sensitivity analyses for survival were conducted. Additional changes were subsequently introduced in the study protocol to address the requests received from a competent authority.

2.1.4. General comments on compliance with GCP

This submission of a Type II Variation for extension of indication includes data from Study JCAR017 BCM-003 (hereafter referred to as Study BCM-003). The MAH stated that all studies in the Breyanzi development program have been conducted in accordance with the principles of Good Clinical Practice (GCP) as defined by the International Council on Harmonisation and were conducted to meet the ethical requirement of European Directive 2001/20/EC.

2.2. Quality aspects

All clinical trial materials supporting the label expansion studies were manufactured per the approved manufacturing process (v4). No changes are being proposed to either the approved manufacturing process or to the finished product specification. Data provided in support of this application are outlined below.

Elucidation of structure and Other Characterisation

While Study 017001 pertained to patients with relapsed or refractory large B cell lymphoma (LBCL) after two or more lines of systemic therapy, Study BCM-003 pertains to LBCL patients who have failed the first line of therapy the following studies are included in this section in support of Study BCM-003:

- Phenotypic and functional Characterisation of CD8+ or CD4+ finished product components manufactured in support of Study BCM-003,

- Exploratory correlative analysis of quality attributes associations with clinical efficacy, safety, and pharmacokinetics in Study BCM-003.

- **CD8+ and CD4+ cell component (2L LBCL)**

The CD8+ finished product component enriches for less differentiated T cells and reduces the presence of terminally differentiated and T cell populations. On the other hand, the CD4+ finished product component memory composition is influenced by the selected material composition.

Variance Component Analysis Results for Finished product Components' Attributes demonstrates that the phenotypic and functional variations in T cell states observed in finished product components are primarily driven by patient/donor heterogeneity.

Exploratory correlative analyses were performed to identify the finished product quality attributes that demonstrate potential effects on or informative relationships to clinical safety, clinical efficacy, and/or pharmacokinetic outcomes. The correlative analyses examine quality attributes associated with product release specifications and Characterisation testing used to define the phenotypic and functional features associated with T cells in the finished product components.

The analysis cohort used in the correlative analysis comprises the liso-cel Treated Analysis Set (Arm B) manufactured using the approved process (v4), which includes subjects with histology of diffuse large B cell lymphoma, not otherwise specified (de novo or transformed from indolent lymphoma, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, T cell/histocyte-rich B cell lymphoma, and follicular lymphoma grade 3B failing one prior line of therapy. All included finished product lots conformed to product release specifications at the time of manufacture.

Only Infused (Y), Conforming (Y) lots from the "Arm B Day 29" Cohort of Study BCM-003 were included in the Clinical-Endpoint × CMC Product Quality-Attribute correlative analyses reported herein (both CD8+ and CD4+ finished product components would have to be conforming). For phenotypic/functional Characterisations and inter-attribute correlation studies, all Conforming (Y) finished product lots, and their associated selected T cell materials (where applicable depending on material availability for extended Characterisation testing) from all manufactured cohorts in Study BCM-003 were analysed.

Statistical assessments of correlative relationships between finished product component quality attributes release and characterisation) and clinical endpoints utilised Wilcoxon rank-sum, linear regression, and Cox-regression analyses to evaluate relationships with binary, continuous, and time-to-event clinical endpoint measurements has been presented. The presence of correlative relationships or potential correlative relationships were determined based on nominal p-values and standardised effect sizes, correlation coefficients, or hazard ratios, depending on the analyses used. Nominal p-values describe the statistical significance of correlative relationships, whereas the standardised effect sizes, correlation coefficients, and hazard ratios describe the magnitude and directionality of correlative relationships.

Wilcoxon rank-sum statistical analyses (non-parametric) were used to evaluate the significance of correlations between continuous quality attributes and categorical clinical endpoints. The nominal p-values from the Wilcoxon rank-sum tests were used to sort the statistical significance of the association between continuous quality attributes and categorical clinical endpoints. The standardised effect size

(parametric) between two groups, calculated as the absolute value of the difference in sample means divided by the pooled standard deviation, was used to determine if the magnitude of an attribute shift is practically meaningful.

Parametric and non-parametric correlations were used to evaluate the strength and directionality of relationships between continuous quality attributes and continuous clinical endpoints. Spearman rank-order correlation coefficients (ρ [rho]) were provided to inform magnitude and directionality of correlations between quality attributes and clinical endpoints. The nominal p-values from regression analyses were used to evaluate whether the correlation coefficients were significantly different than zero. Natural log-transformation of select clinical endpoints was required to achieve normal distributions of the response variables and improve capacity for estimating effect sizes for potential relationships between quality attributes and clinical endpoints.

Cox-regression analyses were used to evaluate the relationships between continuous quality attribute variations and time-to-event clinical endpoints. Specifically, the Cox-regression coefficients (or hazard ratios, HR) informed the effect of quality attribute variations (e.g., measured in units of standard deviation) on the hazard of an event (e.g., progression; death; failure to achieve a complete response (CR) or partial response (PR) by 9 weeks post randomization; or start of a new anti-neoplastic therapy due to efficacy concerns).

HR = 1, increases in the quality attribute are not associated with hazard of an event occurrence.

HR > 1, increases in the quality attribute are associated with increased hazard of an event occurrence.

HR < 1, increases in the quality attribute are associated with decreased hazard of an event occurrence.

Nominal p-values from the Cox-regression analyses were used to evaluate whether the HRs are significantly different than 1 and to rank quality attributes correlations with time-to-event outcomes in order of statistical significance.

Corrections for multiple comparisons were not included in univariate statistical analyses. Although the absence of adjustments for multiple comparisons increases the potential for type I error in the assessment (rejecting the null hypothesis (i.e., no correlative relationship exists) for associations that are null), given that many of the attribute measurements included in the correlative analysis are biologically and/or technically interrelated, correcting for multiple comparisons would increase the potential for type II error (accepting the null hypothesis for associations that are not null) during interpretation of the correlative outputs.

P-values were used as tools to help rank attribute correlations with clinical efficacy, safety, and pharmacokinetics. Standardised effect size, correlation coefficients, or hazard ratios were then used to determine the presence of correlative or potential correlative relationships. Finally, interdisciplinary subject matter experts evaluated the practical significance of correlations and potential correlations using biological first principles and considering the range of quality attribute values observed as well as technical method capabilities.

For the CD8+ finished product component, a summary of the Correlative Analyses of Product Quality Attributes and Clinical Endpoints has been provided. It is shown that no statistically significant correlations between CD8+ finished product component quality attributes and clinical safety outcomes are observed, while the exploratory finished product correlative analysis identifies correlative relationships between some CD8+ finished product component quality attributes and clinical efficacy and/or PK outcomes in Study BCM-003.

For both product components, a summary of the Correlative Analyses of Product Quality Attributes and Clinical Endpoints has been provided. It is shown that several T cell attributes in the drug product exhibit

statistically significant correlative relationships with clinical efficacy or pharmacokinetic outcomes, respectively.

Definitive conclusions could not be made regarding the biological impact of the observed variability in these attributes. Therefore, no definitive correlations are inferred from these analyses for the ranges experienced in Study-BCM-003. These exploratory analyses are post hoc and hypothesis-generating, and signal detection methods may be confounded by multiplicity.

One such T cell attribute was considered for further correlation analyses. Taken together, the MAH's results suggest variance in this T cell attribute is likely due to patient-intrinsic factors.

Exploratory multivariable analysis was performed to rule out potentially confounding factors like patient baseline characteristics. The following baseline factors were considered in multivariable analyses (in this context, "baseline" means randomization timepoint).

Explored Potentially, Confounding Variable:

- Age (continuous variable)
- Sex (F vs M)
- Eastern Cooperative Oncology Group (ECOG) Score (0 vs 1)
- Disease status (Relapsed vs Refractory)
- Secondary Age-Adjusted International Prognostic Index (sAAIPI score; 0/1 vs. 2/3)
- Lactate Dehydrogenase Serum Levels (LDH, continuous variable)
- Tumor Burden (Sum of Perpendicular Diameters, SPD, continuous variable)

Stepwise regression procedure was used for variable selection in the final model.

Exploratory multivariate analyses adjusting for patient baseline characteristics (age, sex, ECOG, relapsed or refractory disease status, sAAIPI score, LDH, and SPD) confirm the univariate results and reveal a statistically significant relationship with PFS as well.

Consistent with correlative analysis results, equal-splitting, quartile-based analysis demonstrates potential correlations between the discussed T cell attribute and EFS and PFS. No significant differences in quartile correlations with duration of response (DOR) were observed.

Notably, all analyses demonstrate that even the highest levels of this T cell attribute improved benefit in median EFS is observed in the liso-cel arm over the standard-of-care arm in Study BCM-003 (2.3 months median EFS).

The significance of the correlative analysis finding and how it informs the finished product integrated control strategy for second-line, transplant-eligible was discussed.

3.2.P.2.3 Manufacturing Process Development (Process)

- **CD8+ cell component/CD4+ cell component (2L LBCL)**

All information and data presented in for 3L LBCL, is applicable to 2L, except the following:

- The Healthy Donor Leukapheresis Product was reassessed for 2L TI to confirm that process Characterisation results are still relevant to this patient population.

2L Healthy Donor Leukapheresis Product Assessment

An assessment was performed comparing quality attributes of the finished product components manufactured from healthy donor leukapheresis product and 2L patient leukapheresis product. Each quality attribute was compared using a three-tiered analysis approach.

Results indicate that the finished product v4 manufacturing process produces similar finished product when using leukapheresis from patients or healthy donors as all attributes passed at least one of the three analyses.

In terms of visual assessments (tier III), the side-by-side plots of the data points show no strong evidence that a biologically relevant difference exists, and the range of outcomes observed for patient leukapheresis product is clearly represented by the range of outcomes observed with healthy donor leukapheresis product.

Quantitative Threshold for Surrogate Attribute

A quantitative threshold was established to objectively identify meaningful effects of process characterisation parameters on the chosen surrogate attribute. Effect sizes across the evaluated range greater than the threshold were considered to have a large impact on this attribute.

Process Characterisation Impact to Surrogate Attribute Results

Process characterisation results were used to develop statistical process models of the surrogate attribute. Models were used to identify parameters with statistically significantly ($p < 0.05$) effects on the attribute of interest when varied across the evaluated ranges.

Two parameters had a statistically significant impact on the surrogate attribute.

However, both parameters were previously identified as CPPs. No new CPPs were identified based on the described analysis as other evaluated parameters did not have large, statistically significant effects on any of the studied T cell attributes.

Process Validation Assessment for 2L

The process validation strategy for the finished product is based on a lifecycle approach. There is no impact to the validated state of the process for 2L as there are no changes to finished product specification or process controls from the Original Application.

☐ A Leukapheresis Product Variability Assessment was performed using PPQ data to quantify variability inherent in the finished product quality attributes relevant to the indication. This assessment supports the conclusions that the finished product manufacturing process and PPQ campaigns are well controlled for the studied T cell attributes.

☐ Quality Attribute Criticality Assessment was performed to identify and categorise quality attributes of the finished product for the 2L TI patient population.

A T cell attribute was classified as a CQA in the 2L setting due to correlations with clinical efficacy outcomes.

Manufacturing Process Development (Integrated Control Strategy)

- **CD8+ cell component/CD4+ cell component (2L LBCL)**

As far as the Integrated Control Strategy (ICS) was concerned, the methodology described in the original Application was unchanged and was applied to Study BCM-003.

A T cell attribute has been identified as a CQA of the finished product for 2L patients, in part based on the strong correlations observed this attribute in one of the two cell components and clinical efficacy outcomes in 2L patients.

The predominant contribution to variance in this attribute derives from inter-patient heterogeneity. The results strongly demonstrate that this T cell attribute is an intrinsic feature of the patients' starting

materials. The T-cell attribute is in a state of control and the process parameters adequately ensure that this attribute remains controlled throughout manufacturing.

In accordance with the Integrated Control Strategy (ICS), to minimise residual risk characterisation data for this T cell attribute will be monitored to demonstrate this attribute remains controlled commercially, thus maintaining the major source of variance in this attribute as due to inter-patient heterogeneity as was observed clinically.

Despite the observation that this attribute correlates with clinical efficacy in 2L patients, favourable outcomes in which improved benefit or at least statistically equivalent outcomes are still observed over the standard-of-care (SOC), even in patients with the highest levels of this T cell attribute as observed in Study BCM-003.

Overall, these results further justify the control strategy that would not exclude patients based on attributes that reflect patient-intrinsic factors and that are not targeted outcomes of any particular unit operation.

Batch analyses

CD8+ cell component/CD4+ cell component (2L LBCL)

Information on lots of finished product (CD8+ components and CD4+ components) that were manufactured to support clinical trial BCM-003 has been provided.

Lots were manufactured by the approved process v4. Lot information (lot number, date of manufacture and vector information) and results from release testing has been provided.

The batch analysis data has been presented in a tabular format.

Justification of specification

CD8+ cell component/CD4+ cell component (2L LBCL)

The approved commercial finished product manufacturing process and container closure are the same for all liso-cel finished product lots.

The acceptance criteria established in the commercial specification of the finished product considered data that were acquired from finished product component lots manufactured under GMP conditions using patient leukapheresis in the manufacturing process v4.

The acceptance criteria established in the commercial specification is based on statistical analyses of data acquired with the commercial analytical procedures which considered the full range of quality attribute experience gained. The data were statistically analysed by two approaches.

- the full range of quality attribute experience were determined with a consideration for the capability of the analytical procedure (i.e., measurement uncertainty). This is justified by the consistent safety and efficacy of finished product across the range of quality attribute experience gained with the commercial process at the commercial target dose and the contribution of interpatient heterogeneity.
- tolerance intervals were calculated based on process capability after statistical outliers were removed from the dataset.

Methodology

The statistical analyses involved first determining the range of experience that has been observed for each attribute (i.e., min/max). Next, the measurement uncertainty for this range of experience was determined based on the validated performance of the analytical procedure (i.e., intermediate precision). Next, statistical outliers were removed and the most appropriate distribution fit for the observed data

were determined, and finally parametric tolerance intervals were calculated based on the chosen statistical distribution model of the observed data. All calculations were performed using JMP 14 and 15 from SAS Institute (JMP).

In terms of results, the authorised release specification test panel remains completely unchanged, and therefore no further consideration from the Applicant's position is reported in this section in terms of justification of acceptance criteria.

In response to a request for supplementary information, the MAH clarified that the proposed control strategy indeed include a limit for monitoring characterisation data of the new CQA. The proposed limit is based on manufacturing experience observed during clinical studies of large B cell lymphoma (LBCL) patients including Study BCM-003 (second-line transplant-intended, 2L) and Study 017001/BCM-001 (third-line or more, 3L+). An additional assessment is provided from 3L+ LBCL clinical lots and commercial Breyanzi lots manufactured over the span of 12 months. These data clearly demonstrate that the new CQA is well-controlled in the commercial setting.

In response to a second Request for Supplementary Information, the MAH agreed to set a revised limit for monitoring the new CQA. The MAH committed to continuously monitor this limit until more and relevant experience is gained, after which an appropriate variation procedure may be initiated to request revision of this limit.

2.2.1. Discussion on quality aspects

The MAH has conducted study BCM-003 to extend Breyanzi's indication to the 2L setting. In support of this study, a reduced quality data package was submitted to account for potential differences in the phenotypic or functional characteristics of the starting material/finished product and the clinical response to the finished product itself, in 2L patients as compared to 3L ones. The quality data submitted does not highlight any remarkable differences or give raise to any further considerations, as compared to the initial MA assessment performed for Breyanzi. Also, the approved manufacturing process (v4) remains unchanged (with a very low rate of OOS), no new CPPs were identified and even the approved release specification acceptance criteria are unaffected when re-evaluated across 3 clinical studies (i.e., study 017001, BCM-001 and BCM-003) conducted in two Continents (US and EU) in two different indications (3L+ and 2L).

One relevant exception observed only for one of the two cell components in the 2L setting (and not in the authorised 3L+ setting), is represented by a T cell attribute that emerged as a specific feature of the patients. According to the correlation analyses conducted, this T cell attribute shows negligible inter-quality attributes correlations. On the other hand, a correlation between this attribute and efficacy profile was highlighted with relevant efficacy clinical outcomes. Yet, across the entire clinical range of this T cell attribute including the worst-case scenario of highest quartile, there is no clear signal pointing towards significantly reduced efficacy of Breyanzi vs the comparator and Breyanzi is still favoured over the SOC treatment in the 2L setting as informed by the data submitted. Therefore, the MAH proposal to classify this T cell attribute as a new CQA due to its impact on the product's efficacy profile, has been regarded as appropriate particularly to avoid unnecessary restrictions to the treatment with Breyanzi due to intrinsic features of 2L patients.

With the aim to gain further knowledge on this specific aspect of the 2L treatment with Breyanzi and the potential impact thereof, in the context of a post-approval recommendation (REC), the MAH agrees to monitor the T cell attribute for the 2L finished product batches.

2.2.2. Conclusion on the quality aspects

In conclusion, the quality dossier submitted in support of Breyanzi's 2L extension of indication does not give raise to concern and may be deemed as approvable. However, the MAH is recommended to continuously monitor the aforementioned T cell attribute according to the agreed limit and to initiate an investigation and a risk assessment in case this limit is exceeded with the aim to document and assess the potential impact thereof. (**REC**).

2.3. Non-clinical aspects

With respect to the previous JCAR017 product assessment (see published EPAR), four additional reports in the Pharmacodynamic Drug Interations section have been presented, that relate to the evaluation of the enhanced activity of JCAR017 by the combination with agents currently under clinical development for the treatment of B-cell lymphomas.

The relevance of these NC studies on the requested extension of indication for Breyanzi is limited. Therefore, no specific data are going to be discussed in this report.

2.3.1. Ecotoxicity/environmental risk assessment

The original ERA for Breyanzi (included in the MAA dossier) concluded that the risk to people and the environment from placing liso-cel on the market is negligible and the applicant indicate that this Type II extension of indication variation in 2L LBCL, to include 2L patients, does not change of the environmental risk of liso-cel.

2.3.2. Conclusion on the non-clinical aspects

In conclusion, the additional NC reports submitted in support of Breyanzi's 2L extension of indication does not give raise to concern but they are not considered relevant for this application.

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of lisocabtagene maraleucel.

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 2. Summary of Liso-cel Clinical Program in Second-Line Large B-cell Lymphoma with Data Included in this Submission

Study Phase	Population	Design	Efficacy Endpoints	Test Drugs and Dose	Number of Subjects Randomized
Pivotal Study					
JCAR017-BCM-003 Phase 3	Adults with transplant-eligible relapsed or refractory LBCL	Global, randomized, multicenter trial to compare the efficacy and safety of liso-cel to standard of care (salvage immunochemotherapy followed by high-dose chemotherapy [HDCT] and hematopoietic stem-cell transplant [HSCT]) in adult subjects with transplant-eligible relapsed or refractory LBCL	**Primary:** Event-free Survival (EFS) **Key Secondary:** Complete response rate (CRR), progression-free survival (PFS), and overall survival (OS) **Other Secondary:** Overall response rate (ORR), duration of response (DoR), PFS on next line of treatment (PFS-2), EFS rate, PFS rate, and OS rate	Liso-cel Arm: Lymphodepleting chemotherapy (fludarabine intravenous [IV] [30 mg/m^2/day for 3 days] and cyclophosphamide IV (300 mg/m^2/day for 3 days) followed by infusion of 100 × 10^6 JCAR017-positive viable transduced T cells. Bridging therapy with one of the protocol-defined salvage immunochemotherapy regimens was allowed for disease control while liso-cel was being manufactured if deemed necessary. Standard of Care Arm: Salvage immunochemotherapy (rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP]; rituximab, ifosfamide, etoposide, and carboplatin [R-ICE]; or rituximab, dexamethasone, gemcitabine, and cisplatin [R-GDP]) for three 21-day cycles followed by HDCT and HSCT.	184

2.4.2. Pharmacokinetics

The clinical pharmacology profile of liso-cel in subjects with 2L LBCL has been characterized based on the results obtained from clinical study BCM-003, a global randomized multicenter Phase 3 trial to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell non-Hodgkin lymphomas (TRANSFORM).
A clinical pharmacology report BMS-98638 for study BCM-003 was submitted in the context of this variation. The clinical pharmacology programme included:

- Characterisation of the PK profile of liso-cel as assessed by droplet digital polymerase chain reaction (ddPCR) and by flow cytometry (liso-cel arm and SOC arm post-cross over).
- Evaluation of the pharmacodynamic markers of liso-cel, including B-cell aplasia and soluble biomarkers such as chemokines and cytokines (liso-cel arm and SOC arm post-cross over).
- Evaluation of the immune responses directed against liso-cel (liso-cel arm and SOC arm post-cross over).
- Evaluation of the relationship between PK endpoints as assessed by ddPCR and by flow cytometry with select efficacy and safety endpoints in subjects receiving liso-cel.
- Evaluation of the relationship between PK endpoints as assessed by ddPCR with select baseline demographic and disease characteristics in subjects receiving liso-cel.
- Evaluation of the relationship between pharmacodynamic biomarker endpoints with select safety endpoints in subjects receiving liso-cel.
- Evaluation of the relationship between immunogenicity endpoints and select efficacy, safety, and PK endpoints as assessed by ddPCR in subjects receiving liso-cel.

Table 3: Summary of Studies Contributing to the Clinical Pharmacology of Liso-cel

Study (Region)	Design	Study Population	Number of Subjects Randomized	Dosing	PCR PK Sampling Timepoints
Study BCM-003 (TRANSFORM) Ongoing (cutoff date: 08-Mar-2021)	Phase 3, randomized, open-label, parallel-group, multi-center trial to determine the efficacy and safety of liso-cel compared to the standard of care (SOC)	Adults eligible for autologous HSCT with relapsed or refractory aggressive B-cell non-Hodgkin lymphomas (NHL) after 1 prior systemic therapy	Arm B (liso-cel Arm): 92 Arm A (SOC Arm): 92	Arm B (liso-cel Arm): Lymphodepleting chemotherapy (fludarabine IV [30 mg/m2/day for 3 days] and cyclophosphamide IV (300 mg/m2/day for 3 days) followed by infusion of 100 × 10^6 liso-cel-positive viable transduced T cells. Bridging therapy with one of the protocol-defined SOC regimens was allowed for disease control while liso-cel was being manufactured if deemed necessary. Arm A (SOC Arm): Salvage immunochemotherapy (rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP]; rituximab, ifosfamide, etoposide, and carboplatin [R-ICE]; or rituximab, dexamethasone, gemcitabine, and cisplatin [R-GDP]) for 3 21-day cycles followed by high-dose chemotherapy and hematopoietic stem cell transplant (HSCT).	Arm B (liso-cel Arm): Screening, Days 29 (pre-infusion), 32, 36, 39, 43, 50, 64, 71, 85, 126, Month 6, 9, 12, 18, 24 and 36 (End of study [EOS] or early termination [ET]) Crossover Group (Arm A post-crossover): Pre-treatment, Days 1 (pre-infusion), 3, 4, 8, 11, 15, 22, 29, Month 2, 3, 6, 9, and 12

Methods

The PK of liso-cel were determined using 2 validated methods:
- **ddPCR** to detect the liso-cel transgene in blood through quantitation of the target viral genomic sequence of gag, that codifies for lentivirus structural proteins and is found in all the lentiviral vectors.
- **Flow cytometry** to enumerate CAR+ T cell subsets via detection of the EGFRt (ie, CD3+ EGFRt+, CD8+ EGFRt+, and CD4+ EGFRt+) in blood. Truncated EGFR (EGFRt) was co-expressed with the CAR and considered a surrogate marker of CAR expression.

In Arm B, PK sampling for ddPCR was performed at Day 29 (pre-infusion), Day 32, 36, 39, 43, 50, 64, 71, 85, 126, Month 6, 9, 12, 24, 36; for flow cytometry sampling was performed at Day 29 (pre-infusion), Day 32, 36, 43, 50, 64, 85. A similar sampling was performed in Arm A, including patients crossed-over to liso-cel. In Arm B, PK data was available for 87 out of 92 patients (ddPCR data) and 84 out of 92 patients (flow cytometry data); In Arm A, PK data was available for 45 out of 50 patients (ddPCR data) and 44 out of 50 patients (flow cytometry data).

For pharmacodynamic assessment, CD19+ B cells in peripheral blood were enumerated by validated flow cytometry.
Soluble biomarkers were analyzed using multiplex MSD electrochemiluminiscence (ECL) validated immunoassays; serum Ig, CRP, and ferritin were measured at the central laboratory.

Immunogenicity was assessed by measuring ATA in serum with an electrochemiluminescence immunoassay.

Table 4. Methods Validation

Assessment	Data Cut-off Date	Laboratory	Status
PK Assessments			
ddPCR (transgene vector sequences)	08-Mar-2021	MolecularMD (Seattle, WA)	Validated
Flow cytometry data acquisition (EGFRt+ T cell subsets)	08-Mar-2021	Charles River Laboratories (Reno, NV, USA for American Sites and Edinburgh, UK for European Sites)	Validated
Analysis of acquired flow cytometry data	08-Mar-2021	Charles River Laboratories (Edinburgh, UK)	Validated
Pharmacodynamic Assessments			
Flow cytometry (B-cell enumeration)	08-Mar-2021	Charles River Laboratories (Reno, NV, USA for American Sites and Edinburgh, UK for European Sites)	Validated
MSD-ECL Immunoassay (Soluble biomarkers)	08-Mar-2021	BioAgilytix, (Boston, MA)	Validated
Serum Ig, CRP, ferritin	08-Mar-2021	Labcorp (Indianapolis, IN, USA and Geneva, CH)	Validated
Immunogenicity Assessments			
Electrochemiluminescence immunoassay (ATA)	08-Mar-2021	Charles River Laboratories (Reno, NV)	Validated

Pharmacokinetics assessment

Assessments of liso-cel PK were determined by ddPCR to detect vector sequences and by flow cytometry (CD3+ EGFRt+, CD8+ EGFRt+, and CD4+ EGFRt+ T-cells) to enumerate and immunophenotype liso-cel cells. The flow cytometry was considered supportive. Pharmacokinetics by flow cytometry was not done at Japanese sites.

Noncompartmental PK parameters such as Cmax, Tmax and AUC(0-28) were calculated for subjects who had PK measurement 28 days after infusion or later. Persistence of liso-cel transgene in blood was assessed by ddPCR and defined as a transgene count greater than or equal to the LOD of 40 copies/µg.

For flow cytometry, persistence is defined as CD3+ EGFRt+ T cell count greater than or equal to the LOD of 0.1 cells/µL, with at least 25 events captured in the EGFRt flow cytometry detection gate. Persistence of CD4+ EGFRt+ and CD8+ EGFRt+ T cells at each available time point is similarly defined. For both assays, data obtained after the start of a new anti-cancer therapy are not included in the determination of persistence. All PK data, including persistence were summarized descriptively.

The PK analysis set included all subjects who took conforming liso-cel study treatment who have both pre-infusion and at least one post-infusion PK measurement. One subject in the liso-cel arm and one subject from the SOC arm who crossed-over to receive liso-cel, received nonconforming product.

The samples were collected (for PK, PD and immunogenicity) at the following time-points for arm B (note that Day 29 correspond to the infusion day):

Table 5. time point for samples collection

		Treatment Period																	Post-Treatment Period		Survival Follow-up
	Screening	Random-ization	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Follow-up Period		
Study Month	-	-	-	-	-	1	-	-	-	-	-	-	-	-	3	-	-	-	6	9, 12, 18, 24 and 36 (EOS or ET)	-
Study Week	-	-	-	-	3	-	-	-	-	-	6	-	9	-	-	-	-	18	-	-	-
Study Day	-28 to -1	1	8	15	22	29	31[b]	32[b]	36	39[b]	43	50	64	71	85	99	106[a]	126	-	-	q3m
Visit Window (days)	-	+3	± 2	± 2	± 7	± 7	± 1	±1	±1	±1	±6	±2	± 6	± 6	± 6	± 7	± 7	± 7	± 10	± 14	± 30
Peripheral blood sample for JCAR017 PK by flow cytometry[x]	x	-	-	-	-	x[b,v]	-	x	x[b]	-	x[b]	x[b]	x[b]	-	x[b]	-	-	-	-	-	-
Peripheral blood sample for viral vector sequence PK by ddPCR	x	-	-	-	-	x[b,v]	-	x	x[b]	x	x[b]	x[b]	x[b]	x[b]	x[b]	-	-	x[b]	x[b]	x[b]	-
Peripheral Blood Sample for Flow Cytometry (B-cell aplasia)	x	-	-	-	-	x[b] pre-infusion	-	-	x[b]	-	x[b]	x[b]	x[b]	-	x[b]	-	-	x[b]	x[b]	x[b] M12, M18, M24, M36	-
Peripheral blood sample for immunogenicity to JCAR017 (serum)	x	-	-	-	-	-	-	-	-	-	x[b]	-	x[b]	-	x[b]	-	-	x[b]	-	x[b] M36	-
Peripheral blood sample for immunogenicity to JCAR017 (PBMC)	x	-	-	-	-	-	-	-	-	-	x[b]	-	x[b]	-	x[b]	-	-	x[b]	-	x[b] M36	-

b- Only for subject randomized to Arm B. Day 39 visit was mandatory and could not be combined with Day 43 visit. v- To be performed pre-infusion.

Table 6. Total Events for Subjects from Arm A Who Crossover to JCAR017

		Treatment Period										Post-Treatment Period					Survival Follow-up
	Pre-Treat-ment Evalua-tion	LDC	JCAR017 Infusion									Follow-up					
Study Month	-	-	-	-	-	-	-	-	-	-	1	2	3	6	9	12	
Study Day	Within 7 Days Before LDC	Start 5 to 10 Days Before Day 1	1	2	3	4	8	11	15	22	29	-	-	-	-	(EOS or ET)	q3m
Visit Window (Days)	-	-	-	-	-	+1	±1	±1	±2	±2	±2	±14	±14	±14	±14	±30	±30
Peripheral blood sample for immunogenicity to JCAR017 (serum)	x	-	-	-	-	-	-	-	x	-	x	x	x	-	-	x	-
Peripheral blood sample for immunogenicity to JCAR017 (PBMC)	x	-	-	-	-	-	-	-	x	-	x	x	x	-	-	x	-
Peripheral blood sample for JCAR017 PK by flow cytometry[i]	x		x (pre-infusion)			x	x	x	x	x	x	x					
Peripheral blood sample for viral vector sequence PK by ddPCR	x	-	x (pre-infusion)		x	x	x	x	x	x	x	x	x	x	x	x	-
Peripheral blood sample for flow cytometry (B-cell aplasia)	x	-	x (pre-infusion)	-	-	-	x	-	x	x	x	x	x	x	x	x	-

The analysis set was the following:

Table 7. Analysis Populations

Analysis Populations

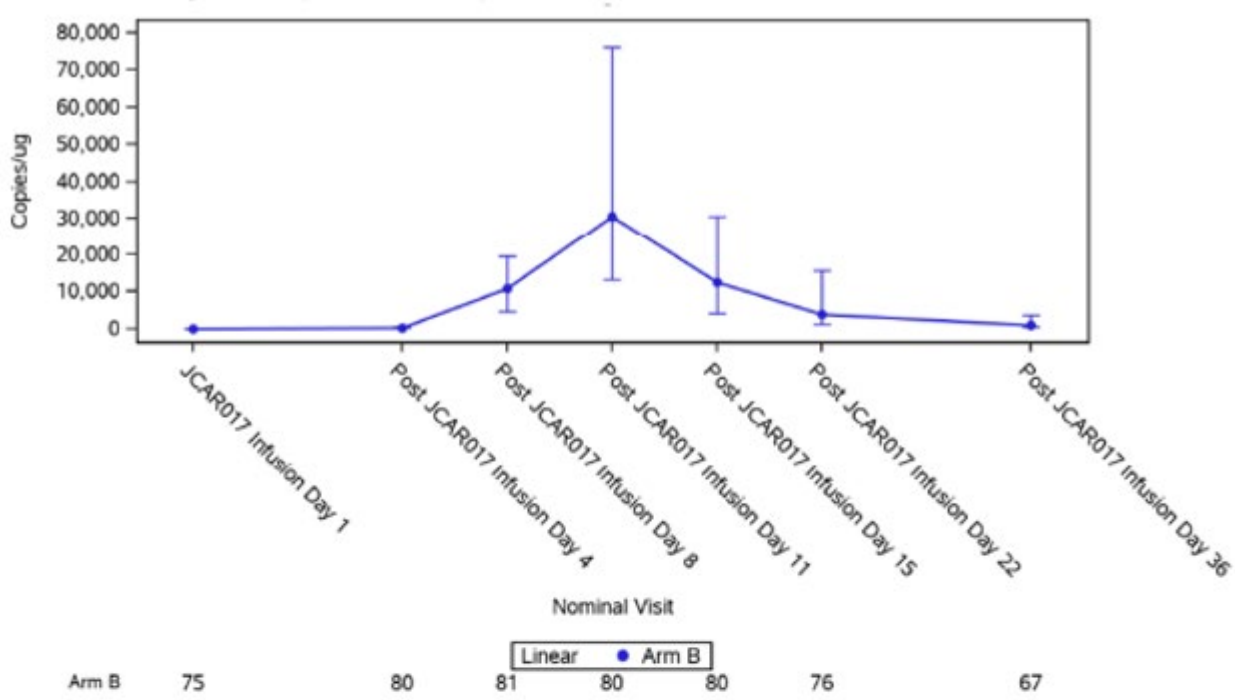
Population	SOC Arm n (%)	Liso-cel Arm n (%)	Total [a] n (%)	SOC Arm Post-cross Over n (%)
Intent-to-treat Analysis Set [b]	92 (100)	92 (100)	184 (100)	50 (100)
Per-protocol Analysis Set [c]	89 (96.7)	88 (95.7)	177 (96.2)	47 (94.0)
Safety Analysis Set [d]	91 (98.9)	92 (100)	183 (99.5)	47 (94.0)
Pharmacokinetic Analysis Set - Conforming Product [e]				
ddPCR Pharmacokinetic Analysis Set	-	87 (94.6)	-	45 (90.0)
Flow Cytometry Pharmacokinetic Analysis Set	-	84 (91.3)	-	44 (88.0)
Pharmacokinetic Analysis Set - Nonconforming Product [f]				
ddPCR Pharmacokinetic Analysis Set	-	1 (1.1)	-	1 (2.0)
Flow Cytometry Pharmacokinetic Analysis Set	-	1 (1.1)	-	1 (2.0)

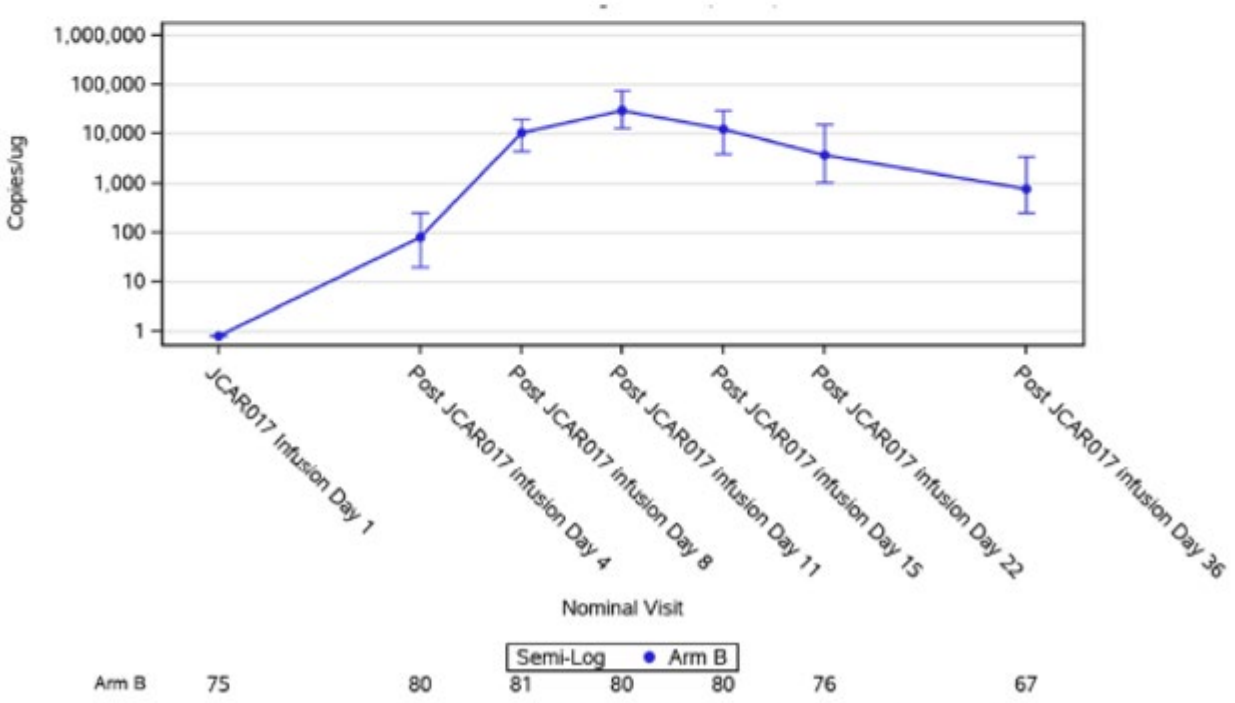
Results

The PK analyses were based on ddPCR. PK assessments by flow cytometry (CD3+ EGFRt+, CD8+ EGFRt+, and CD4+ EGFRt+ T-cells) were considered supportive data that allow for the evaluation of PK parameters per drug product component.

Following infusion, the liso-cel concentration in the peripheral blood detected by ddPCR (validation limit range of 8 copies/400ng to 720000 copies/400ng) in the liso-cel arm exhibited a rapid expansion followed by a monophasic decline up to 35 days after infusion (Figure 2). Nominal visits based on day of liso-cel infusion were used for the summary of the liso-cel concentration (eg, Visit JCAR017 Infusion Day 1 corresponds to Study Day 29).

Figure 2. Median [Q1,Q3] ddPCR-based Lios-cel Concentrations in Peripheral Blood Time Profiles (Linear and Semi-log Scales) – ddPCR PK Analysis Set (Liso-cel Arm)





Only the nominal visits up to Visit Post JCAR017 Infusion Day 36 are displayed in this figure.

The median liso-cel transgene level versus time profiles for the SOC Arm post-cross over were similar to those observed for the liso-cel arm B (Table 8).

Table 8. Summary of JCAR017in Peripheral Blood Detected by ddPCR by Nominal Timepoints ddPCR PK Analysis Set (Conforming Product)

	Nominal Timepoint	JCAR017 Concentration (copies/ug) n	Mean	StD	Min	Q1	Median	Q3	Max	CV%	Geometric Mean [a]	Geometric CV% [b]
Arm B (N = 87)	JCAR017 Infusion Day 1	75	0.00	0.000	0.0	0.00	0.00	0.00	0.0	NA	NA	NA
	Post JCAR017 Infusion Day 4	80	300.05	769.179	20.0	20.00	81.35	253.58	6468.8	256.35	93.33	264.93
	Post JCAR017 Infusion Day 8	81	25261.99	48413.349	20.0	4380.01	10623.19	19511.94	334242.7	191.65	8908.21	364.23
	Post JCAR017 Infusion Day 11	80	53697.53	60313.055	213.7	13093.22	30482.80	76114.95	287500.0	112.32	26899.84	245.01
	Post JCAR017 Infusion Day 15	80	29375.39	53377.051	405.8	3942.68	12552.15	30560.28	342851.6	181.71	11349.72	257.82
	Post JCAR017 Infusion Day 22	76	30942.25	82523.674	20.0	1030.48	3735.58	15576.78	475990.7	266.70	4024.67	982.08
	Post JCAR017 Infusion Day 36	67	8447.67	28646.097	20.0	253.86	771.07	3495.68	177803.3	339.10	909.17	878.90
	Post JCAR017 Infusion Day 43	61	3568.01	15171.414	20.0	123.69	355.47	1254.48	110923.9	425.21	380.34	623.09

	Nominal Timepoint	JCAR017 Concentration (copies/ug) n	Mean	StD	Min	Q1	Median	Q3	Max	CV%	Geometric Mean [a]	Geometric CV% [b]
Arm B (N = 87)	Post JCAR017 Infusion Month 2	67	1797.83	7489.605	20.0	20.00	212.90	382.18	44824.9	416.59	158.69	624.43
	Post JCAR017 Infusion Month 3	59	837.09	3959.101	20.0	20.00	58.93	208.59	29903.0	472.96	80.45	431.97
	Post JCAR017 Infusion Month 5	43	145.48	309.389	20.0	20.00	20.00	100.03	1860.1	212.66	49.94	211.09
	Post JCAR017 Infusion Month 8	26	223.66	351.950	20.0	20.00	83.45	309.89	1516.3	157.36	79.26	277.97
	Post JCAR017 Infusion Month 11	22	95.84	147.158	20.0	20.00	20.00	93.57	569.3	153.55	44.66	162.76
	Post JCAR017 Infusion Month 17	8	20.00	0.000	20.0	20.00	20.00	20.00	20.0	0.00	20.00	0.00

	Nominal Timepoint	JCAR017 Concentration (copies/ug) n	Mean	StD	Min	Q1	Median	Q3	Max	CV%	Geometric Mean [a]	Geometric CV% [b]
Arm A Post-cross Over (N = 45)	JCAR017 Infusion Day 1	38	1.47	9.031	0.0	0.00	0.00	0.00	55.7	616.44	55.67	NA
	Post JCAR017 Infusion Day 3	35	65.36	113.221	20.0	20.00	20.00	83.32	663.9	173.23	36.72	116.54
	Post JCAR017 Infusion Day 4	31	105.40	125.650	20.0	20.00	53.00	134.40	476.2	119.21	57.86	150.63
	Post JCAR017 Infusion Day 8	42	22982.02	27621.540	20.0	3641.80	10867.08	32195.18	104301.2	120.19	7608.28	830.44
	Post JCAR017 Infusion Day 11	35	41314.11	43125.028	20.0	10194.97	26641.41	54603.41	185925.2	104.38	21015.54	350.01
	Post JCAR017 Infusion Day 15	41	35679.88	58694.623	20.0	6592.47	10986.90	35798.92	309528.9	164.50	12832.54	458.35
	Post JCAR017 Infusion Day 22	36	30250.81	74613.448	20.0	1479.22	5040.01	17118.55	411032.3	246.65	4887.23	912.15
	Post JCAR017 Infusion Day 29	33	22749.84	79705.417	20.0	462.49	1675.41	8744.66	454083.5	350.36	1959.03	1388.36

	Nominal Timepoint	JCAR017 Concentration (copies/ug) n	Mean	StD	Min	Q1	Median	Q3	Max	CV%	Geometric Mean [a]	Geometric CV% [b]
Arm A Post-cross Over (N = 45)	Post JCAR017 Infusion Month 2	35	13670.23	63812.555	20.0	86.97	345.08	1555.74	376358.3	466.80	455.91	1636.86
	Post JCAR017 Infusion Month 3	28	1658.93	6250.051	20.0	20.00	129.09	617.38	33136.4	376.75	155.58	734.51
	Post JCAR017 Infusion Month 6	12	1577.95	4954.822	20.0	20.00	109.84	269.53	17303.6	314.00	123.41	672.30
	Post JCAR017 Infusion Month 9	6	141.00	159.361	20.0	20.00	60.20	305.58	380.0	113.02	73.56	207.55
	Post JCAR017 Infusion Month 12	5	300.95	549.714	20.0	20.00	20.00	167.08	1277.7	182.66	70.22	559.45

The liso-cel concentration in the peripheral blood detected by flow cytometry was also assessed for both arms (Figure 3, Figure 4, Figure 5).

Figure 3. Median [Q1, Q3] Flow Cytometry-based CD3+ JCAR017+ Concentrations in Peropheral Blood Time Profiles (Linear and Semi-Log Scales)- Flow Cytometry PK Analysis Set (Arm B)

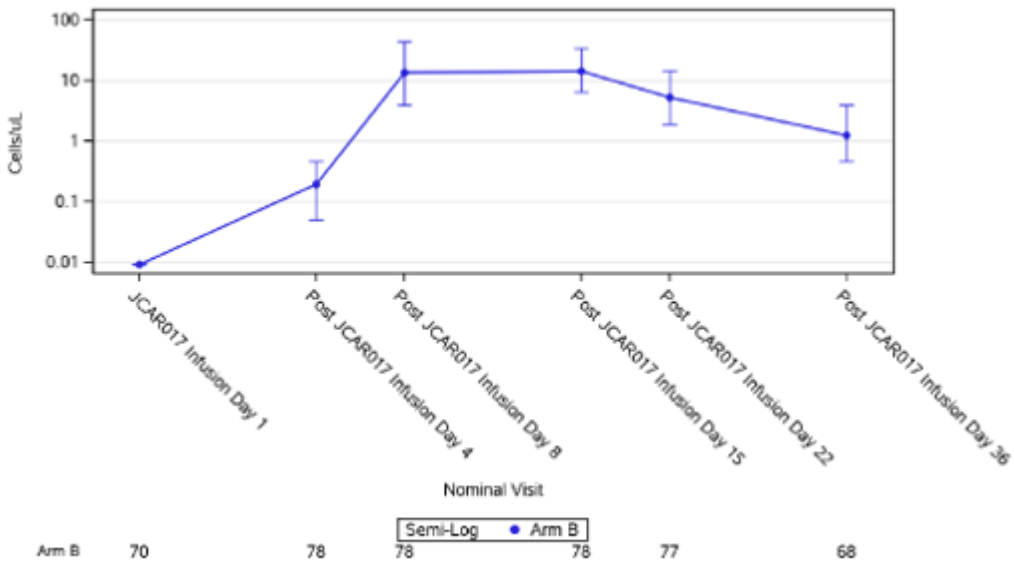


Figure 4. Median [Q1, Q3] Flow Cytometry-based CD3+ CD4+ JCAR017+ Concentrations in Peropheral Blood Time Profiles (Linear and Semi-Log Scales)- Flow Cytometry PK Analysis Set (Arm B)

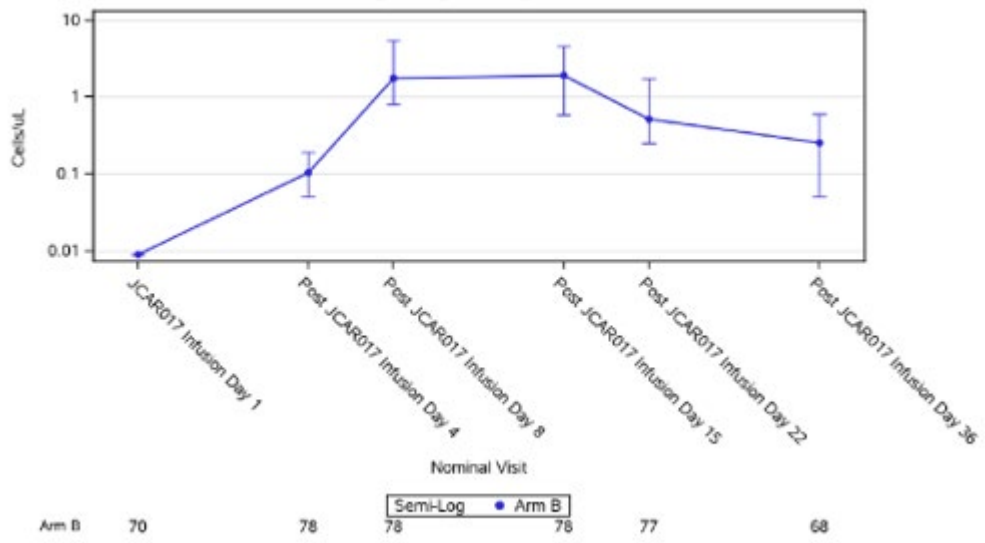
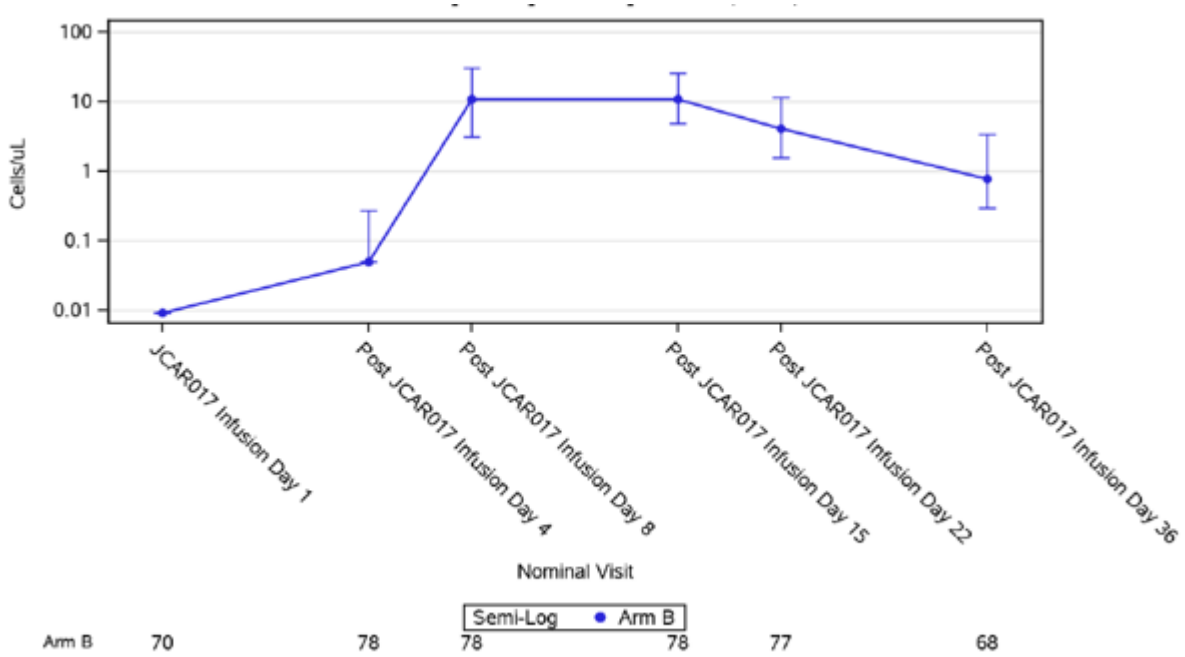


Figure 5. Median [Q1, Q3] Flow Cytometry-based CD3+ CD8_JCAR017+ Concentrations in Peropheral Blood Time Profiles (Linear and Semi-Log Scales)- Flow Cytometry PK Analysis Set (Arm B)



There was no flow cytometry-based PK data on Visit Post JCAR017 Infusion Day 11 (corresponding to Study Day 39) in the liso-cel arm, when the peak was observed for ddPCR based PK and comparison of flow cytometry-based and ddPCR-based PK shodul be exercised with caution.

Flow cytometry-based PK assessment showed the ability of both CD4+ and CD8+ drug product components to expand following the liso-cel infusion. Higher expansion of CD8+ EGFRt+ T cells was observed compared with CD4+ EGFRt+ T cells in both treated subjects in the liso-cel arm and subjects from the SOC arm who crossed-over to receive liso-cel.

The PK parameters estimated by ddPCR were similar between subjects in Arm B and subjects from SOC arm who crossed over to receive liso-cel. The median Tmax occurred 10 days after infusion in both treated subjects.

Table 9. Summary of Liso-cel Pharmacokinetic Parameters by ddPCR – ddPCR PK Analysis Set (Conforming Product)

	Statistic	AUC(0-28) (day*copies/µg)	Cmax (copies/µg)	Tmax (day)
Arm B (N = 87)	n	83	83	83
	Median	270345.09	33349.23	10.0
	Q1, Q3	111550.33, 793715.95	13872.86, 95617.53	9.0, 11.0
	Min, Max	5116.0, 4836898.5	549.0, 475990.7	6, 22
	Geometric mean (geometric CV%)	291943.747 (215.5)	35469.2 (205.2)	-
Arm A post-cross Over (N = 45)	n	38	38	38
	Median	305969.92	35894.73	10.0
	Q1, Q3	145995.19, 788819.00	12603.48, 71776.68	8.0, 13.0
	Min, Max	2139.7, 5999080.3	143.1, 454083.5	6, 28
	Geometric mean (geometric CV%)	318654.555 (265.3)	30675.4 (261.3)	-

Note: n is the number of subjects who had PK parameters. Noncompartmental PK parameters were calculated for subjects who had a PK measurement 28 days after infusion or later. Noncompartmental PK parameters were not calculated in the following cases: 1) if there were less than 2 PK measurements up to 28 days after infusion; 2) if all PK measurements were below the limit of detection.

Median Cmax and AUC(0-28) of CD3+ EGFRt+ and CD8+ EGFRt+ T cells estimated by flow cytometry from treated subjects in the liso-cel arm were numerically lower than that for subjects from the SOC arm who crossed-over to receive liso-cel (Table 10). Median Tmax of CD3+ EGFRt+, CD4+ EGFRt+ and CD8+ EGFRt+ T cells from treated subjects in the liso-cel arm and that for subjects from the SOC arm who crossed-over to receive liso-cel were 14 days and 10 days, respectively.

There was no flow cytometry-based PK data on Visit Post JCAR017 Infusion Day 11 (corresponding to Study Day 39) in the liso-cel arm, when the peak was observed for ddPCR-based PK. Comparison flow cytometry based and ddPCR based Parameters should be conducted with caution.

Table 10. Summary of JCAR017 Phamacokinetic Parameters by Flow Cytometry – Flow Cytometry PK Analysis Set (Conforming product)

	Cell Population Identified	Statistic	AUC_{0-28} (day*cells/uL)	C_{max} (cells/uL)	T_{max} (day)	Expansion Rate (cells/uL/day)
Arm B (N=84)	CD3+ JCAR017+	n	77	77	77	77
		Mean	1050.79	124.86	12.4	11.128
		StD	3768.161	463.390	5.68	38.4347
		Median	297.61	31.14	14.0	2.865
		Q1, Q3	119.64, 693.90	13.20, 72.44	7.0, 15.0	1.020, 7.936
		Min, Max	7.8, 30419.1	1.3, 3710.2	6, 35	0.09, 265.01
		CV%	358.6	371.1	45.7	345.4
		Geometric Mean [a]	303.690	31.9	11.3	2.829
		Geometric CV% [b]	213.8	235.8	46.3	267.2
Arm A Post-cross Over (N=44)	CD3+ JCAR017+	n	35	35	35	35
		Mean	4575.14	616.35	11.4	26.019
		StD	23606.582	3281.613	5.34	116.6518
		Median	496.37	48.39	10.0	3.692
		Q1, Q3	198.86, 891.02	22.89, 93.20	7.0, 14.0	2.282, 8.872
		Min, Max	3.3, 140212.0	0.3, 19473.5	3, 28	0.09, 695.48
		CV%	516.0	532.4	46.8	448.3
		Geometric Mean [a]	437.326	46.1	10.4	4.420
		Geometric CV% [b]	324.5	355.4	45.4	264.0

	Cell Population Identified	Statistic	AUC_{0-28} (day*cells/uL)	C_{max} (cells/uL)	T_{max} (day)	Expansion Rate (cells/uL/day)
Arm B (N=84)	CD3+ CD4+ JCAR017+	n	77	77	77	77
		Mean	167.60	19.14	13.6	1.549
		StD	839.336	102.503	8.94	7.3260
		Median	40.36	4.35	14.0	0.329
		Q1, Q3	15.26, 88.50	1.32, 10.09	7.0, 15.0	0.134, 0.919
		Min, Max	1.8, 7365.9	0.2, 900.8	3, 56	0.01, 64.35
		CV%	500.8	535.6	65.7	473.1
		Geometric Mean [a]	38.305	3.9	11.7	0.331
		Geometric CV% [b]	231.0	248.4	56.2	303.7
Arm A Post-cross Over (N=44)	CD3+ CD4+ JCAR017+	n	34	34	34	34
		Mean	696.05	81.50	12.1	3.406
		StD	3530.839	423.183	5.61	15.0755
		Median	39.73	4.14	10.0	0.381
		Q1, Q3	21.17, 107.22	2.12, 9.49	7.0, 14.0	0.201, 1.189
		Min, Max	4.3, 20664.5	0.4, 2475.2	6, 28	0.06, 88.40
		CV%	507.3	519.3	46.4	442.6
		Geometric Mean [a]	55.853	5.5	11.1	0.494
		Geometric CV% [b]	301.4	318.0	42.5	270.5

	Cell Population Identified	Statistic	AUC_{0-28} (day*cells/uL)	C_{max} (cells/uL)	T_{max} (day)	Expansion Rate (cells/uL/day)
Arm B (N=84)	CD3+ CD8+ JCAR017+	n	77	77	77	77
		Mean	887.13	106.76	12.5	9.680
		StD	3035.959	377.191	5.74	33.2999
		Median	223.50	24.11	14.0	2.489
		Q1, Q3	86.77, 609.58	10.51, 60.19	7.0, 15.0	0.801, 5.884
		Min, Max	5.8, 23226.3	0.4, 2835.3	6, 35	0.03, 216.40
		CV%	342.2	353.3	46.0	344.0
		Geometric Mean [a]	240.059	25.2	11.3	2.230
		Geometric CV% [b]	250.0	287.9	46.7	337.7
Arm A Post-cross Over (N=44)	CD3+ CD8+ JCAR017+	n	35	35	35	35
		Mean	4006.03	547.30	11.4	23.095
		StD	20769.537	2921.876	5.34	103.8835
		Median	422.10	36.10	10.0	3.313
		Q1, Q3	175.32, 701.49	17.10, 84.31	7.0, 14.0	1.567, 8.219
		Min, Max	1.7, 123337.7	0.1, 17337.2	3, 28	0.05, 619.10
		CV%	518.5	533.9	46.8	449.8
		Geometric Mean [a]	355.993	38.2	10.4	3.663
		Geometric CV% [b]	359.6	396.7	45.4	295.3

A high correlation between ddPCR (transgene) and flow cytometry (CD3+ EGFRt+ T cell) PK parameters was observed in the liso-cel arm for Cmax and AUC(0-28), with a correlation coefficient of 0.7583 (p <0.0001) and 0.8300 (p <0.0001), respectively (Figures below).

Figure 6. Log Cmax by ddPCR vs. Log Cmax by Flow Cytometry – PK Analysis Set (Arm B)

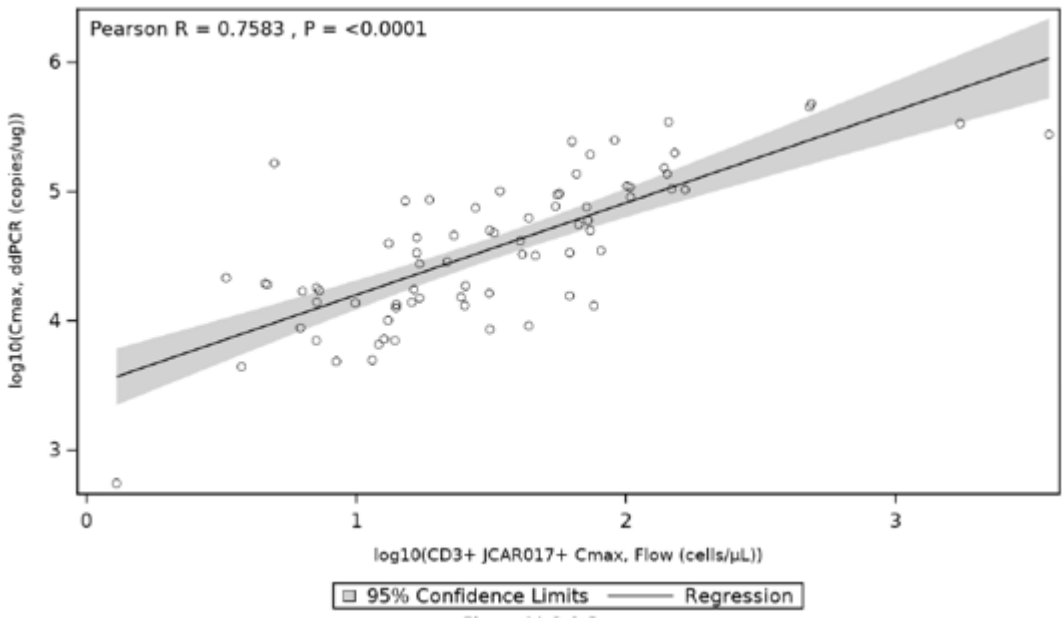
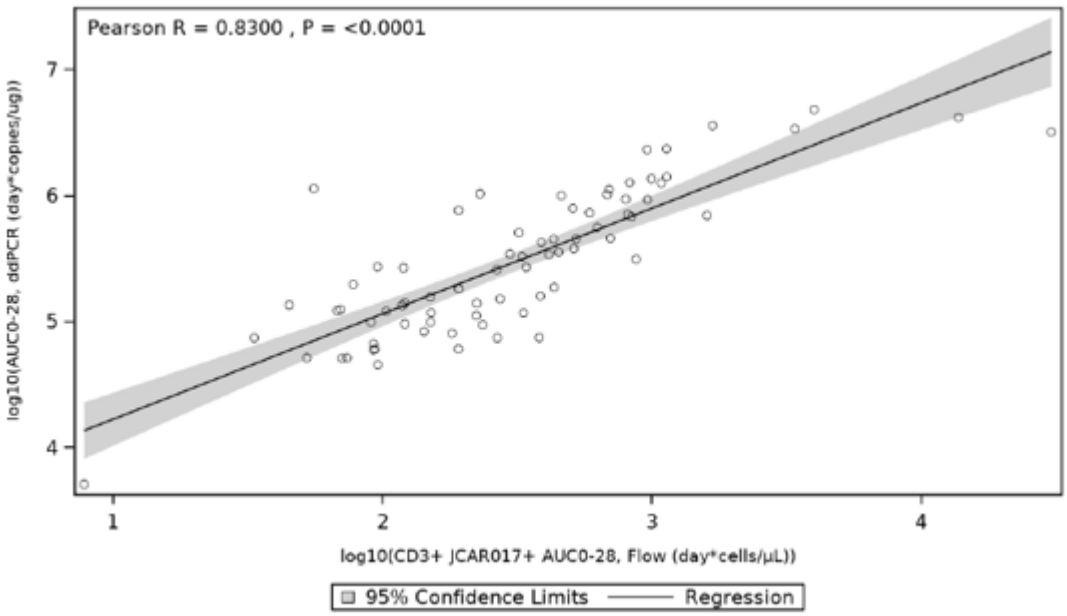
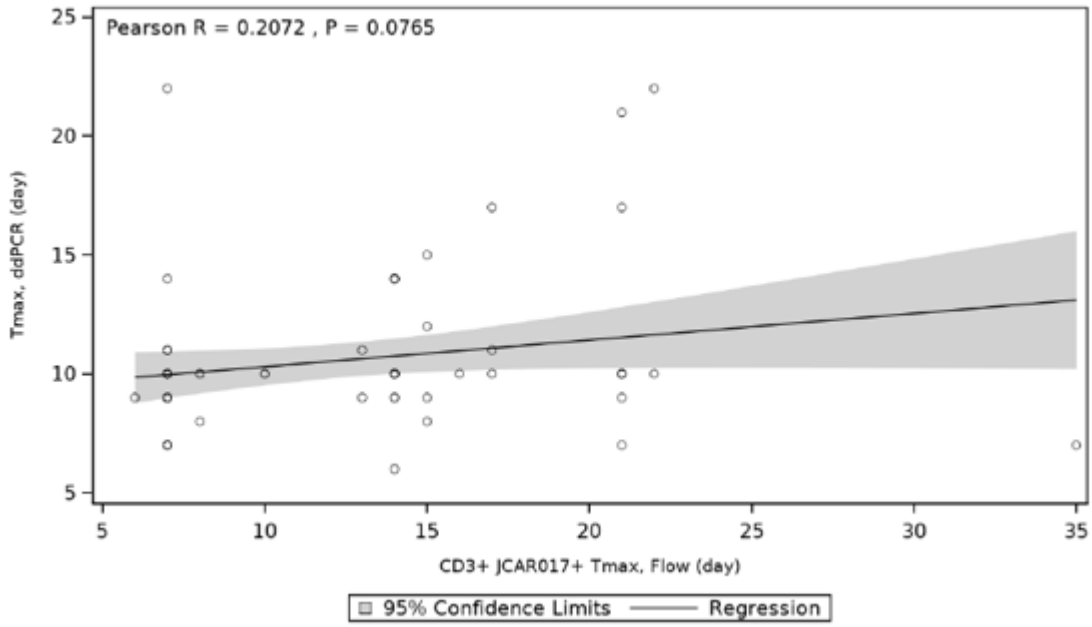


Figure 7. Log AUC0-28 by ddPCR vs. Log AUC0-28 by Flow Cytometry – PK Analysis Set (Arm B)



Correlation between ddPCR (transgene) and flow cytometry (CD3+ EGFRt+ T cell) Tmax was not high (a
correlation coefficient of 0.2072 (p=0.0765), Figure below).

Figure 8. Tmax by ddPCR vs, Tmax by Flow Cytometry – PK Analysis Set (Arm B)



There was no flow cytometry-based PK data on Visit Post JCAR017 Infusion Day 11 (corresponding to Study Day 39) in the liso-cel arm, when the peak was observed for ddPCR-based PK.

Pharmacokinetic Parameters by Subgroup Analysis

No apparent differences in ddPCR PK parameters by subgroups of age (< 65 versus ≥ 65 to < 75 years old), sex, region (Unites States, Europe versus Japan), and baseline SPD (≥ 50 versus < 50 cm2) were

observed in the liso-cel arm, except for Cmax and sex. A potential association was observed between higher Cmax and female sex (17656.18 copies/µg [IQR, 10783.0 to 74166.7] in male subjects and 45492.20 copies/µg [IQR, 18490.4 to 104090.7] in female subjects, p = 0.0411), however, the IQRs overlapped.

Persistence

Persistence of liso-cel transgene in blood was assessed by ddPCR and defined as a transgene count greater than or equal to the LOD of 40 copies/µg. Persistence of liso-cel transgene was observed up to Visit Post JCAR017 Infusion Month 11 in the liso-cel arm (Table 11). Liso-cel transgene was not detected in any subjects at Visit Post JCAR017 Infusion Month 17 in the liso-cel arm. However, the number of evaluable subjects was small (n = 6).

Table 11. Persistence of Lios-cel in the Blood as Assessed by ddPCR by Nominal Timepoint – ddPCR PK Analysis Set (Conforming Product – Liso-cel Arm)

Cell Type Nominal Timepoint	Arm B (N = 87)
Transgene – n/m (%)	
Post JCAR017 Infusion Day 36	61/67 (91.0)
Post JCAR017 Infusion Day 43	52/61 (85.2)
Post JCAR017 Infusion Month 2	45/67 (67.2)
Post JCAR017 Infusion Month 3	30/58 (51.7)
Post JCAR017 Infusion Month 5	17/38 (44.7)
Post JCAR017 Infusion Month 8	11/20 (55.0)
Post JCAR017 Infusion Month 11	6/17 (35.3)
Post JCAR017 Infusion Month 17	0/6

n/m (%) = number of subjects with persistence of JCAR017 in the blood/number of subjects with an available sample at the specific timepoint. Percentage is 100 times n divided by m

Persistence is defined as a transgene count greater than or equal to the LOD. Data obtained after the start of a new anti-cancer therapy are not included in the determination of persistence.

Similarly, in subjects from the SOC arm who crossed-over to receive liso-cel, persistence of liso-cel transgene was observed up to Month 12 (the end of the follow-up period in subjects from the SOC arm who crossed-over to receive liso-cel) (Table 12).

Table 12. Persistence of JCAR017 in the Blood as Assessed by ddPCR by Nominal Timepoint ddPCR PK Analysis Set (Conforming Product – Arm A Post-cross Over)

Cell Type Nominal Timepoint	Arm A Post-cross Over (N = 45)
Transgene – n/m (%)	
Post JCAR017 Infusion Day 29	31/33 (93.9)
Post JCAR017 Infusion Month 2	25/31 (80.6)
Post JCAR017 Infusion Month 3	17/26 (65.4)
Post JCAR017 Infusion Month 6	7/10 (70.0)
Post JCAR017 Infusion Month 9	3/4 (75.0)
Post JCAR017 Infusion Month 12	2/4 (50.0)

Results from analyses of persistence by flow cytometry has been provided for day 36 and Month 2 and are concordant with data showed for ddPCR.

2.4.3. Pharmacodynamics

Pharmacodynamic variables including B-cell aplasia, serum Ig, soluble biomarkers, CRP, and ferritin were summarized descriptively.

B-cell aplasia

B-cell aplasia (defined as CD19+ B-cells <3% of peripheral blood lymphocytes), is an on-target effect of anti-CD19 CAR T-cell therapies, that may be seen as CAR T cells persist long term, functioning as a surrogate marker of CAR T-cell persistence and activity.

The incidence of B-cell aplasia was assessed for both the liso-cel arm and SOC post-cross over arms (table below) and sampling was performed as reported in the table below. An increase in the proportion of subjects with B-cell aplasia was observed from 80.7% of subjects at screening to 95.9% of subjects at Day 29, which remained elevated through Day 85 (2 months post-infusion), in the liso-cel arm.

Table 13. Incidence of B-cell Aplasia in Liso-cel Arm

Visit	< 3% CD19+ B cells N (%)	Total N
Screening	67 (80.7)	83
Day 29 (Pre-Infusion)	70 (95.9)	73
Day 32	77 (96.3)	80
Day 36	76 (95.0)	80
Day 43	79 (98.8)	80
Day 50	74 (96.1)	77
Day 64	68 (95.8)	71
Day 85	58 (96.7)	60

Day 29 is the infusion day of liso-cel. B-cell aplasia is defined as <3% of CD19+ B cells in peripheral blood lymphocytes.
Data obtained after the start of a new anti-cancer therapy are not included in the determination of persistence

In Arm A (cross-over arm), B-cell aplasia was assessed pre-lymphodepletion [39 out of 47 (97.5%)] and post-infusion at Day 1 [37 out of 39 (94.9%)], Day 4 [30 out of 34 (88.2%)], Day 8 [41 out of 42 (97.6%)], Day 11 [37 out of 39 (94.9%)], Day 15 [37 out of 38 (97.4%)], Day 22 [38 out 38 (100%)], Day 29 [37 out of 38 (97.4%)], Month 2 [30 out of 30 (100%)].

No difference in B-cell aplasia was observed between the liso-cel arm and SOC post-cross over arm.

More mature data have been provided during the procedure on the percent of subjects with CD19+ B-cell presence <3%, B-cell aplasia (BCA), based on the latest data (data cut-off date: 13-May-2022) for Study BCM-003.

Updated data from this assay from the 13-May-2022 data cut-off date confirm the proportion of subjects with B-cell aplasia from 80.7% at screening to 95.9% at Day 29, and included an additional patient at Day 85 (2 months post-infusion).

To enable additional B-cell monitoring between Day 85 (when the PK collections end) through Month 36, a TBNK (T cell, B cell, NK cell) flow cytometry panel was added after study start. Due to the initiation of this panel after study start and the need for additional subject consenting, a reduced number of subject samples were able to be assessed with this exploratory output. Subject CD19+ B-cell <3% percentages from the TBNK assay are provided in Table below. BCA levels at screening are consistent across assays as is the increase in BCA through Day 85, where both assays demonstrated the on-target pharmacodynamic effect of liso-cel.

Table 14. Incidence of BCA Assessed by the TBNK Flow Cytometry Assay by Nominal Timepoint - Safety Analysis Set - Liso-cel Arm

Nominal Timepoint	<3% CD19+ B cells N (%)	Total N
Screening	28 (80.0)	35
Day 29 (Pre-infusion)	32 (94.1)	34
Day 36	41 (100)	41
Day 43	41 (97.6)	42
Day 50	42 (97.7)	43
Day 64	44 (100)	44
Day 85	40 (100)	40
Day 126	40 (90.9)	44
Month 6	32 (80.0)	40
Month 12	19 (55.9)	34
Month 18	16 (44.4)	36
Month 24	6 (37.5)	16

Day 29 is the infusion day of liso-cel. BCA is defined as <3% of CD19+ B-cells in peripheral blood lymphocytes. Data obtained after the start of a new anti-cancer therapy are not included in the determination of BCA

Serum immunoglobulins

Serum IgA, IgG, and IgM were measured by the central lab (Labcorp, Indianapolis). The level of IgG and incidence of hypogammaglobulinemia (defined as IgG < 500 mg/dL) for the liso-cel arm was summarized by scheduled visits in Table below. The percentage of subjects with hypogammaglobulinemia was 31.5% (28 of 89 subjects) at baseline and increased numerically at Month 9 to 58.6% (20 of 46 subjects), followed by a decrease to 50% (5 of 10 subjects) by Month 18. However, subject numbers decreased from Month 6 through Month 18. The analysis of serum IgG levels did not take into account potential confounding by the administration of IVIG for the treatment of hypogammaglobulinemia.

Table 15. Summary of Serum IgG and Hypogammaglobulinemia in Liso-cel Arm

Parameter Statistic	Pre-Infusion N = 89	Day 64 N = 85	Day 85 N = 74	Day 126 N = 67	Month 6 N = 46	Month 9 N = 29	Month 12 N = 26	Month 18 N = 10
IgG (mg/dL)								
Median	638.0	576.0	566.5	530.0	520.5	463.0	441.0	537.0
Q1, Q3	441.0, 794.0	426.0, 699.0	488.0, 718.0	408.0, 659.0	386.0, 623.0	366.0, 591.0	312.0, 712.0	338.0, 884.0
< 500 mg/dL - n/m (%)	28/89 (31.5)	29/85 (34.1)	19/74 (25.7)	28/67 (41.8)	20/46 (43.5)	17/29 (58.6)	14/26 (53.8)	5/10 (50.0)
IgG (Change from Pre-Infusion)								
Median	--	-46.0	-79.0	-91.0	-112.5	-147.0	-162.5	-176.0
Q1, Q3	--	-120.0, 20.0	-181.0, 63.0	-184.0, 35.0	-217.0, -3.0	-342.0, -28.0	-283.0, -22.0	-256.0, -28.0

n/m (%) = number (percentage) of subjects in the category/number of subjects available for evaluation
Change from pre-infusion is only calculated for post-infusion timepoints and is to be intended as change from Day 29, which is the date of liso-cel administration.
Pre-infusion is the last measurement prior to the liso-cel administration.

Table 16. IgA and IgM change from pre-infusion

	Pre-infusion (mg/dL)	Day 64	Day 85	Day 126	Month 6	Month 9	Month 12	Month 18	Month 36/EoS
IgA									
N	89	85	74	67	46	29	26	10	1
Median	104.0	44.0	38.5	35.0	32.0	30.0	29	37	52
Q1, Q3	63.0-153.0	31.0-60.0	28.0-48	28.0-45.0	28.0-44.0	28-46	28-55	28-53	52-52
IgM									
N	89	85	73	67	46	29	26	10	1
Median	29	23	22	22	20	23	32	40	185
Q1, Q3	20-55	20-36	20-42	20-39	20-34	20-45	20-61	24-74	185-185

Soluble biomarkers

A total of 37 soluble biomarkers were analyzed to examine changes in cytokine and chemokine levels following liso-cel infusion. The concentration of the biomarkers has been performed in compliance with GCLP using an electrochemiluminescence-based immunoassay (ECL) in human EDTA plasma in order to monitor the cytokine immune responses to JCAR17.

C-reactive protein and ferritin

Soluble analytes CRP and ferritin were measured by the central lab. In the liso-cel arm, median post-infusion serum CRP was higher than median pre-infusion value (Day 29) up to Day 39 (10 days post infusion). However, median CRP decreased at Day 43 (14 days post infusion) and remained lower than the pre-infusion median from Day 43 through Day 126.

Median serum ferritin from Day 31 onward was lower than the pre-infusion serum ferritin. However, a wide range of ferritin levels were observed at each timepoint.

Immunogenicity

In the liso-cel arm, the prevalence and incidence of ATA was 1.1% (1 of 89 subjects) (Table below).

Table 19. Summary of Anti-Therapeutic Antibodies in Serum as Assessed by Electrochemiluminescence Immunoassay – Safety Analysis Set, Liso-cel Arm

	Liso-cel Arm [a] Conforming Product (N=89)
Prevalence of Anti-therapeutic Antibodies [b]	
Total subjects for evaluation	89
Yes – n/m (%)	1/89 (1.1)
No – n/m (%)	88/89 (98.9)
Incidence of Anti-therapeutic Antibodies [c]	
Total subjects for evaluation	89
Yes – n/m (%)	1/89 (1.1)
No – n/m (%)	88/89 (98.9)
Treatment-induced Antibodies	
Total subjects for evaluation	88
Yes – n/m (%)	1/88 (1.1)
No – n/m (%)	87/88 (98.9)
Treatment-boosted Antibodies	
Total subjects for evaluation	1
Yes – n/m (%)	0/1
No – n/m (%)	1/1 (100)

N = number of subjects in analysis set; n/m (%) = number of subjects in the category/number of subjects available for evaluation. Percentage is 100 times n divided by m. Immunogenicity assessments post-cross over are not included in this table.
[a] Only infused subjects are included.
[b] Prevalence of anti-therapeutic antibodies is defined as the percentage of subjects with pre-existing antibodies that bind to liso-cel.
[c] Incidence of anti-therapeutic antibodies is defined as the percentage of subjects with treatment-induced or treatment-boosted antibodies that bind to liso-cel. In a subject without pre-existing antibodies, development of antibodies after first infusion of liso-cel is considered treatment-induced. In a subject with pre-existing antibodies, an increased level of antibodies after first infusion of liso-cel is considered treatment-boosted.

In subjects from the SOC arm who crossed-over to receive liso-cel, the prevalence of ATA was 2.2% (1 of 46 subjects) and the incidence of ATA was 0 (0 of 46 subjects) (Table below).

Table 20. Summary of Anti-Therapeutic Antibodies in Serum as Assessed by Electrochemoluminescence Immunoassay Cross Over Analysis Set

	Arm A Post-cross Over [a]		
	Conforming Product (N = 46)	Non-conforming Product (N = 1)	Total (N = 47)
Prevalence of Anti-therapeutic Antibodies [b]			
Total subjects for evaluation	46	1	47
Yes - n/m(%)	1/46 (2.2)	1/1 (100)	2/47 (4.3)
No - n/m(%)	45/46 (97.8)	0/1	45/47 (95.7)
Incidence of Anti-therapeutic Antibodies [c]			
Total subjects for evaluation	46	1	47
Yes - n/m(%)	0/46	0/1	0/47
No - n/m(%)	46/46 (100)	1/1 (100)	47/47 (100)
Treatment-induced Antibodies			
Total subjects for evaluation	45	0	45
Yes - n/m(%)	0/45	0/0	0/45
No - n/m(%)	45/45 (100)	0/0	45/45 (100)

The subject who had a **pre-existing ATA** in the liso-cel arm achieved a BOR of a CR and did not experience any CRS or iiNT. Cmax and AUC(0-28) estimated by ddPCR of this subject were 6983.2 copies/µg and 45503.97 day*copies/µg, respectively, which were lower than the median values of overall population.

The subject who had a **treatment-induced ATA** in the liso-cel arm achieved a BOR of a CR and did not experience any CRS or iiNT. Cmax and AUC(0-28) by ddPCR of this subject were 13872.86 copies/µg and 51639.09 day*copies/µg, respectively, which were lower than the median values of overall population.

One subject in the liso-cel arm and one subject from the SOC arm who crossed-over to receive liso-cel received nonconforming product because the CD4+ component purity was OOS (out of specification). Expansion of liso-cel was observed in both subjects who received nonconforming product. No ATAs were detected in the subject who received nonconforming product in the liso-cel arm. The subject from the SOC arm who crossed-over to receive liso-cel and received nonconforming product had pre-existing ATA but no treatment-boosted ATA.

Relationship between PK and efficacy/safety endpoints

This relationship was evaluated for liso-cel arm only. The efficacy endpoints considered for the analysis are EFS, BOR, PFS, DoR. The safety endpoints are TEAE of CRS categorized as Grade 0 versus Grade ≥1, CRS categorized as Grade ≤2 versus Grade ≥3, iiNT categorized as Grade 0 versus Grade ≥1 and iiNT categorized as Grade ≤2 versus Grade ≥3. The TEAE were assessed by the investigators.

The relationship between PK parameters (Cmax, Tmax, and AUC(0-28)) and dichotomous parameters such as BOR, CRS, and iiNT were assessed by Wilcoxon tests. The relationship between PK parameters and multi-categorical parameters were assessed by Kruskal-Wallis tests. The relationship between PK parameters and time-to-event parameters such as EFS, DoR and PFS were assessed by univariable Cox proportional hazards models. Unless otherwise specified, all p-values are reported as 2-sided without multiplicity adjustment.

Table 21. Relationship Between Pharmacokinetic Parameters of Liso-cel and Clinical Efficacy (Liso-cel Arm)

	Transgene			CD4+ EGFRt+			CD8+ EGFRt+		
Variable/ Statistic	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
Efficacy (assessed per IRC)									
Response (CR or PR)									
Cmax			0.4173			0.2917			0.1253
N	76	7		70	7		70	7	
Median	33285.45	95617.53		3.96	10.09		21.82	46.70	
(Q1, Q3)	(13848.5, 87789.7)	(15495.6, 136135.2)		(1.3, 9.5)	(1.0, 17.6)		(8.7, 60.1)	(24.1, 90.2)	
Tmax			0.8516			0.3474			0.7006
N	76	7		70	7		70	7	
Median	10.0	10.0		14.0	13.0		13.5	14.0	
(Q1, Q3)	(9, 11)	(9, 10)		(7, 15)	(7, 14)		(7, 15)	(7, 16)	
AUC(0-28)			0.1871			0.2681			0.1538
N	76	7		70	7		70	7	
Median	268887.00	733405.56		37.06	90.50		218.81	517.07	
(Q1, Q3)	(98941.6, 738189.1)	(159802.7, 1264857.6)		(15.3, 71.9)	(9.8, 146.4)		(83.2, 555.1)	(182.5, 876.4)	
CR									
Cmax			0.1388			0.2065			0.2359
N	60	23		54	23		54	23	
Median	44616.56	18490.41		4.93	2.65		30.29	24.01	
(Q1, Q3)	(14373.7, 101327.0)	(13064.3, 74166.7)		(1.8, 10.3)	(0.9, 8.5)		(10.5, 69.8)	(7.6, 38.0)	
Tmax			0.4696			0.8098			0.5422
n	60	23		54	23		54	23	
Median	10.0	10.0		14.0	13.0		13.5	14.0	
(Q1, Q3)	(9, 11)	(9, 10)		(7, 15)	(7, 15)		(7, 15)	(7, 15)	
AUC(0-28)			0.2126			0.2403			0.2105
n	60	23		54	23		54	23	
Median	335323.75	151558.44		45.40	26.31		288.59	182.47	
(Q1, Q3)	(117756.4, 970461.5)	(95976.7, 710734.5)		(18.6, 88.5)	(9.7, 90.5)		(86.8, 666.9)	(83.2, 404.3)	
EFS									
Cmax			0.8827			0.6667			0.8384
Hazard ratio	0.96			0.87			1.06		
(95% CI)	(0.52, 1.75)			(0.47, 1.62)			(0.60, 1.89)		
AUC(0-28)			0.9970			0.9248			0.7689
Hazard ratio	1.00			1.03			1.10		
(95% CI)	(0.55, 1.80)			(0.55, 1.93)			(0.59, 2.02)		
PFS									
Cmax			0.6216			0.4698			0.5487
Hazard ratio	1.19			1.31			1.23		
(95% CI)	(0.60, 2.38)			(0.63, 2.70)			(0.62, 2.44)		
AUC(0-28)			0.6249			0.2641			0.4785
Hazard ratio	1.18			1.52			1.30		
(95% CI)	(0.61, 2.30)			(0.73, 3.16)			(0.63, 2.70)		
DoR									
Cmax			0.4723			0.3482			0.5986
Hazard ratio	0.78			0.69			0.83		
(95% CI)	(0.40, 1.53)			(0.32, 1.50)			(0.41, 1.68)		
AUC(0-28)			0.4829			0.7848			0.6993
Hazard ratio	0.79			0.90			0.86		
(95% CI)	(0.40, 1.54)			(0.41, 1.96)			(0.41, 1.82)		

Table 22. ***Relationship Between Pharmacokinetic Parameters of Liso-cel and Safety (Liso-cel Arm)***

	Transgene			CD4+ EGFRt+			CD8+ EGFRt+		
Variable/ Statistic	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
CRS									
Cmax			0.0225			0.2430			0.1671
n	41	42		37	40		37	40	
Median	49730.58	27112.54		5.39	3.72		36.74	23.82	
(Q1, Q3)	(16840.2, 151635.9)	(13064.3, 55286.1)		(1.6, 10.8)	(1.2, 9.0)		(10.8, 85.7)	(9.2, 45.7)	
Tmax			0.1634			0.2962			0.6242
n	41	42		37	40		37	40	
Median	10.0	10.0		14.0	13.0		14.0	13.0	
(Q1, Q3)	(9, 10)	(9, 11)		(7, 15)	(7, 15)		(7, 15)	(7, 15)	
AUC(0-28)						0.3055			0.2270
n	41	42	0.0327	37	40		37	40	
Median	347980.79	190686.63		58.60	33.93		277.57	206.26	
(Q1, Q3)	(122371.9, 1039230.1)	(80791.4, 459856.2)		(18.0, 88.5)	(12.3, 80.5)		(112.0, 720.2)	(83.2, 408.9)	
iiNT									
Cmax			0.0745			0.0111			0.3754
n	10	73		10	67		10	67	
Median	93019.47	32475.61		13.25	3.72		29.23	24.11	
(Q1, Q3)	(16840.2, 274571.4)	(13824.1, 84151.9)		(5.4, 35.5)	(1.2, 8.5)		(12.0, 138.9)	(9.6, 60.1)	
Tmax			0.9653			0.2646			0.2103
n	10	73		10	67		10	67	
Median	10.0	10.0		14.0	13.0		14.0	13.0	
(Q1, Q3)	(10, 10)	(9, 11)		(14, 14)	(7, 15)		(14, 14)	(7, 15)	
AUC(0-28)			0.0222			0.0075			0.2112
n	10	73		10	67		10	67	
Median	779679.83	259771.37		161.63	34.14		296.62	214.12	
(Q1, Q3)	(197778.4, 3212868.5)	(99030.0, 681935.4)		(52.4, 516.1)	(12.4, 70.7)		(124.1, 1636.4)	(84.2, 555.1)	

P-value, Hazard ratio and associated 95% confidence interval based on a Cox proportional hazards model with the PK parameter as the explanatory variable in the model.

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology profile of liso-cel in subjects with 2L LBCL has been characterized based on the results from clinical study BCM-003 and included a characterization of the PK profile of liso-cel by ddPCR and by flow cytometry, evaluation of the PD markers of liso-cel and immune responses directed against liso-cel. It is also evaluated the relationship between PK endpoints as assessed by ddPCR and by flow cytometry with selected efficacy and safety endpoints in subjects receiving liso-cel, relationship between PK endpoints with selected baseline demographic and disease characteristics in subjects receiving liso-cel, relationship between PD biomarker endpoints with select safety endpoints in subjects receiving liso-cel and relationship between immunogenicity endpoints and select efficacy and safety.

The PK of liso-cel were determined using 2 validated methods:

- the ddPCR to detect the liso-cel transgene in blood and
- flow cytometry to enumerate CAR+ T cell subsets via detection of the EGFRt (ie, CD3+ EGFRt+, CD8+ EGFRt+, and CD4+ EGFRt+) in blood (. The flow cytometry was considered supportive.

Moreover, soluble biomarkers were analyzed using multiplex MSD electrochemiluminescence (ECL) immunoassays; serum Ig, CRP, and ferritin were measured at the central laboratory.
Finally, immunogenicity was assessed by measuring ATA in serum with an electrochemiluminescence immunoassay (a partial validation was submitted in the current variation).

The MAH submitted the analytical report of ddPCR for samples relative to the study JCAR017-BCM-003 and values fall within the validated ranges. It is observed that the maximum expression of the virus is within the first 2 weeks and few samples showed persistence of the virus until Month 11.

Data from ddPCR showed that a higher *expansion* of cells occurred at Day 39 corresponding to 10 days post-infusion, that is in line with data previously observed in the initial MA. The median liso-cel transgene level versus time profiles for the SOC Arm post-cross over were similar to those observed for the liso-cel arm B, however, as already observed in the IMA, there is a high variability in the absolute count of cells, due to the nature of product. For flow cytometry (intended as supportive analysis) no sampling was performed at Day 11 post-infusion, precluding the availability of data on CD3+ EGFRt+, CD4+ EGFRt+ and CD8+ EGFRt+ T cells at Tmax and the possibility to compare data from ddPCR and flow cytometry at that time point. Based on data provided, in Arm A (crossed-over pts) a higher expansion of cells seems to be observed respect to Arm B, however also the variability is higher precluding a punctual comparison of such data.

Persistence of liso-cel transgene in blood was assessed by ddPCR and defined as a transgene count greater than or equal to the LOD of 40 copies/µg. Data on persistence are available until Month 11 in Arm B; however, it is of note that on Month 11 data for only 17 patients are available and the transgene persistence was observed in 6 out of 17 (35.3%). Moreover, in SOC Arm, persistence was observed only in 2 out of 4 patients (50%) at Month 12. Updated data on persistence until Month 23 in Arm B and until Month 12 in the SOC Arm have been provided during the procedure. The updated data on persistence showed that at Month 11, 19 out of 44 patients had transgene persistence (43.2%), on Month 17 transgene persistence was observed in 11 out of 34 (32.4%) and on Month 23 was observed in 5 out of 15 (33.3%). The percentage of transgene persistence ranged from 91% at day 36 to 33.3% at Month 23. The updated data on persistence for Arm A, showed that the percentage of transgene persistence ranged from 91.3% at Day 29 to 55.6% at Month 12 (18 patients are now available at this timepoint).
The updated data showed that the transgene persistence is maintained over time in both Arm.

A qualitative electrochemiluminescence (ECL) method was employed to evaluate the presence of anti-JCAR017 antibodies (*anti-treatment antibodies*; ATA) in human serum samples. Since it was observed that the assay signal had decreased over time a partial method validation was performed to re-establish the assay system suitability ranges, sensitivity, precision and the LPC (5 ng/ml instead of previously 15 ng/ml). After the partial validation the value of LPC was 2.686 ng/mL for the Screening Assay (previously was 3.480 ng/ml) and to 2.715 ng/mL for the confirmatory Assay (previously was 3.247 ng/ml). Precision was between 0% to 12% CV in the Screening and Confirmatory assays for the HPC (7500 ng/mL), LPC2 (50 ng/mL), and LPC (15 ng/mL). After the partial validation, precision was CV% = 19% (HPC 7500 ng/mL) and CV% = 13% (LPC 5 ng/mL).
The number of samples for immunogenicity assessment, as per cut-off date 08 Mar 2021, was 714 that were stored frozen at -80°C for a maximum of 663 days which was within the established long-term stability of 3 years, 1 month, 7 days. The LTS previously established was 608 days at -80°C, however, literature data supports a storage period until 3.5 years at -80°C for the immunotherapeutic antibodies in human serum (Michaut, 2014). Therefore, the little exceeding time of sample storage is not considered an issue.
Updated data in responses to first RSI were provided on ATA prevalence and incidence and the MAH clarifies the number of ATA previously and actually reported in terms of prevalence and incidence. In the liso-cel arm (Arm B) of Study BCM-003, 2 of 89 subjects who received conforming product had detectable ATAs. Of which one had pre-existing ATA and one had treatment induced ATA. In the SOC arm (Arm A), 6 of 90 subjects (6.7%) had pre-existing ATA. In subjects from the SOC arm who crossed over to receive liso-cel or nonconforming product (47 subjects), 2 of these (4.3%) had pre-existing ATA and none had detectable treatment-boosted ATA. One subject with positive ATA (4011005) was excluded from the summaries due to screen failure. Data provided confirmed a low incidence of ATAs.

Pharmacodynamic variables including B-cell aplasia, serum Ig, soluble biomarkers, CRP, and ferritin were summarized descriptively.

B-cell aplasia (defined as CD19+ B-cells <3% of peripheral blood lymphocytes), is an on-target effect of anti-CD19 CAR T-cell therapies, that may be seen as CAR T cells persist long term, functioning as a surrogate marker of CAR T-cell persistence and activity. At the updated data cut-off 13-May-2022, just one additional patient was included at the timepoint Day 85. The percentage of B-cell aplasia remains the same (96.7%). The BCA was measured as part of the PK flow cytometry assay, which was assessed through study Day 85. Moreover, to enable additional B-cell monitoring between Day 85 (when the PK collections end) through Month 36, a TBNK (T cell, B cell, NK cell) flow cytometry panel was added after study start and the results at the additional timepoints (Day 126, Month 6, 12, 18 and 24) were provided. The percentage of B-cell aplasia are consistent between the two assays at screening and at Day 85; this percentage remains elevated at the subsequent timepoints, with a decrease at Month 12, 18, 24 (55.9%, 44.4% and 37.5, respectively). Data on B-cell aplasia are in line with the observed persistence in which the transgene expression is observed until Month 23 in liso cell Arm.

Serum IgA, IgG, and IgM were measured by the central lab (Labcorp, Indianapolis). The percentage of subjects with hypogammaglobulinemia was 31.5% (28 of 89 subjects) at baseline and increased numerically at Month 9 to 58.6% (20 of 46 subjects), followed by a decrease to 50% (5 of 10 subjects) by Month 18. However, subject numbers decreased from Month 6 through Month 18.

Concentration of 39 *soluble biomarkers* has been analyzed and data showed that many analytes did not meet the acceptance criteria, their use in the present study is considered appropriated based on the "fit-for-purpose" concept as stated by FDA and EMA Guidelines (Bioanalytical Method Validation 05/24/18, FDA; EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). According to these recommendations "the level of validation should be appropriate for the intended purpose of the study" and "method for determining quantitative concentrations of biomarkers used in assessing pharmacodynamic endpoints are out of the scope of this guidance". As requested, the MAH provides the method and absolute values for IL-6 and IFN-γ measured in patients. The two analytes were measured in the context of the analysis of 38 biomarkers with the MESO scale discovery panels. All accepted values are within the chosen criteria and are considered valid.

A total of 37 soluble biomarkers were analyzed to examine changes in cytokine and chemokine levels following liso-cel infusion. Data on soluble biomarkers collected at Day 32, 36, 43 and 64 shows a rapid and transient increase in some of them). The eventual increase of biomarkers occurs essentially within Day 36 after the infusion (Day 29).

Soluble analytes CRP and ferritin were measured by the central lab. As expected also the behavior of IL-6, CRP and ferritin is aligned with the shape observed for liso-cel expansion.

The *relationship between PK and efficacy/safety endpoints* was evaluated for liso-cel arm only. No apparent relationships were observed between transgene PK parameters and any efficacy endpoints (BOR, EFS, PFS and DoR).

A potential association was observed between higher transgene Cmax or AUC(0-28) and higher incidence of any grade CRS. Although potential association was not observed for these PK parameters of CD4+ EGFRt+ and CD8+ EGFRt+ T cells, the median Cmax and AUC(0-28) were numerically higher in subjects with any grade CRS. The relationship between PK parameters and grade $\geq$ 3 CRS was not assessed because the number of subjects with grade $\geq$ 3 CRS (n = 1) was less than 5.

A potential association was observed between higher transgene AUC(0-28) and higher incidence of any grade iiNT. For CD4+ EGFRt+ T cells, a potential association was observed between higher Cmax or AUC(0-28) and higher incidence of any grade iiNT. A potential association was not observed for CD8+ EGFRt+ T cells. The relationship between PK parameters and grade $\geq$ 3 iiNT was not assessed because the number of subjects with grade $\geq$ 3 iiNT (n = 4) was less than 5.

The relationships of baseline and peak values (i.e Cmax) of soluble biomarkers and CRP/ferritin with selective safety endpoints was studied. The safety endpoints include CRS, categorized as no CRS versus any grade CRS and iiNT, categorized as no iiNT versus any grade iiNT.

The number of subjects with Grade ≥ 3 CRS (N=1) and Grade ≥ 3 iiNT (N=4) analyzed in the liso-cel arm was insufficient to assess a relationship.

Among the evaluated soluble biomarkers, only Cmax of IFNγ and IL-6 were associated with any grade CRS versus no CRS. Additionally, peak IFNγ was also associated with any grade iiNT versus no iiNT. There was no statistically significant association of peak CRP or ferritin levels with CRS or NT status.

2.4.5. Conclusions on clinical pharmacology

The pharmacology of liso-cel in 2L LBCL has been well characterized.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The dose range seen in study BCM-003 falls within the existing approved range of 44-120 × 10^6 CAR+ T cells. Overall, the median total liso-cel dose was 99.92 × 10^6 CAR+ cells (range: 97.1 to 102.5); the median CD8 and CD4 component doses were 49.97 × 10^6 CAR+ cells (range: 48.0 to 51.8) and 49.89 × 10^6 cells (range: 48.1 to 51.5), respectively. The CD4:CD8 ratio was tightly controlled around the target 1:1. This dose of liso-cel demonstrated a statistically significant improvement in EFS based on Independent Review Committee (IRC) assessment compared to the SOC arm in study BCM-003: HR=0.349 (95% CI: 0.229, 0.530); p value based on a stratified Cox-PH model <0.0001.

The overall safety profile of a liso-cel target dose of 100 × 10^6 CAR+ T cells was consistent with that previously observed in the marketed indication of 3L+ LBCL.

Results from the PK/PD analyses in Study BCM-003 demonstrated that the benefit-risk profile is not expected to be impacted by liso-cel exposure at the proposed target dose, and the PK outcomes for subjects in 2L LBCL were similar to those for subjects with 3L+ LBCL.

2.5.2. Main study

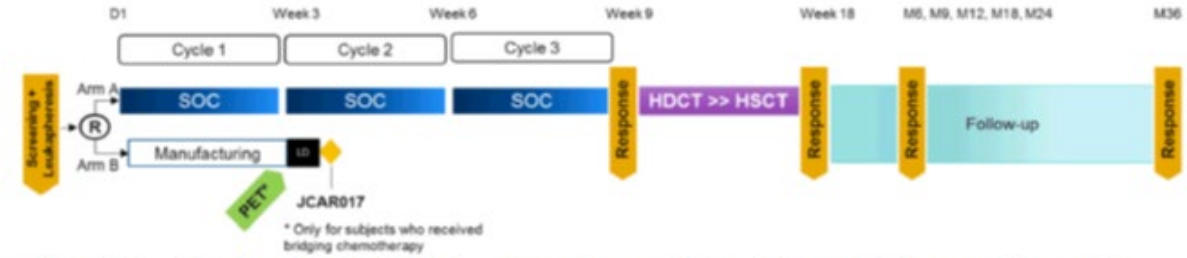
Title of Study

Study Jcar017-Bcm-003 - A Global Randomized Multicenter Phase 3 Trial to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult Subjects With High-Risk, Transplant-Eligible Relapsed or Refractory Aggressive B-Cell Non-Hodgkin Lymphomas (TRANSFORM)

Methods

Study BCM-003 was a randomized, open-label, parallel-group, multi-centre, Phase 3 study to demonstrate the efficacy and safety of liso-cel versus standard of care (SOC, i.e. salvage immunochemotherapy followed by high-dose chemotherapy [HDCT] and autologous hematopoietic stem cell transplant [ASCT or HSCT]) in subjects with large B-cell lymphomas (LBCLs) who were refractory to or have relapsed within 12 months from 1L therapy and are eligible for HDCT and ASCT.

Figure 10. Overall study Design



Abbreviations: D = day; HDCT = high-dose chemotherapy; HSCT = hematopoietic stem-cell transplant; IRC = independent review committee; JCAR017 = liso-cel; LD = lymphodepleting; M = month; PET = positron emission tomography; R = randomization; SOC = standard of care.
Note: For subjects in Arm A, eligibility criteria for crossover to receive liso-cel was also defined. The criteria included central confirmation by the IRC of 1 of the following: failure to achieve CR or PR by 9 weeks post-randomization (after 3 cycles of SOC), progression at any time, or need to start a new antineoplastic therapy due to efficacy concerns after 18 weeks post-randomization (see Protocol JCAR017-BCM-003 Section 6.3.2). For subjects in Arm B, bridging chemotherapy with 1 cycle of a SOC regimen was allowed for disease control while liso-cel was being manufactured, if deemed necessary by the investigator.

The study consisted of 4 periods:

• Screening (Study Days -28 to -1).

• Treatment Period (Study Days 1 [+ 3 days] to 126 [± 7 days]).

• Post-treatment Period.

• Survival Follow-up.

The duration of participation for subjects who completed the study is approximately 37 months from randomization under this protocol (trial ongoing).

Cross-over to liso-cel: subjects in the SOC arm could be allowed to cross-over to liso-cel (see the "Treatment" section below for details). Subjects who crossed over to liso-cel are followed in the study for 12 months after the liso-cel infusion.

Study participants

The key inclusion and exclusion criteria are summarised below:

Main inclusion criteria

- Aged ≥18 years and ≤75 years and Eastern Cooperative Oncology Group (ECOG) performance status ≤1
- Histologically proven DLBCL NOS (de novo or transformed from indolent NHL), HGBCL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (DHL/THL), PMBCL, T-cell/histiocyte rich B-cell lymphoma (THRBCL) or FL3B. Enough tumour material collected at the time of the most recent relapse must have been available for confirmation by central pathology, otherwise a new tumour biopsy was mandatory (for primary refractory patients a tumour biopsy sample from disease diagnosis could be used)
- Subjects with secondary central nervous system (CNS) involvement were eligible if the Investigator assessed that the potential benefit outweighed the risk for the subject

- Refractory disease (SD, PD, PR or CR with relapse before 3 months) or relapsed disease (defined as CR with relapse on or after lasting at least 3 months but <12 disease under study). The time of relapse was calculated from the date of the first disease assessment confirming a complete response (CR) obtained with 1L treatment to the date of first assessment demonstrating a relapse
- [18F] FDG PET positive lesion per Lugano criteria at screening (Deauville score 4 or 5)
- Adequate bone marrow function, defined as ANC ≥1.0 x 10^9 cells/L and platelets ≥50 x 10^9 cells/L (in the absence of bone marrow involvement)
- Adequate organ function, defined as serum creatinine <1.5 x upper limit of normal (ULN) or creatinine clearance > 45 mL/min (estimated by Cockcroft Gault), ALT ≤5 x ULN and total bilirubin <2.0 mg/dL (or <3.0 mg/dL for subjects with Gilbert's syndrome or liver infiltration), NCI CTCAE Grade ≤1 dyspnoea, SaO2 ≥92% on room air, FEV1 ≥50%, LVEF ≥40% by echocardiogram or multigated acquisition scan (MUGA) within 4 weeks of randomization

Main exclusion criteria

- Significant medical condition, laboratory abnormality, or psychiatric illness that placed the subject at unacceptable risk based on investigator's judgment
- Not eligible for hematopoietic stem-cell transplantation (HSCT) or planned to undergo allogeneic stem-cell transplantation
- Primary cutaneous large B-cell lymphoma (LBCL), Epstein-Barr virus positive DLBCL, Burkitt lymphoma, or Richter transformation
- Active malignancy or recent history of malignancies (i.e. <2 years) other than aggressive R/R NHL
- Treatment with any prior gene therapy product or previous CD19-targeted therapy
- Active hepatitis B, or active hepatitis C (subjects with negative PCR assay were permitted); subjects positive for HBsAg and/or anti-HBc antibody with negative viral load were eligible (prophylactic antiviral therapy to be considered)
- Subjects with a history of or active human immunodeficiency virus (HIV) or with uncontrolled systemic fungal, bacterial, viral or other infection (including tuberculosis); active autoimmune disease requiring immunosuppressive therapy
- History of any one of the following cardiovascular conditions within the past 6 months prior to signing the ICF: NHYA Class III/IV heart failure, cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease
- History or presence of clinically relevant CNS pathology such as epilepsy, seizure, aphasia, stroke, cerebral oedema, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis
- Progressive vascular tumour invasion, thrombosis, or embolism
- Use of therapeutic doses of corticosteroids (>20 mg/day prednisone or equivalent) within 7 days prior to leukapheresis; lymphotoxic chemotherapy 2 weeks prior to leukapheresis (chemotherapeutic agents not considered lymphotoxic and intrathecal chemotherapy must have been stopped ≥7 days prior to leukapheresis); immunosuppressive therapies within 4

weeks prior to leukapheresis; radiation within 4 weeks prior to signing the ICF, systemic immunostimulatory agents within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to liso-cel infusion.

Treatments

Arm A

Subjects randomized to "Arm A" were administered one of the following three SOC regimens, as per the investigator's decision:

1. R-DHAP: Rituximab 375 mg/m² on Day 1, dexamethasone 40 mg on Days 1 to 4, cytarabine 2 x 2000 mg/m² on Day 2, and cisplatin 100 mg/m² on Day 1;

2. R-ICE: Rituximab 375 mg/m² on Day 1, ifosfamide 5000 mg/m² on Day 2, etoposide 100 mg/m² on Days 1 to 3, carboplatin area under the curve (AUC) 5 (maximum dose 800 mg) on Day 2; or

3. R-GDP: Rituximab 375 mg/m² on Day 1, dexamethasone 40 mg on Days 1 to 4, gemcitabine 1000 mg/m² on Days 1 and 8, cisplatin 75 mg/m² on Day 1.

Treatment compliance was adequate: R-ICE was the most used combination in the SOC arm (63.7%), followed by R-GDP (26.4%) and R-DHAP (16.5%). Only 12 patients had to switch salvage regimen because of efficacy (42%) or toxicity (33%) concerns.

All subjects randomized to Arm A received 3 cycles of SOC salvage therapy, during which peripheral blood hematopoietic stem cells for HSCT were harvested. After 3 cycles, response was evaluated by PET-CT. Subjects responding to SOC (CR and PR) were to proceed to HDCT and HSCT. In case of toxicity or not satisfactory response as per investigator judgment to the selected SOC regimen, a switch within the 3 defined SOC regimen was allowed.

The standard HDCT used in this study prior to the HSCT was BEAM, defined as carmustine (BCNU) 300 mg/m² on Day 1, etoposide 200 mg/m² on Days 2 to 5, cytarabine 200 mg/m² on Days 2 to 5, melphalan 140 mg/m² on Day 6.

Dose adjustment for toxicities and premedication were done as per site standard, local label, and investigator's decision. In Japan, due to unavailability of intravenous BCNU, ranimustine (MCNU) was used at the same dosage and schedule as BCNU.

Arm B

Bridging chemotherapy administered prior to liso-cel

Bridging chemotherapy with one of the protocol-defined SOC regimens (i.e., rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP], rituximab, ifosfamide, carboplatin, and etoposide [R-ICE], or rituximab, gemcitabine, dexamethasone, and cisplatin [R-GDP]) (or local radiation on a single site) was allowed for disease control while liso-cel was being manufactured (i.e., after leukapheresis and prior to LDC) if deemed necessary by the Investigator. Bridging therapy must have been stopped at least 7 days prior to LDC. Local radiation to a single lesion or subset of lesions was allowed as bridging therapy if other non-irradiated PET-positive lesions were present and if completed at least 7 days prior to the start of LDC. Subjects who received bridging treatments were re-evaluated with PET/TC before liso-cel infusion to disentangle the effect of bridging chemotherapy and liso-cel in response induction.

Lymphodepleting Chemotherapy (LDC)

Subjects randomized to Arm B were treated with LDC consisting of fludarabine IV (30 mg/m^2/day for 3 days) and cyclophosphamide IV (300 mg/m^2/day for 3 days) prior to liso-cel infusion. LDC was to start 5 to 7 days before liso-cel infusion and was to be completed at least 2 days before liso-cel infusion.

Liso-cel infusion

Prior to the administration of liso-cel subjects were assessed to confirm that they met the criteria for liso-cel administration.

Eligible subjects were premedicated with 500 to 650 mg paracetamol PO and 25 to 50 mg diphenhydramine hydrochloride or another H1 antihistamine (PO or IV) 30 to 60 minutes prior to liso-cel infusion. Steroids at therapeutic doses (> 20 mg/day of prednisone or equivalent) and other immunosuppressive therapies were not allowed. Higher doses of steroids were only allowed for the treatment of CRS and NT or other life-threatening situations.

Liso-cel was infused at a dose of 100 × 10^6 CAR+ viable T cells (CAR+ T cells) on Day 29 (2 to 7 days after completion of LDC) for subjects randomized in Arm B. The CD8 and CD4 components were thawed and administered separately with the CD8 component administered first, followed by the CD4 component.

Cross-over to liso-cel

If requested by the investigator, subjects randomized to Arm A were allowed to crossover to receive liso-cel upon central confirmation of one of the following criteria:

- failure to achieve CR or PR by 9 weeks post-randomization (after 3 cycles of SOC);
- progression at any time;
- need to start a new antineoplastic therapy due to efficacy concerns after 18 weeks post-randomization.

For subjects from Arm A who crossed over to liso-cel, bridging with non-investigational therapy was allowed.

Intrathecal treatment

Intrathecal treatment (IT) with methotrexate and/or cytarabine was allowed in both treatment arms for the prophylaxis and treatment of subjects with secondary CNS involvement (a minimum of 7 days wash-out period prior to the start of LC chemotherapy was required in Arm B).

Objectives

Primary Objective

To compare the efficacy in subjects treated with liso-cel vs. subjects treated according to standard of care (SOC) defined as event-free survival (EFS).

Key Secondary Objectives

To compare the efficacy in subjects treated with liso-cel vs. subjects treated according to SOC defined as CRR, progression-free survival (PFS), and overall survival (OS).

Other Efficacy Secondary Objectives

To compare other parameters of efficacy, defined as duration of response (DoR), overall response rate (ORR), PFS on next line of treatment (PFS-2), efficacy rates (EFS, PFS, OS) at 6, 12, 24 and 36 months after randomization and to compare efficacy in clinical, histological and molecular subgroups

To compare health-related quality of life (HRQoL) using the global health/QoL, fatigue, physical and cognitive functioning subscales of the European Organisation for Research and Treatment of Cancer – Quality of Life C30 Questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy – Lymphoma "Additional concerns" subscale (FACT-LymS)

To describe the rate of completion of high-dose chemotherapy (HDCT) and hematopoietic stem-cell transplant (HSCT) and to assess the response 3 months after HSCT

Efficacy Exploratory Objectives

To evaluate the role of the tumour and the tumour microenvironment in mechanisms of response and resistance to liso-cel

Outcomes/endpoints

Primary endpoint

The primary efficacy endpoint of the study is EFS, defined as the time from randomization to death from any cause, progressive disease (PD), failure to achieve complete response (CR) or partial response (PR) by 9 weeks post-randomization, or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first. Failure to achieve CR or PR was evaluated after 3 cycles of SOC for Arm A (expected 9 weeks post-randomization) and 5 weeks after the liso-cel infusion for Arm B.

The censoring rules for the primary EFS analysis are summarised in Table below. Event and censoring rules were consistent between the two treatment arms.

Table 26. Event and Censoring Rules for EFS

No baseline, or no postbaseline response assessment and no death	Randomization date	Censor
Death	Death date	Event
PD	PD date	Event
Failure to achieve CR or PR by 9 weeks post-randomization (after 3 cycles of SOC for Arm A and 5 weeks after the JCAR017 infusion)	9 weeks post-randomization assessment date (after 3 cycles of SOC for Arm A and 5 weeks after the JCAR017 infusion)	Event
Start of a new antineoplastic therapy due to efficacy concerns	Date of imaging (or other objective finding) that serves as the basis of starting a new antineoplastic therapy[a]	Event
Start of a new antineoplastic therapy for reasons other than efficacy concerns	Last adequate response assessment date	Censor
Failure to proceed to HDCT and HSCT due to refusal or failure to collect or mobilize stem cells	Last adequate response assessment date	Censor
No death, no PD, no failure to achieve CR or PR by 9 weeks post-randomization (after 3 cycles of SOC for Arm A and 5 weeks after the JCAR017 infusion) and no start of new antineoplastic therapy due to efficacy concerns	Last adequate response assessment date	Censor

a The event date should be interpreted as the latest disease assessment available before start of a new antineoplastic therapy due to efficacy concerns, either based on IRC or investigator's assessment.
CR = complete response; EFS = event-free survival; HDCT = high-dose chemotherapy; HSCT = hematopoietic stem cell transplant; IRC = Independent Review Committee; PD = progressive disease; PR = partial response; SOC = standard of care.

In addition to the event and censoring rules described in Table above, the following conditions were taken into account: allo-HSCT was considered as a new antineoplastic therapy for efficacy concerns; ASCT was considered as a new antineoplastic therapy for efficacy concerns when initiated for lack of efficacy (i.e., disease response pre-transplant of SD or PD) in Arm B; ASCT initiated after JCAR017 infusion for consolidation (i.e., disease response pre-transplant other than SD or PD) was considered as a new antineoplastic therapy for reasons other than efficacy concerns; for Arm A, in case of toxicity or not satisfactory response as per investigator judgment to the selected SOC regimen, a switch within the 3 defined SOC regimen was allowed and not considered as a new antineoplastic therapy; Radiation therapy was considered as a new antineoplastic therapy for efficacy concerns when not planned in the treatment strategy.

Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are CRR, PFS and OS. Full description of these endpoints is provided in Table below:

Table 27. Key Secondary Efficacy Endpoints

Endpoint	Name	Description	Timeframe
Key Secondary Efficacy	Complete response rate (CRR)	Percentage of subjects achieving a CR	Up to 3 years post-randomization
Key Secondary Efficacy	Progression-free survival (PFS)	Time from randomization to PD, or death from any cause, whichever occurs first	Up to 3 years post-randomization
Key Secondary Efficacy	Overall survival (OS)	Time from randomization to time of death due to any cause	Up to last subject last visit

Responses will be assessed according to the Celgene "Guidelines for Efficacy Evaluation in PET-avid Non-Hodgkin Lymphoma" by an IRC based on radiographic tumor evaluation by PET/CT scans. These guidelines are based on "The Lugano Classification" (Cheson, 2014).

Secondary Efficacy Endpoints

Secondary efficacy endpoints are listed and described in Table below:

Table 28. Secondary Efficacy Endpoints

Endpoint	Name	Description	Timeframe
Secondary Efficacy	Overall response rate (ORR)	Percentage of subjects achieving an objective response of partial response (PR) or better	Up to 3 years post-randomization
Secondary Efficacy	Duration of response (DoR)	Time from first response to disease progression, start of new antineoplastic therapy due to efficacy concerns or death from any cause	Up to 3 years post-randomization
Secondary Efficacy	PFS on next line of treatment (PFS-2)	Time from randomization to second objective disease progression or death from any cause, whichever occurs first.	Up to 3 years post-randomization
Secondary Efficacy	EFS rate	Percentage of subjects free of any EFS event at fixed timepoints	At 6, 12, 24 and 36 months post-randomization
Secondary Efficacy	PFS rate	Percentage of subjects free of any PFS event at fixed timepoints	At 6, 12, 24 and 36 months post-randomization
Secondary Efficacy	OS rate	Percentage of subjects alive at fixed timepoints	At 6, 12, 24 and 36 months post-randomization
Secondary Efficacy	Clinical, histological and molecular subgroup analyses	Response rate, EFS, PFS, OS in clinical, histological and molecular subgroups	Up to 3 years post-randomization
Secondary Efficacy	Rate of HDCT completion	Percentage of subjects in Arm A completing HDCT	Up to 3 years post-randomization
Secondary Efficacy	Rate of HSCT completion	Percentage of subjects in Arm A completing HSCT	Up to 3 years post-randomization
Secondary Efficacy	Response rate post-HSCT	Percentage of subjects in response after undergoing HSCT	At 3 months post-HSCT

Responses will be assessed according to the Celgene "Guidelines for Efficacy Evaluation in PET-avid Non-Hodgkin Lymphoma" by an IRC based on radiographic tumor evaluation by PET/CT scans. These guidelines are based on "The Lugano Classification" (Cheson, 2014).

Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are listed and described in Table below:

Table 29. Exploratory Efficacy Endpoints

Endpoint	Name	Description	Timeframe
Exploratory Efficacy	Efficacy analyses for subjects who crossed over to JCAR017	PFS, EFS, DoR, ORR and CRR for subjects who crossed over to JCAR017	Up to 1year post-JCAR017 infusion
Exploratory Efficacy	Efficacy analyses for subjects who crossed over to JCAR017	OS for subjects who crossed over to JCAR017	Up to last subject last visit

Responses will be assessed according to the Celgene "Guidelines for Efficacy Evaluation in PET-avid Non-Hodgkin Lymphoma" by an IRC based on radiographic tumor evaluation by PET/CT scans, with the exception of post-cross over evaluations. These guidelines are based on "The Lugano Classification" (Cheson, 2014).

Efficacy assessments

Efficacy was assessed according to the Lugano criteria (Cheson, 2014) by an IRC based on radiographic tumor evaluation by PET/ CT scans. Disease was assessed using diagnostic quality CT/ magnetic resonance imaging (MRI) scans (chest, neck, abdomen, and pelvis) and PET scans. Assessment of bone marrow involvement by lymphoma was performed by PET scan only; bone marrow aspirates and biopsies were not required for assessment of disease response.

Efficacy assessments were performed at Weeks 9 (after 3 cycles of SOC for Arm A and 5 weeks after liso-cel infusion for Arm B) and 18 (8 weeks after the start of HDCT for Arm A and 14 weeks after liso-cel infusion for Arm B) and Months 6, 9, 12, 18, 24 and 36.

The Investigator's assessment of response was collected in the eCRF. The IRC confirmed the response to therapy and the time of PD for each subject. 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 (ie, tumour flare, which is a local inflammatory reaction indicating early tumour response at sites of disease such as lymph nodes) (Cheson, 2016).

Start of a new antineoplastic therapy due to efficacy concerns was based on investigator's assessment and related data was collected in the eCRF. Start of a new antineoplastic therapy was captured from time of randomization to date of imaging (or other objective finding) that served as the basis of starting a new antineoplastic therapy. A pseudo-progression at Week 9 post-randomization was not considered as failure to achieve CR or PR for EFS.

HR-QoL evaluations were performed at randomisation and then at day 29, at week 9 and 18, and then at month 6, 9, 12, 18, 24 and 36 (or at EOS or ET visit).

Sample size

It was hypothesized that subjects treated with SOC had median EFS of 3 months. Subjects receiving experimental treatment JCAR017 were expected to have an increase of ~ 81% in the median EFS (equivalent to a hazard ratio [HR] of 0.55 under the exponential distribution assumption) compared to subjects treated with SOC, bringing the median EFS in the experimental group to 5.455 months.

Given these assumptions, using a log rank test with 2.5% one-sided significance level, 119 EFS events were expected to provide at least 90% power to reject the null hypothesis of HR greater than or equal to 1. The null hypothesis was to be rejected if the p-value associated to the test is ≤ 0.004 at the time of the interim analysis for efficacy (i.e., when 71 EFS events were expected, see the Statistical method session below) or ≤ 0.024 at the time of the primary efficacy analysis (i.e., when 119 EFS events were expected). The significance thresholds were adjusted based on the actual number of EFS events

observed at the time of each efficacy analysis in order to ensure the nominal significance level was maintained.

Based on an expected randomization rate up to 12 subjects per month (2, 4, 6, 8 and 10 subjects randomized during 1st, 2nd, 3rd, 4th, 5th month and 12 subjects per month after 6th month) with a 20% dropout rate before week 9 response assessment and a yearly dropout rate of 10% (30% cumulative), a sample size of 182 subjects was expected to be randomized and 215 subjects to be screened (assuming a screen failure rate of 15%). The estimated accrual duration was 17.6 months.

Randomisation

Subjects were randomized at a 1:1 ratio via an IRT system into 1 of the 2 arms (Arm A[SOC] or Arm B [liso-cel]). Randomization was based on a permuted-blocks randomization method, with the following stratification factors: best overall response (BOR) to first-line therapy (refractory vs. relapsed); sAAIPI (0 or 1 vs. 2 or 3).

Blinding (masking)

This was an open-label study. The Applicant was blinded to the aggregated data in each arm. The IRC, which was responsible to review data related to disease response assessments during the study and determine remission and relapse for the interim and primary analyses, was also blinded to the treatment arm assigned to the subjects, even in case of expedited reviews for subjects in Arm A crossing over to liso-cel.

Statistical methods

Data safety monitoring board (DSMB) and independent review committee (IRC)

An independent DSMB was assembled under a dedicated charter specifically developed for safety oversight of this study. The DSMB reviewed cumulative study data over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial. The DSMB was to meet approximately every 6 months throughout the trial and as needed to address any safety issues that may have risen.

An IRC was established to review data related to disease response assessments during the study and determine remission and relapse for the interim analyses as well as the primary analysis. Subject management was based upon local investigator assessments. For subjects in Arm A who were eligible for crossover to receive liso-cel, confirmation of crossover criteria was to be approved by the IRC under expedited review.

Analysis sets

The following analysis sets were used for the analysis and presentation of the data:

Intention-to-treat (ITT) Analysis Set: all subjects randomized to a treatment arm.

Per-protocol (PP) Analysis Set: all subjects of the ITT analysis set characterized by: having a minimal exposure to treatment (Arm A: one cycle of SOC; Arm B: per protocol dose of conforming JCAR017); having a baseline assessment and at least one post-baseline response assessment; without important protocol deviations.

Cross over Analysis Set: all subjects of the ITT analysis set randomized in Arm A who crossed over to JCAR017.

Health-related Quality of Life (HRQoL) Analysis Set: the HR-QoL analysis set was defined as subjects in the ITT population who filled in a baseline and at least one post-baseline HRQoL assessment.

Interim analyses (IAs)

Two IAs, one for futility and one for efficacy, were planned.

The purpose of the first IA was to stop for futility in case of no efficacy signal on CRR at 9 weeks after randomization when ~30 evaluable subjects had their response assessment (after 3 cycles of SOC for Arm A and 5 weeks after the JCAR017 infusion) or have been confirmed with PD prior to this timepoint. The study was to be terminated if the CRR in JCAR017 arm had been lower than the CRR in the SOC arm. No formal statistical test was performed, and no type I error adjustment was implemented. This futility IA was performed based on a data cut-off date of 26 Nov 2019: the DSMB recommended that the study should be continued with no modifications.

The purpose of the second IA was to demonstrate the superiority of liso-cel vs. SOC based on EFS. This analysis was based on the data cutoff date of 10 Nov 2020, at 63% information fraction (i.e. 75 EFS events). The O'Brien-Fleming boundary was used to define the efficacy boundary and the null hypothesis could be rejected if the p-value was ≤0.005: the recommendation from the DSMB was that the pre-defined criteria for superiority of the liso-cel arm versus the SOC arm were met.

Following consultation a competent authority indicated that the IA at 63% of the information fraction was not mature enough for a regulatory filing. The competent authority recommended that another efficacy IA be performed at 80% information fraction (i.e., at approximately 96 EFS events) and the SAP was revised accordingly. The purpose of this additional efficacy IA was to demonstrate superiority of liso-cel vs. SOC on EFS. The O'Brien-Fleming boundary was used to define the efficacy boundary and incorporated an alpha penalty for the previous interim analysis. The alpha spending function ensured that the overall type I error rate for the study was 2.5%: the null hypothesis was to be rejected if the p-value was ≤0.012 based on the actual number of EFS events observed at the time of this analysis (cut-off date of 08 Mar 2021, at 82% information fraction and 98 EFS events). In order to prevent bias in the study conduct, an independent and external statistical group was responsible for conducting the efficacy IA at 80% information fraction. The DSMB reviewed the results of this additional IA on 03 Jun 2021, and their recommendation was that the pre-defined criteria for superiority of the liso-cel arm vs. the SOC arm had been met and that the results could be disclosed.

Control of multiplicity

A hierarchical testing strategy was used to control the family-wise type I error rate across the primary and key secondary endpoints. The primary efficacy endpoint EFS was analysed first: if null hypothesis for EFS could be rejected, then hypothesis testing on CRR and subsequently on PFS and OS was to be performed hierarchically. No further testing was allowed once the testing sequence broke. O'Brien-Fleming boundary alpha spending function was used to adjust for multiplicity for the IAs for efficacy and the primary analysis, to ensure that the overall type I error rate for the study was 2.5%.

Statistical Analysis

Time-to-event endpoints were analysed using a stratified Cox-PH model with treatment as the only covariate for analysis, if the proportional hazards assumption held. The proportional hazards assumption was evaluated via inspection of Schoenfeld residuals (Grambsch, 1994). The Kaplan-Meier (KM) product limit were used to provide summary information on EFS. The 25th percentile, median, and 75th percentile along with CI were extracted from KM curves (using log-log transformation). In addition, the EFS rate at 6, 12, 24 and 36 months were computed, along with the standard errors and associated two-sided 95% confidence intervals (Greenwood's formula).

For response analyses, Cochran-Mantel-Haenszel (CMH) test with stratification factors as strata was used for analysis and calculation of p-values.

Sensitivity analyses for the primary endpoint included: unstratified Cox-PH model; restricted mean survival approach or piecewise stratified Cox-PH model in case the proportional hazard assumption was violated; PP and safety analysis sets; Investigator response assessment; censoring at the last adequate efficacy assessment before missing 2 or more consecutive scheduled assessments before or on study month 12 or before missing 1 or more consecutive scheduled assessments after study month 12; censoring at the time of starting a (planned or unplanned) radiation therapy; using the "FDA imaging interpretation (i.e. also categorizing the below 3 scenarios as PD regardless of PET-based metabolic response at that time point: metabolic CR/PR/SD on PET and disease progression on CT scan, new lesion on CT scan indicating PD which was not FDG avid on PET and clinical (non-radiographic) PD per Investigator).

For OS, as subjects from Arm A had the possibility to cross over to JCAR017, a 2-stage Weibull approach was used. For PFS, subjects who crossed over to JCAR017 without progression or death were censored. In addition, rank preserving structural failure time (RPSFT) method (Ishak, 2014) and inverse probability of censoring weighting (IPCW) method (Ishak, 2014) were to be investigated for OS as supportive analyses and for PFS as sensitivity analyses, if applicable depending on the rate of subjects crossing over to JCAR017 without previous disease progression.

Quality of Life Analysis

Completion and compliance rates for HRQoL were calculated for each instrument based on the ITT analysis set. All HRQoL analyses were conducted on the HRQoL analysis set and are to be interpreted as descriptive. Missing values were addressed according to questionnaire guidelines. Reasons for missing questionnaires were captured so that the appropriate imputation method could be applied according to questionnaire guidelines. The primary domains of interest for the HRQoL analysis were Global Health/Quality of Life (GH/QoL), Physical Functioning, Cognitive Functioning, Fatigue, Pain, and FACT LymS. For the individual-level analysis (ie. proportion of subjects' with HRQoL improved/stable/deteriorated compared to their baseline), the thresholds contained in Table below and pre-specified in the SAP were used to determine a clinically important difference.

Table 30. Clinically Meaningful Thresholds for Individual-Level Analysis

HRQoL domain	Responder Definition (RD)[b]
GH/QoL[a]	±5
Physical Functioning	±5
Fatigue	±10
Cognitive Functioning	±15
Pain	±15
FACT-LymS[c]	±3

FACT-LymS = Functional Assessment of Cancer Therapy-Lymphoma Subscale; HRQoL = Health-related quality of life.

[a] GH/QoL = Global Health/Quality of Life

[b] RD estimates were rounded down to the nearest 5 for transparency and consistency (Cocks, 2015).

[c] There are no established RDs for the FACT-LymS, therefore, the RD value of 3 (+3 for improvement and -3 for deterioration) will be used as recommended by Hlubocky (Hlubocky, 2013).

There is no consensus in the literature regarding the methods (anchor-based versus distribution-based approach) and populations used to derive these cut off values and the results from the analyses of clinically meaningful change may be altered if different RDs are used. Therefore, the cumulative distribution frequency (CDF) curves were generated to plot the proportion of subjects experiencing different degrees of change at Day 29, Day 64, Day 126 and Months 6 and 12 for each treatment group for the key domains of interest to support the findings from pre-specified RDs.

Analysis of subjects undergoing cross-over in Arm A

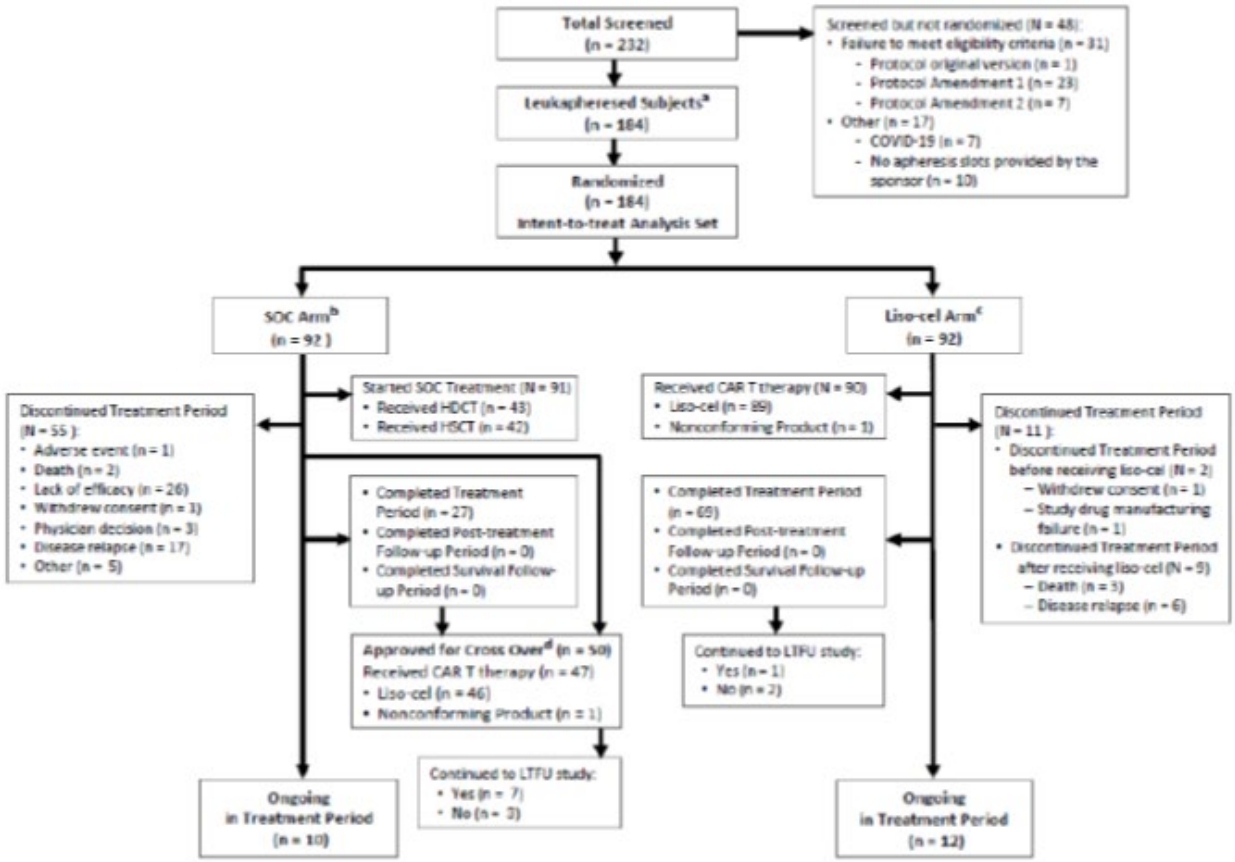
Exploratory efficacy analyses for subjects randomized to Arm A who cross over to JCAR017 were based on the JCAR017-treated analysis set (Arm A Post-cross Over) and included: CRR, ORR, EFS (defined as the time from JCAR017 infusion to death due to any cause, PD, or start of a new antineoplastic therapy, whichever occurs first), PFS (defined as the time from JCAR017 infusion to death from any cause or PD, whichever occurs first), OS, DoR (defined as the time from first post-infusion response to PD, start of new antineoplastic therapy or death due to any cause). Response assessments after cross over were based on investigator's assessment.

Results

Participant flow

A summary of overall subject disposition for subjects in the ITT analysis set, up to the end of the treatment period, is shown in Figure below:

Figure 11. subject disposition



CAR-T: Chimeric antigen receptor T-cell; COVID-19: Coronavirus disease 2019; HDCT = high dose chemotherapy; HSCT = hematopoietic stem cell transplant; IRC = Independent review committee; LDC = lymphodepleting chemotherapy; liso-cel = lisocabtagene maraleucel; LTFU = long-term follow up; SOC = standard of care.

[a] During screening, subjects are assessed for eligibility for randomization and unstimulated leukapheresis.

[b] Arm A: Subjects randomized to Arm A were to receive 3 cycles of SOC salvage therapy (rituximab, dexamethasone, cytarabine and cisplatin [R-DHAP], rituximab, ifosfamide, carboplatin and etoposide [R-ICE], or rituximab, gemcitabine, dexamethasone, and cisplatin [R-GDP]) followed by HDCT and HSCT.

[c] Arm B: Subjects randomized to Arm B were to receive LDC followed by liso-cel infusion; bridging therapy was allowed per protocol.

[d] See Section 9.4.1.3 for eligibility criteria for subjects to cross over from Arm A to receive LDC followed by liso-cel infusion. Subjects were approved to crossover by the Medical Monitor after IRC confirmation of a qualifying event. Disposition for subjects included in the cross over analysis set is shown in Table 13.

Note: This diagram presents details only up to the end of the treatment period. More information for the other study periods is in Table 12. The subject who received all HDCT agents but who was not recorded as having HSCT received the last dose of HDCT on 08 Mar 2021, the date of the cutoff date for this clinical study report

During study enrollment, a liso-cel contamination issue was identified in several subject lots. Due to this sterility issue, some subjects in the liso-cel arm had delayed liso-cel product availability and screened subjects were unable to be enrolled due to the lack of available leukapheresis slots until an investigation could be conducted. Ten subjects were not randomized because of this contamination issue since no apheresis slot was available.

Seven (14.6%) subjects were not randomized due to a hold in recruitment activities as a result of the COVID-19 pandemic. In the liso-cel arm, 3 (3.3%) subjects died due to COVID-19 (1 while on treatment and 2 during post-treatment follow-up) and 1 (1.1%) subject died due to SARS-CoV-2 infection during survival follow-up. In the SOC arm, 1 (1.1%) subject died due to SARS-CoV-2 acute respiratory disease during post-treatment follow-up.

Subjects who Crossed Over from the SOC Arm

Of the 92 subjects randomized to the SOC arm, 50 (54.3%) were approved to crossover after IRC confirmation of a qualifying event. Reasons for crossing over were progression (36 [72.0%] subjects), suboptimal response (8 [16.0%] subjects), and relapse (6 [12.0%] subjects. Of these 50 subjects, 3 were approved to cross-over but did not go on to receive liso-cel or nonconforming product, 46 received liso-cel and 1 subject received nonconforming product. Forty (80%) subjects completed the treatment period post-crossover, 3 (6.0%) subjects are ongoing, and 6 (12.0%) subjects discontinued in the treatment period: the reasons for discontinuation were disease relapse (4 [8.0%] subjects) and death (2 [4.0%] subjects)

Recruitment

The first subject signed an ICF for the study on 23 Oct 2018. The first and last subjects were randomized on 03 Dec 2018 and 08 Dec 2020, respectively. The study was conducted at 53 sites in 11 countries: Belgium, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, Switzerland, the United Kingdom, and the United States

Conduct of the study

Changes in the Conduct of the Study

The original protocol (dated 07 Mar 2018) was amended 2 times prior to the data cut-off date of 08 Mar 2021. In addition, there were 2 country-specific protocols for Germany and the UK. A country-specific addendum to Protocol Amendment 2 for Japan and a country-specific addendum to Protocol Amendment 1 for Sweden were also approved.

Protocol Amendment 1 was dated 06 Feb 2019; the main changes introduced are summarized as follows:

- PMBCL and THRBCL were added given that these histologies have similar biological behaviour, are treated according to the DLBCL treatment algorithm, and supporting preliminary data became available from Study 017001
- The definition of EFS was modified since the original protocol did not include the failure to achieve CR or PR by 9 weeks post-randomization as an event; the definition of PFS was modified since the original protocol also included SD at the first response assessment as an event
- In Arm A (SOC), subjects were to receive 3 cycles of SOC: cycle time was updated from 28 days to 21 days to be in line with clinical practice; accordingly, start of HDCT was moved from Day 85 to Day 71. The first efficacy assessment was moved from Day 57 to Day 64 and the second efficacy assessment was moved from Day 113 to Day 126
- Crossover criteria were updated since the original protocol permitted crossover only for subjects with a confirmed EFS event
- Recommendation for the selection of subjects with secondary CNS involvement was added and IT treatment was allowed
- Inclusion criterion 4 was restricted to ECOG performance status ≤1, and subjects with deep venous thrombosis (DVT) and/or pulmonary embolism (PE) and vascular tumour invasion were not eligible

One subject was enrolled in the study prior to the change of EFS primary endpoint, enrolment was resumed only after approval of Protocol Amendment 1. The 1 subject enrolled under the original protocol continued in the study as planned and the change in EFS and PFS definition did not impact the subject's outcome and analysis.

Protocol Amendment 2 was dated 09 Dec 2019; the main changes introduced are summarized as follows:

- Exclusion criteria were revised to only exclude patients with DVT or PE not managed on a stable regimen of anticoagulation or patients with progressive vascular tumour invasion, thrombosis, or embolism
- Pseudo-progression was specified not being an event for EFS
- Analyses to assess the impact of the COVID-19 pandemic were introduced

The **SAP JCAR017-BCM-003 Addendum** (version 1.1) was separately approved on 14 Apr 2021: updates primarily pertained to the addition of an additional efficacy interim analysis at approximately 80% information fraction (see the statistical methods section above for details).

Protocol deviations

Screening and randomization for this trial was ongoing when WHO declared the COVID-19 outbreak a global pandemic on 11 Mar 2020. Completion of study enrolment was delayed by approximately 4 months due to the pandemic. Monitoring activities were adapted to accommodate changes to site, Sponsor, and/or country policies during the COVID-19 pandemic: on-site monitoring visits were not conducted while sites could not accept visitors or due to limitations on travel to sites, and the use of remote SDV was implemented on a site-by-site basis.

Important protocol deviations (IPDs) were defined as a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect the subject's rights, safety, or well-being. In the ITT analysis set, a total of 9 (9.8%) subjects in the liso-cel arm and 9 (9.8%) subjects in the SOC arm had at least 1 important protocol deviation. The most frequently reported important protocol deviations were related to failure to report SAEs/suspected unexpected serious adverse reaction (SUSARs) per regulations (9 [9.8%] subjects in the SOC arm and 8 [8.7%] subjects in the liso-cel arm). None of the important protocol deviations were related to eligibility criteria and none were attributed to COVID-19.

A total of 19 (20.7%) subjects in the liso-cel arm and 10 (10.9%) subjects in the SOC arm had at least 1 COVID-19-related protocol deviation. Overall, the most frequently reported COVID-19-related protocol deviation was procedures not performed per protocol (12 [6.5%] subjects) followed by visits performed outside protocol windows (9 [4.9%] subjects). None of the imaging or procedure deviations were missed efficacy assessments impacting the primary endpoint.

The impact of the pandemic's disruption on study conduct, as measured by its effect on the primary and key secondary objectives, was considered to be minimal based on the following criteria: none of the important protocol deviations were attributed to COVID-19; lack of subjects with missed efficacy assessments impacting the primary endpoint; no subject discontinued in the treatment period and no treatments were delayed due to COVID-19; a relatively low number (1 [0.5%] subjects) of out of window assessments occurred due to COVID-19; low frequency of COVID-19-related AEs and deaths.

Baseline data

Baseline disease characteristics for subjects in the ITT analysis set were balanced between the liso-cel arm and the SOC arm (see Table below).

Table 31. Baseline Characteristics

Characteristic	**Breyanzi (N=92)**	**SOC (N=92)**
Median age, years (range)	60.0 (20, 74)	58.0 (26, 75)
≥ 65 to <75 years, n (%)	36 (39.1)	23 (25.0)
≥ 75 years, n (%)	0	2 (2.2)
Sex, n (%)		
Male	44 (47.8)	61 (66.3)
Female	48 (52.2)	31 (33.7)
ECOG Performance Status (at Screening)		
ECOG 0, n (%)	48 (52.2)	57 (62.0)
ECOG 1, n (%)	44 (47.8)	35 (38)
Disease histology subtype, n (%)		
DLBCL, NOS	53 (57.6)	50 (54.3)
DLBCL transformed from indolent lymphoma	7 (7.6)	8 (8.7)
High-grade B cell lymphoma	22 (23.9)	21 (22.8)
PMBCL	8 (8.7)	9 (9.8)
FL3B	1 (1.1)	0
T cell rich/histiocyte rich large B-cell lymphoma	1 (1.1)	4 (4.3)
Chemorefractory[a], n (%)	26 (28.3)	18 (19.6)
Refractory[b], n (%)	67 (72.8)	70 (76.1)
Relapsed[c], n (%)	25 (27.2)	22 (23.9)
Confirmed CNS involvement, n (%)	1 (1.1)	3 (3.3)
Never achieved CR from prior therapies, n (%)	62 (67.4)	64 (69.6)
sAAIPI at screening, n(%)		
0 or 1	56 (60.9)	55 (59.8)
2 or 3	36 (39.1)	37 (40.2)

Characteristic	Breyanzi (N=92)	SOC (N=92)
Sum of Product Diameters, n (%)ù		
>50 cm^2	10 (10.9)	10 (10.9)
≤50 cm^2	77 (83.7)	76 (82.6)
Missing	5 (5.4)	6 (6.5)
Lactate Dehydrogenase (LDH), n (%)		
<500 u/L	79 (85.9)	81 (88.0)
≥500 u/L	10 (10.9)	11 (12.0)
Missing	3 (3.3)	0
Number of Extranodal Involvement for DLBCL		
Median (range)	1.0 (0, 15)	1.0 (0, 12)

All 184 subjects in the ITT analysis set received prior anti-cancer therapies. As of the data cutoff date, it was recorded that all 184 (100%) subjects received 1 prior systemic anti-cancer therapy. Post-database lock it was confirmed that all 184 randomized subjects received both anti-CD20 monoclonal antibodies and anthracycline-containing first-line therapy.

Numbers analysed

The ITT analysis set was the primary population used for the efficacy analysis. The number (%) of subjects included in each analysis population is summarized in Table below.

Table 32. Analysis Population

Population	SOC Arm n (%)	Liso-cel Arm n (%)	Total [a] n (%)	SOC Arm Post-cross Over n (%)
Intent-to-treat Analysis Set [b]	92 (100)	92 (100)	184 (100)	50 (100)
Per-protocol Analysis Set [c]	89 (96.7)	88 (95.7)	177 (96.2)	47 (94.0)
Safety Analysis Set [d]	91 (98.9)	92 (100)	183 (99.5)	47 (94.0)
Pharmacokinetic Analysis Set - Conforming Product [e]				
ddPCR Pharmacokinetic Analysis Set	-	87 (94.6)	-	45 (90.0)
Flow Cytometry Pharmacokinetic Analysis Set	-	84 (91.3)	-	44 (88.0)
Pharmacokinetic Analysis Set - Nonconforming Product [f]				
ddPCR Pharmacokinetic Analysis Set	-	1 (1.1)	-	1 (2.0)
Flow Cytometry Pharmacokinetic Analysis Set	-	1 (1.1)	-	1 (2.0)
Crossover Analysis Set [g]	50 (54.3)	-	-	-
Liso-cel-treated Analysis Set [h]	-	89 (96.7)	-	46 (92.0)
Health-related Quality of Life Analysis Set [i]				
EORTC QLQ-C30 Health-related Quality of Life Analysis Set	43 (46.7)	47 (51.1)	90 (48.9)	
EQ-5D-5L Health-related Quality of Life Analysis Set	41 (44.6)	46 (50.0)	87 (47.3)	
FACT-Lym Health-related Quality of Life Analysis Set	40 (43.5)	45 (48.9)	85 (46.2)	

ddPCR = Droplet digital polymerase chain reaction; FACT-Lym = Functional Assessment of Cancer Therapy-Lymphoma; ITT = intent-to-treat; n (%) = number (percentage) of subjects; PK = pharmacokinetic; SOC = standard of care.
[a] Contains all subjects in the SOC arm or the liso-cel arm.
[b] All subjects randomized to a treatment arm.
[c] All subjects of the ITT analysis set characterized by having a minimal exposure to treatment assigned to the subject (SOC arm: one cycle of SOC; liso-cel arm: per protocol dose (CD4 and CD8) of liso-cel), having a baseline tumor assessment and at least one post-baseline response assessment and without important protocol deviations.
[d] All subjects who have taken at least one dose of study treatment.
[e] All subjects who have taken at least one dose of liso-cel study treatment who have both pre-infusion and at least one post-infusion PK measurement.
[f] All subjects who have taken at least one dose of nonconforming product study treatment who have both pre-infusion and at least one post-infusion PK measurement.
[g] All subjects of the ITT analysis set randomized in the SOC arm who crossed over to liso-cel treatment.
[h] All subjects who have received liso-cel.
[i] All subjects in the ITT population who filled in a baseline and at least one post-baseline health-related quality of life assessment.

Outcomes and estimation

Treatment exposure and compliance

Ninety-one subjects in the SOC arm received salvage immunochemotherapy. The most frequently used regimen of salvage immunochemotherapy was R-ICE (n=63, 63.7%), followed by R-GDP (n=24, 26.4%) and R-DHAP (n=15, 16.5%). Twelve (13.2%) subjects switched salvage immunochemotherapy and received more than one regimen. The most frequently reported reason to switch salvage immunochemotherapy was suboptimal response (5 subjects [5.5%]) followed by AE (4 subjects [4.4%]). Of the 91 subjects who received salvage immunochemotherapy, 48 (52.7%) discontinued from treatment before starting HDCT. All 43 subjects who started HDCT went on to receive all HDCT agents and 42 (46.2%) subjects in the SOC arm received HSCT after completing HDCT. The 1 subject who received all HDCT agents but who was not recorded as having HSCT received their last dose on the date of the cut-off date used for this study analysis.

Ninety-two subjects were randomized to the liso-cel arm. Two subjects discontinued before starting LDC. All 90 subjects who received LDC received all LDC agents for the expected 3 days (i.e., no agent was omitted); 89 (96.7%) went on to receive liso-cel and 1 (1.1%) received nonconforming product. A total of 58 (63.0%) subjects received bridging therapy to stabilize their disease during liso-cel manufacturing: 28 (30.4%) received it due to high tumour burden and 23 (25.0%) due to rapid progression. The most frequently used bridging therapy was R-ICE. Nine subjects in the liso-cel arm were PET-negative at their pre-LDC assessment after receiving bridging therapy. The median time from randomization to liso-cel

infusion was 34 days (range: 24 to 104). Four subjects in the liso-cel arm had delayed liso-cel product availability due to a contamination issue at the manufacturing site. The median total liso-cel dose was 99.92 × 10^6 cells (range: 97.1 to 102.5); the median CD8 and CD4 doses were 49.97 × 10^6 cells (range: 48.0 to 51.8) and 49.89 × 10^6 cells (range: 48.1 to 51.5), respectively.

Primary endpoint (EFS by IRC)

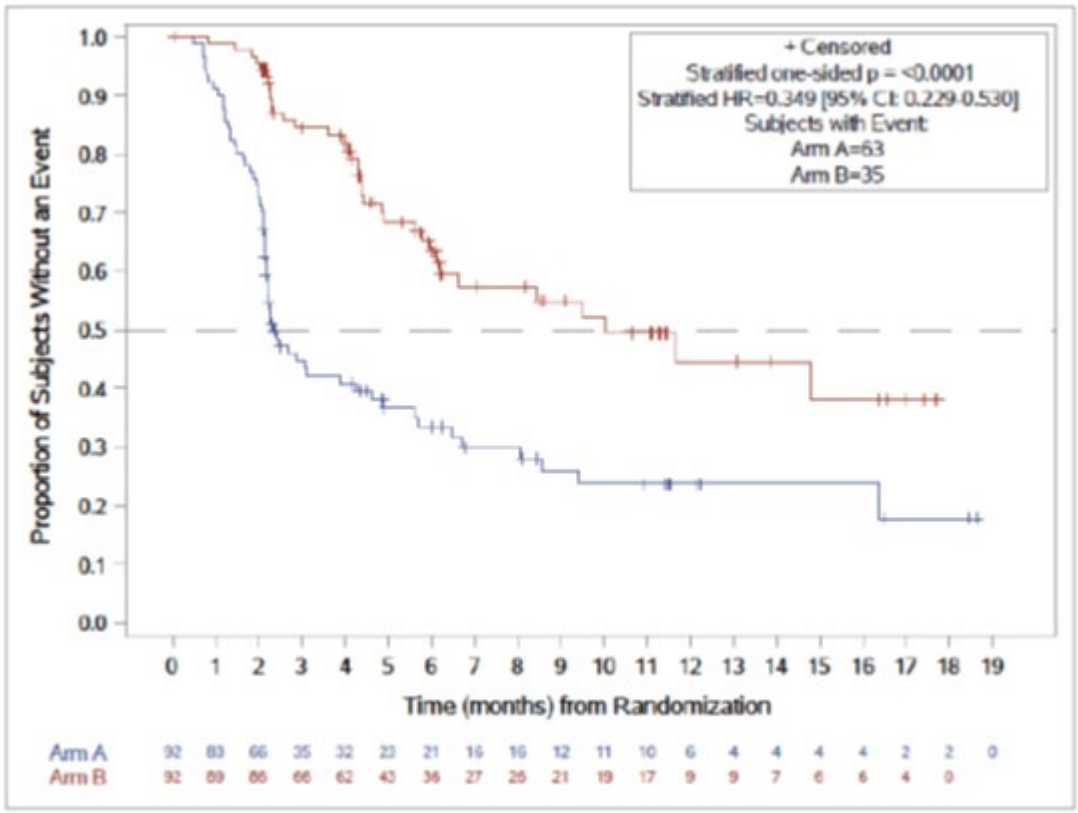
At a pre-specified interim analysis at 80% of the information fraction with a median on-study follow up time of 6.2 months (range 0.9 to 20 months) a statistically significant and clinically meaningful improvement in EFS was observed in the liso-cel arm compared to the SOC arm: HR = 0.349 (95% CI: 0.229, 0.530); p-value < 0.0001 (see Table and Figure below).

Table 33. Summary of Event-free Survival Based on IRC Assessment in Study BCM-003 (ITT Analysis Set)

Parameter	SOC Arm (N = 92)	Liso-cel Arm (N = 92)
Time to Event - n (%)		
Number of Patients with Event	63 (68.5)	35 (38.0)
Death	2 (2.2)	2 (2.2)
Progressive Disease	39 (42.4)	26 (28.3)
Failure to Achieve CR or PR by 9 Weeks Post-randomization	17 (18.5)	4 (4.3)
Start a New Anti-cancer Therapy due to Efficacy Concerns	5 (5.4)	3 (3.3)
Censored	29 (31.5)	57 (62.0)
Time to Event (Months)		
25th Percentile (95% CI) [a]	1.9 (1.3, 2.1)	4.4 (2.9, 5.8)
Median (95% CI)[a]	2.3 (2.2, 4.3)	10.1 (6.1, NE)
75th Percentile (95% CI) [a]	9.4 (5.6, NE)	NE (14.8, NE)
EFS Rate		
EFS Rate at 6 Months % (SE)	33.4 (5.30)	63.3 (5.77)
Two-sided 95% CI [b]	23.0, 43.8	52.0, 74.7
EFS Rate at 12 Months % (SE)	23.7 (5.28)	44.5 (7.72)
Two-sided 95% CI [b]	13.4, 34.1	29.4, 59.6
Stratified Hazard Ratio (95% CI) [c] (Experiment vs. Control)		0.349 (0.229, 0.530)
One-sided p-value [c]		<0.0001

[a] Median, 25th, and 75th percentile estimates of time to event are from Kaplan-Meier product-limit estimates.
[b] Greenwood's formula.
[c] Based on a stratified Cox proportional hazards model.
CI = confidence interval; CR = complete response; EFS = event-free survival; IRC = independent review committee; ITT = intent-to-treat; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; NE = not evaluable; PR = partial response; SE = standard error.
EFS is defined as the time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.

Figure 12. Klaplan-Meier Plot of Event-free Survival Based on IRC Assessment in Study BCM-003 (ITT Analysis Set)



Arm A = SOC arm; Arm B = liso-cel arm; CI = confidence interval; HR = hazard ratio; IRC = independent review committee; ITT = intent-to-treat; SOC =standard of care.

Sensitivity analyses for EFS

- Liso-cel vs. SOC when not adjusting for stratification factors: HR = 0.376 (95% CI: 0.248, 0.569)
- Liso-cel vs. SOC based on Investigator's assessment: HR = 0.343 (95% CI: 0.225, 0.522)
- Liso-cel vs. SOC according to the RMST analysis showed an increase in EFS of 3.8 months (95% CI: 2.1, 5.6) for subjects in the liso-cel arm compared to those in the SOC arm during the period from 0 to 14.78 months
- Liso-cel vs. SOC when using the FDA imaging interpretation: HR = 0.383 (95% CI: 0.254, 0.576)
- Liso-cel vs. SOC when including only subjects who were PET-positive at pre-LDC assessment after receiving bridging therapy: HR = 0.353 (95% CI: 0.209, 0.595)
- Liso-cel vs. SOC when censoring for missing scheduled assessments: HR = 0.346 (95%CI 0.226, 0.558)
- Liso-cel vs. SOC when censoring for any radiation therapy: HR = 0.344 (95%CI 0.266, 0.523)

<u>Key secondary endpoints</u>

Complete Response Rate (CRR), Overall Response Rate (ORR) and measures of response duration

A statistically significant improvement in CRR based on IRC assessment was seen in the liso-cel arm (66.3% [95% CI: 55.7, 75.8]) compared to the SOC arm (39.1% [95% CI: 29.1, 49.9]); stratified one sided p-value < 0.0001. A higher ORR, based on IRC assessment, was also seen in the liso-cel arm compared to the SOC arm (see Table below).

Table 34. Summary of Best Overall Response Based on IRC Assessment in Study BCM-003 (ITT Analysis Set)

Parameter	SOC Arm (N=92)	Liso-cel Arm (N=92)
Best Overall Response – n(%)		
Complete Response	36 (39.1)	61 (66.3)
Partial Response	8 (8.7)	18 (19.6)
Stable Disease	21 (22.8)	4 (4.3)
Progressive Disease	24 (26.1)	6 (6.5)
Non-evaluable	3 (3.3)	3 (3.3)
Complete Response Rate – n(%)	36 (39.1)	61 (66.3)
Two-sided 95% CI	29.1, 49.9	55.7, 75.8
Stratified One-sided p-value [a]		<0.0001
Overall Response Rate – n(%)	44 (47.8)	79 (85.9)
Two-sided 95% CI	37.3, 58.5	77.0, 92.3

Complete response rate is defined as the proportion of subjects achieving a best overall response of CR. Overall response rate is defined as the proportion of subjects achieving a best overall response of PR or CR. Subjects with unknown or missing response will be counted as non-evaluable in the analysis. Any responses after a start of a new antineoplastic therapy taken for efficacy concerns were not considered.

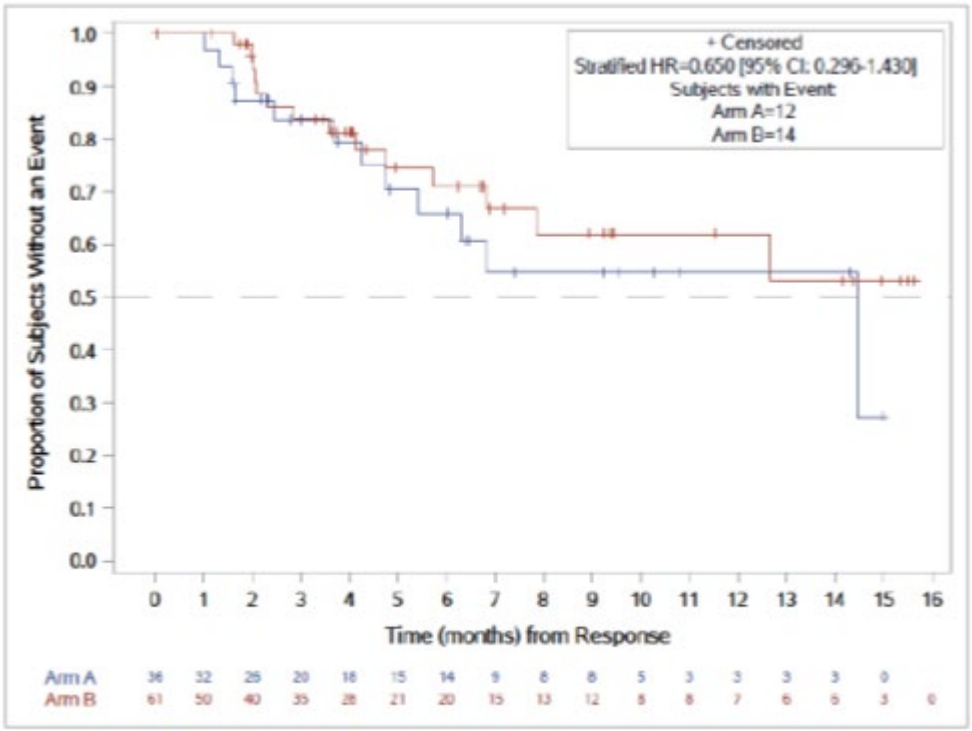
[a] Cochran-Mantel-Haenszel test.

CI = confidence interval; CR = complete response; IRC = independent review committee; ITT = intent-to-treat; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; PR = partial response.

Based on Investigator's assessment, a numerically higher CRR was observed in the liso-cel arm (57.6% [95% CI: 46.9, 67.9]) compared to the SOC arm (41.3% [95% CI: 31.1, 52.1]). The concordance rate of IRC and investigator's assessments of disease response for responders and non-responders was 95.1%. All the remaining sensitivity analyses for CRR showed consistent results with the primary analysis.

The median duration of complete response (DoCR) was 14.5 months (95% CI: 4.7, not evaluable) and NE (95% CI: 6.8, not evaluable) in the SOC and liso-cel arms, respectively (see Table and Figure below).

Figure13. Kaplan-Meier Plot of Duration of Complete Responses Based on IRC Assessment in Study BCM-003 (ITT Analysis Set)



Arm A = SOC arm; Arm B = liso-cel arm; CI = confidence interval; HR = hazard ratio; IRC = independent review committee; ITT = intent-to-treat; SOC = standard of care.

Forty-four subjects in the SOC arm had a response and the median DoR was 14.5 months (95% CI: 4.2, not estimable [NE]); 28 (30.4%); 79 (85.9%) subjects in the liso-cel arm had a response and the median DoR was 12.6 months (95% CI: 5.7, NE, see Table below).

Table 35. Sumary of Duration of Complete Response Based on IRC assessment in Study BCM-003 (ITT Analysis Set

Parameter	SOC Arm (N = 92)	Liso-cel Arm (N = 92)
Time to Event - n (%)		
Number of Patients with Event	12 (13.0)	14 (15.2)
Death	1 (1.1)	1 (1.1)
Progressive Disease	11 (12.0)	12 (13.0)
Start a New Anti-cancer Therapy due to Efficacy Concerns	0	1 (1.1)
Censored	24 (26.1)	47 (51.1)
Time to Event (Months)		
25th Percentile (95% CI) [a]	4.2 (1.6, 6.8)	4.8 (2.1, 12.6)
Median (95% CI)[a]	14.5 (4.7, NE)	NE (6.8, NE)
75th Percentile (95% CI) [a]	NE (14.5, NE)	NE (NE, NE)
DoCR Rate		
DoCR Rate at 6 Months % (SE)	65.9 (9.52)	71.0 (7.62)
Two-sided 95% CI [b]	47.2, 84.5	56.1, 86.0
DoCR Rate at 12 Months % (SE)	54.7 (10.72)	62.1 (8.92)
Two-sided 95% CI [b]	33.7, 75.7	44.6, 79.6
DoCR Rate at 24 Months % (SE)	NE (NE)	NE (NE)
Two-sided 95% CI [b]	NE, NE	NE, NE
DoCR Rate at 36 Months % (SE)	NE (NE)	NE (NE)
Two-sided 95% CI [b]	NE, NE	NE, NE
Stratified Hazard Ratio (95% CI) [c] (Experiment vs. Control)		0.650 (0.296, 1.430)

Duration of complete response (DoCR) is defined as the time from complete response to disease progression, start of new antineoplastic therapy due to efficacy concerns or death, whichever occurs first.

The analysis is restricted to subjects having a complete response.

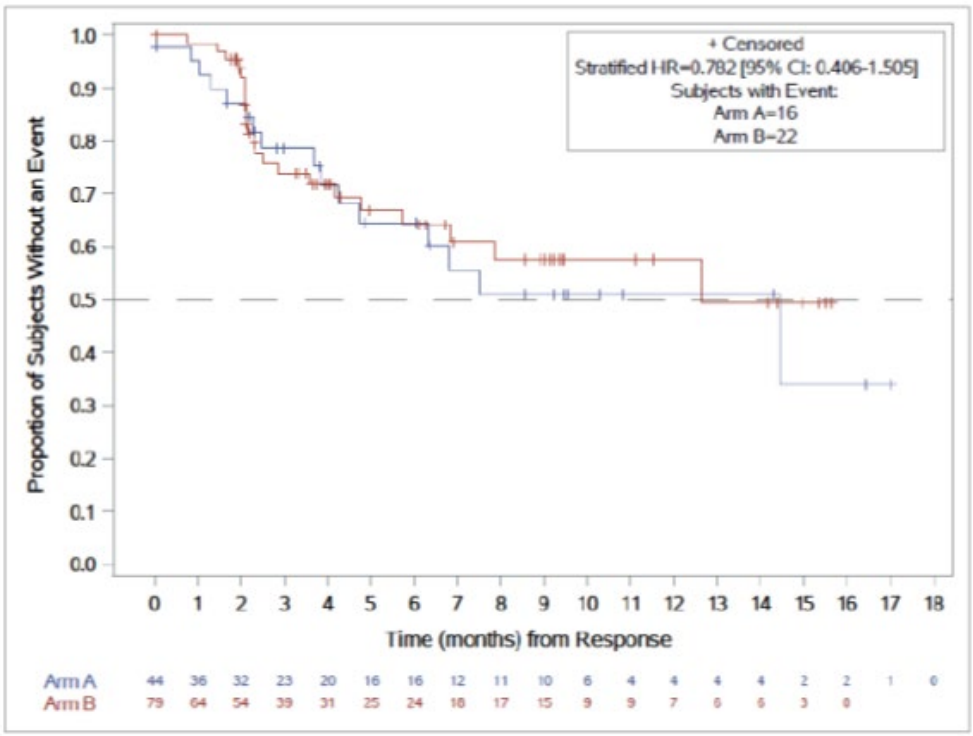
[a] Median, 25th, and 75th percentile estimates of time to event are from Kaplan-Meier product-limit estimates.

[b] Greenwood's formula.

[c] Based on a stratified Cox proportional hazards model.

CI = confidence interval; IRC = independent review committee; ITT = intent-to-treat; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; NE = not evaluable; SE = standard error; SOC = standard of care.

Figure 14. Kaplan-Meier Plot of Duration of Responses Based on IRC Assessment (ITT Analysis Set)



Arm A = SOC arm; Arm B = liso-cel arm; CI = confidence interval; HR = hazard ratio; IRC = independent review committee; ITT = intent-to-treat; SOC =standard of care.

Progression-free survival (PFS)

A statistically significant improvement in PFS was observed in the liso-cel arm compared to the SOC arm: HR = 0.406 (95% CI: 0.250, 0.659); p-value = 0.0001 (see Table and Figure below).

Table 36. Summary of Progression-free Survival Based on IRC Assessment in Study BCM-003 – ITT Principle (ITT Analysis Set)

Parameter	SOC Arm (N = 92)	Liso-cel Arm (N = 92)
Time to Event - n (%)		
Number of Patients with Event	43 (46.7)	28 (30.4)
Death	2 (2.2)	2 (2.2)
Progressive Disease	41 (44.6)	26 (28.3)
Censored	49 (53.3)	64 (69.6)
Time to Event (Months)		
25th Percentile (95% CI) [a]	2.1 (1.4, 3.1)	4.9 (4.3, 6.6)
Median (95% CI)[a]	5.7 (3.9, 9.4)	14.8 (6.6, NE)
75th Percentile (95% CI) [a]	NE (8.6, NE)	NE (NE, NE)
PFS Rate		
PFS Rate at 6 Months % (SE)	47.8 (6.53)	69.4 (5.74)
Two-sided 95% CI [b]	35.0, 60.6	58.1, 80.6
PFS Rate at 12 Months % (SE)	33.9 (7.03)	52.3 (7.96)
Two-sided 95% CI [b]	20.1, 47.7	36.7, 67.9
Stratified Hazard Ratio (95% CI) [c] (Experiment vs. Control)		0.406 (0.250, 0.659)
One-sided p-value [c]		0.0001

PFS is defined as the time from randomization to death from any cause or to progressive disease, whichever occurs first.

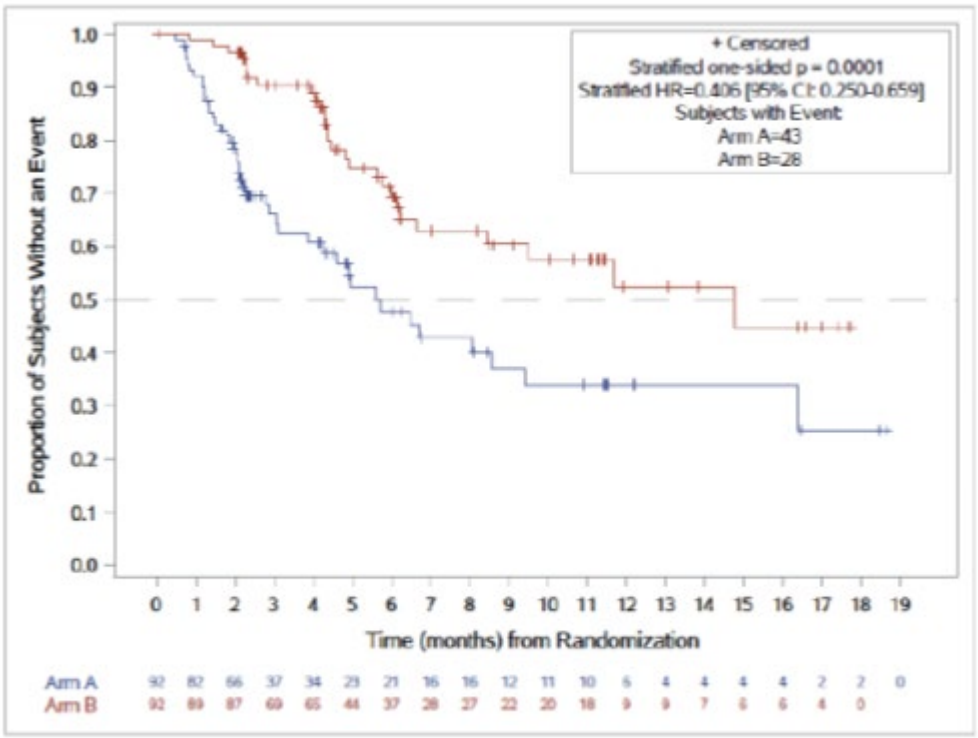
[a] Median, 25th, and 75th percentile estimates of time to event are from Kaplan-Meier product-limit estimates.

[b] Greenwood's formula.

[c] Based on a stratified Cox proportional hazards model.

CI = confidence interval; IRC = independent review committee; ITT = intent-to-treat; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; NE = not evaluable; PFS = progression-free survival; SE = standard error; SOC = standard of care.

Figure 15. Kaplan-Meier Plot of Progression-free Survival Based on IRC Assessment in Study BCM-003 – ITT Principle (ITT Analysis Set)



Arm A = SOC arm; Arm B = liso-cel arm; CI = confidence interval; HR = hazard ratio; IRC = independent review committee; ITT = intent-to-treat; SOC = standard of care.

An improvement in PFS based on IRC assessment (HRs in the range 0.414 – 0.457) continued to be observed in the liso-cel arm compared to the SOC arm in all the pre-specified sensitivity analyses for PFS.

Overall survival (OS)

At this interim analysis with a median follow up of 6 months, a numerical trend in favour of the liso-cel arm was observed: HR = 0.509 (95% CI: 0.258, 1.004); p-value = 0.0257 (see Table and Figure below).

Table 37. Summary of Overall Survival Based in Study BCM-003 – ITT Principle (ITT Analysis Set)

Parameter	SOC Arm (N = 92)	Liso-cel Arm (N = 92)
Time to Event - n (%)		
Death	24 (26.1)	13 (14.1)
Censored	68 (73.9)	79 (85.9)
Time to Event (Months)		
25th Percentile (95% CI) [a]	9.5 (6.6, 13.6)	14.3 (7.9, NE)
Median (95% CI)[a]	16.4 (11.0, NE)	NE (15.8, NE)
75th Percentile (95% CI) [a]	NE (NE, NE)	NE (NE, NE)
OS Rate		
OS Rate at 6 Months % (SE)	89.4 (3.36)	91.8 (3.29)
Two-sided 95% CI [b]	82.9, 96.0	85.4, 98.2
OS Rate at 12 Months % (SE)	64.2 (6.99)	79.1 (6.13)
Two-sided 95% CI [b]	50.5, 77.9	67.1, 91.1
OS Rate at 24 Months % (SE)	NE (NE)	NE (NE)
Two-sided 95% CI [b]	NE, NE	NE, NE
OS Rate at 36 Months % (SE)	NE (NE)	NE (NE)
Two-sided 95% CI [b]	NE, NE	NE, NE
Stratified Hazard Ratio (95% CI) [c] (Experiment vs. Control)		0.509 (0.258, 1.004)
One-sided p-value [c]		0.0257

OS is defined as the time from randomization to death from any cause.

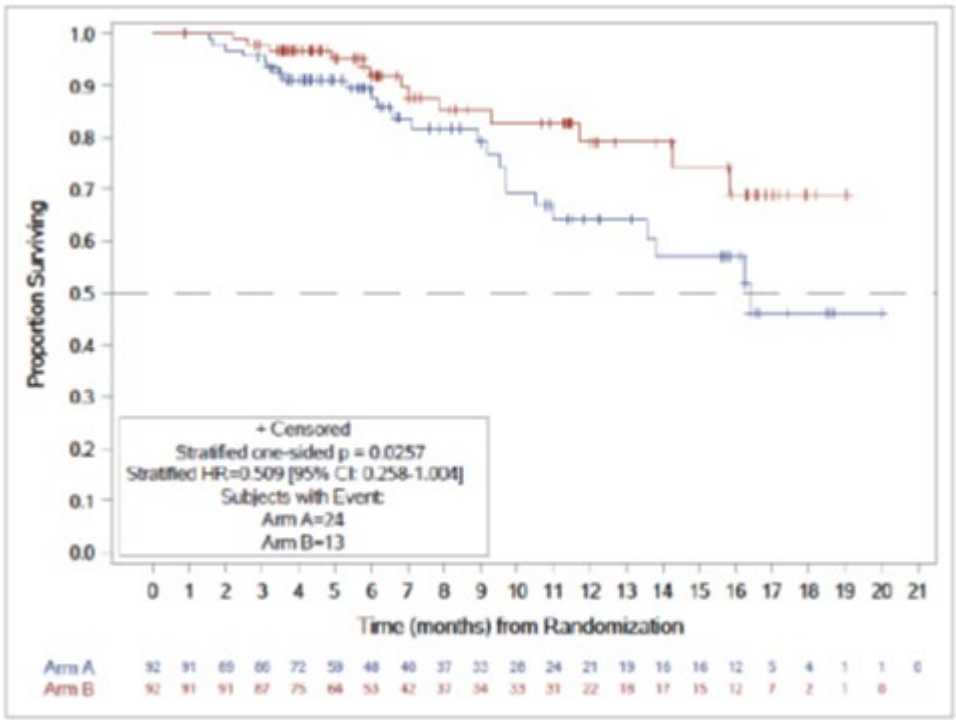
[a] Median, 25th, and 75th percentile estimates of time to event are from Kaplan-Meier product-limit estimates.

[b] Greenwood's formula.

[c] Based on a stratified Cox proportional hazards model.

CI = confidence interval; ITT = intent-to-treat; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; NE = not evaluable; OS = overall survival; SE = standard error; SOC = standard of care.

Figure 16. Kaplan-Meier Plot of Overall Survival in Study BCM-003 – ITT Principle (ITT Analysis Set)



Arm A = SOC arm; Arm B = liso-cel arm; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; SOC =standard of care.

At this interim analysis, the liso-cel arm did not demonstrate a statistically significant improvement in OS compared to the SOC arm. When adjusted for the confounding effect of subjects in the SOC arm crossing over to receive liso-cel using the 2-stage Accelerated Failure Time Model, the results for OS are consistent with the ITT principle and generate a HR = 0.321 (95% CI: 0.160, 0.644). When adjusted for the confounding effect of subjects in the SOC arm crossing over to receive liso-cel using the rank-preserving structural failure time (RPSFT) model, the results for OS are consistent with the ITT principle and generate a HR = 0.268 (95% CI: 0.117, 0.615).

Other secondary endpoints

Progression-free Survival on Next Line of Treatment

A summary of PFS-2 based on the Investigator's assessment is shown in Table below:

Table 38. Summary of Progression-free Survival on the Next Line of Treatment (PFS-2) Based on investigator's Assessment (ITT Analysis Set)

Parameter	SOC Arm (N = 92)	Liso-cel Arm (N = 92)
Time to Event - n (%)		
Number of Patients with Event	53 (57.6)	33 (35.9)
Death	6 (6.5)	3 (3.3)
First Progression	51 (55.4)	31 (33.7)
Second Progression	2 (2.2)	2 (2.2)
Number of Events		
None	39 (42.4)	59 (64.1)
One	47 (51.1)	30 (32.6)
Two	6 (6.5)	3 (3.3)
Censored	55 (59.8)	67 (72.8)
Randomization	2 (2.2)	2 (2.2)
Last Disease Assessment	53 (57.6)	65 (70.7)
Stratified HR (95% CI)		0.494 (0.321, 0.760)

CI = confidence interval; HR = Hazard Ratio; ITT = intent-to-treat; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; SE = standard error; SOC = standard of care.
PFS-2 is defined as time from randomization to second objective disease progression or death from any cause, whichever occurs first. The recurrent event approach based on a Prentice, Williams and Peterson (PWP) model is used.

High Dose Chemotherapy and Hematopoietic Stem Cell Transplant

Forty-three (46.7%) subjects in the SOC arm completed HDCT; 42 (45.7%) of subjects went on to complete HSCT. Three months post-HSCT, the CR rate in subjects who completed HSCT was 76.2%. No subject in the liso-cel arm went on to receive HSCT for consolidation post-liso-cel infusion.

HR-QoL

The HRQoL analysis set consisted of 90 subjects for the EORTC QLQ-C30 questionnaire, and 85 for the FACT-LymS questionnaires (48.9% and 46.2% of the ITT analysis set, respectively). The analysis focuses on time points with number of available PRO assessments ≥10, i.e., up to Month 6.

Compliance rates were moderate (≥40%) across all visits and comparable between groups for all measures. The suboptimal compliance rate was due to technical challenges associated with the administration of the questionnaires during the COVID-19 pandemic.

Baseline values are reported in Table below:

Table 39. baseline Mean Scores on the EORTC QLQ-C30 Primary Domain of Interest and FACT-LymS

HRQoL Domains of Interest	SOC Arm (n = 43 for EORTC QLQ C30 n = 40 for FACT LymS)		Liso-cel Arm (n = 47 for EORTC QLQ C30 n = 45 for FACT LymS)		General Population (N = 11,343[a])
EORTC QLQ-C30	Mean (StD)	Median (Q1, Q3)	Mean (StD)	Median (Q1, Q3)	Mean
Fatigue	26.87 (20.18)	33.33 (11.11, 33.33)	34.52 (24.76)	33.33 (22.22, 44.44)	28.1
Pain	25.58 (27.06)	16.67 (0.00, 50.00)	30.50 (29.96)	16.67 (0.00, 50.00)	24.0
Physical Functioning	87.91 (14.93)	93.33 (80.00,100.0)	83.26 (17.19)	86.67 (73.33, 100.0)	84.7
Cognitive Functioning	92.25 (12.25)	100.0 (83.33,100.0)	83.69 (20.11)	83.33 (66.67, 100.0)	85.6
Global Health Status/QoL	68.22 (22.07)	75.00 (50.00, 83.33)	67.73 (21.54)	66.67 (50.00, 83.33)	65.8
FACT-LymS[b]	48.95 (5.85)	49.00 (44.00, 53.00)	46.24 (9.61)	48.00 (43.00, 53.00)	No reference available

HRQoL = health-related quality of life; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer – Quality of Life C30 questionnaire; FACT-LymS = Functional Assessment of Cancer Therapy – Lymphoma Subscale; Q1 = first quartile; Q3 = third quartile; QoL = quality of life; SOC = standard of care; StD = standard deviation

[a] Reference: Nolte, 2019; The EORTC QLQ-C30 normative scores are from the European general population data based on 11 European Union countries andre-weighted with age and gender distributions

[b] Reference data is not available for the FACT-LymS.

Note: Higher scores reflect better HRQoL for the functioning (i.e., physical and cognitive) and global health/QoL domains and more symptoms (i.e., worse HRQoL) for the symptom domain (i.e., fatigue) of the EORTC QLQ-C30.

Group-level Analysis: Mean Changes from Baseline

Subjects treated with liso-cel showed a trend to improvement in lymphoma specific symptoms (FACT LymS scores), global health (GH/QoL), pain, cognitive functioning and fatigue during the first 6 months post infusion. The improvement crossed the MID line in several domains during multiple time points and was particularly prominent in GH/QoL, cognitive functioning, and fatigue. Subjects treated with SOC demonstrated a tendency to deterioration (sometimes beyond the MID line) in all these domains. Physical Functioning scores mostly remained stable and within MID and comparable in both arms. Results should be interpreted with caution due to the small sample size.

Individual-level Analysis: Proportion of Subjects Improved/No Change/Deteriorated

Overall, more subjects improved and fewer worsened over time in most domains in the liso-cel arm and in some domains in the SOC arm. Overall, for most time points, more subjects experienced improvement (and fewer subjects experienced deterioration) in the liso-cel arm than in the SOC arm in the following domains: fatigue, pain, cognitive functioning, GH/QOL, FACT-LymS.

The results, however, should be interpreted with caution due to the small sample size and as no statistical testing has been performed to detect potential differences between the arms. Not collecting PRO data in subjects in the SOC arm after crossover could also have contributed to the limited number of subjects in the SOC arm with PRO assessments after 3 cycles of SOC treatment.

Updated efficacy results from the Primary Analysis of study BCM-003 (13-May-2022 DCO Cutoff Date)

With 17.53 months median follow up in the liso-cel arm and 17.49 months in the SOC arm (an additional 11.3 months compared to the 6.19 months reported in the 80% interim analysis IA [data cutoff date 08-Mar-2021]), the clinically meaningful improvements in EFS, CRR, and PFS with liso-cel compared to SOC were maintained in the ITT analysis set. The updated minimum follow-up for both arms was 0.9 months.

The updated efficacy outcomes are summarised in Table and Figures below.

Table 40: Summary of Primary and Key Secondary Efficacy Endpoints (ITT Analysis Set)

	BCM-003 Interim 80% Analysis (data cut off: 08-Mar-2021)		**BCM-003 Primary Analysis (data cut off: 13-May-2022)**	
Parameter	**SOC Arm (Arm A) (N = 92)**	**Liso-cel Arm (Arm B) (N = 92)**	**SOC Arm (Arm A) (N = 92)**	**Liso-cel Arm (Arm B) (N = 92)**
EFS Based on IRC Assessment (Primary Endpoint)				
Number of subjects with events, n (%)	63 (68.5)	35 (38.0)	71 (77.2)	44 (47.8)
Median EFS (95% CI) (months) [a]	2.3 (2.2, 4.3)	10.1 (6.1, NE)	2.4 (2.2, 4.9)	NE (9.5, NE)
Stratified HR (95% CI) [b]	-	0.349 (0.229, 0.530)	-	0.356 (0.243, 0.522)
One-sided p-value	-	< 0.0001	-	< 0.0001
6-month EFS rate (SE)	33.4 (5.30)	63.3 (5.77)	36.2 (5.05)	68.1 (4.88)
Two-sided 95% CI [c]	23.0, 43.8	52.0, 74.7	26.3, 46.1	58.6, 77.7
12-month EFS rate (SE)	23.7 (5.28)	44.5 (7.72)	22.5 (4.42)	57.1 (5.19)
Two-sided 95% CI [c]	13.4, 34.1	29.4, 59.6	13.9, 31.2	47.0, 67.3
18-month EFS rate (SE)	-	-	20.8 (4.41)	52.6 (5.25)
Two-sided 95% CI [c]	-	-	12.2, 29.5	42.3, 62.9
24-month EFS rate (SE)	-	-	20.8 (4.41)	50.1 (5.57)
Two-sided 95% CI [c]	-	-	12.2, 29.5	39.2, 61.0
CRR Based on IRC Assessment (Key Secondary Endpoint)				
Complete response rate, n (%) [d]	36 (39.1)	61 (66.3)	40 (43.5)	68 (73.9)
Two-sided 95% CI	29.1, 49.9	55.7, 75.8	33.2, 54.2	63.7, 82.5
Stratified one-sided p-value	-	< 0.0001	<0.0001	

Table 40: Summary of Primary and Key Secondary Efficacy Endpoints (ITT Analysis Set)

	BCM-003 Interim 80% Analysis (data cut off: 08-Mar-2021)		**BCM-003 Primary Analysis (data cut off: 13-May-2022)**	
Parameter	**SOC Arm (Arm A) (N = 92)**	**Liso-cel Arm (Arm B) (N = 92)**	**SOC Arm (Arm A) (N = 92)**	**Liso-cel Arm (Arm B) (N = 92)**
PFS Based on IRC Assessment (Key Secondary Endpoint				
Number of subjects with event, n (%)	43 (46.7)	28 (30.4)	52 (56.5)	37 (40.2)
Median time to event (95% CI) (months)	5.7 (3.9, 9.4)	14.8 (6.6, NE)	6.2 (4.3, 8.6)	NE (12.6, NE)
Stratified HR (95% CI) [b]	-	0.406 (0.250, 0.659)	-	0.400 (0.261, 0.615)
One-sided p-value	-	0.0001	<0.0001	
6-month PFS rate (SE)	47.8 (6.53)	69.4 (5.74)	51.7 (5.83)	73.7 (4.72)
Two-sided 95% CI [c]	35.0, 60.6	58.1, 80.6	40.2, 63.1	64.5, 83.0
12-month PFS rate (SE)	33.9 (7.03)	52.3 (7.96)	31.2 (5.65)	63.1 (5.19)
Two-sided 95% CI [c]	20.1, 47.7	36.7, 67.9	20.2, 42.3	53.0, 73.3
18-month EFS rate (SE)	-	-	28.8 (5.70)	58.2 (5.34)
Two-sided 95% CI [c]	-	-	17.7, 40.0	47.7, 68.7
24-month EFS rate (SE)	-	-	28.8 (5.70)	55.6 (5.72)
Two-sided 95% CI [c]	-	-	17.7, 40.0	44.4, 66.8
OS (Key Secondary Endpoint)				
Number of subjects with event, n (%)	24 (26.1)	13 (14.1)	38 (41.3)	28 (30.4)
Median time to event, n (%)	16.4 (11.0, NE)	NE (15.8, NE)	29.9 (17.9, NE)	NE (29.5, NE)
Stratified HR (95% CI) [b]	-	0.509 (0.258, 1.004)	-	0.724 (0.443, 1.183)
One-sided p-value	0.0257		0.0987	
6-month OS rate (SE)	89.4 (3.36)	91.8 (3.29)	88.9 (3.31)	93.4 (2.60)
Two-sided 95% CI [c]	82.9, 96.0	85.4, 98.2	82.4, 95.4	88.3, 98.5
12-month OS rate (SE)	64.2 (6.99)	79.1 (6.13)	72.0 (4.76)	83.4 (3.92)

Table 40: Summary of Primary and Key Secondary Efficacy Endpoints (ITT Analysis Set)

	BCM-003 Interim 80% Analysis (data cut off: 08-Mar-2021)		**BCM-003 Primary Analysis (data cut off: 13-May-2022)**	
Parameter	**SOC Arm (Arm A) (N = 92)**	**Liso-cel Arm (Arm B) (N = 92)**	**SOC Arm (Arm A) (N = 92)**	**Liso-cel Arm (Arm B) (N = 92)**
Two-sided 95% CI [c]	50.5, 77.9	67.1, 91.1	62.7, 81.3	75.7, 91.1
18-month EFS rate (SE)	-	-	60.6 (5.32)	73.1 (4.70)
Two-sided 95% CI [c]	-	-	50.2, 71.1	63.9, 82.3
24-month EFS rate (SE)	-	-	55.4 (5.68)	65.0 (6.16)
Two-sided 95% CI [c]	-	-	44.3, 66.6	52.9, 77.1
36-month EFS rate (SE)	-	-	46.2 (9.67)	NE (NE)
Two-sided 95% CI [c]	-	-	27.2, 65.1	NE, NE

[a]Median estimates of time to event is from a Kaplan-Meier product-limit estimate. [b] Based on a stratified Cox proportional hazards model. [c] Greenwood's formula [d] Cochran-Mantel-Haenszel test. CI = confidence interval, NE = not evaluable, SE = standard error, SOC = standard of care

Figure 17. Kaplan-Meier Plot of Event-free Survival based on IRC Assessment (ITT Analysis Set)

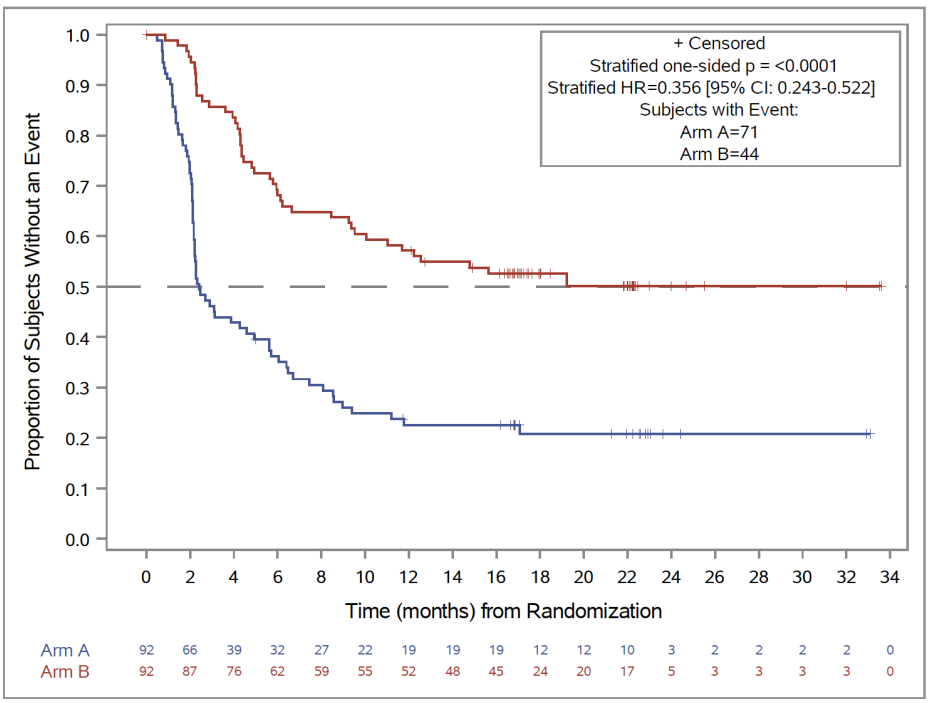
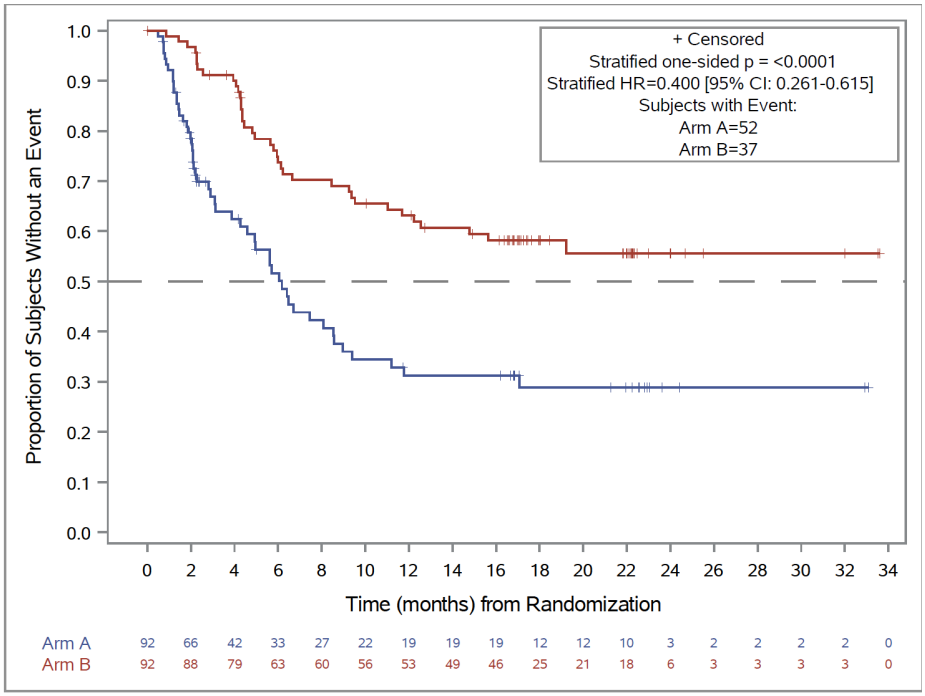
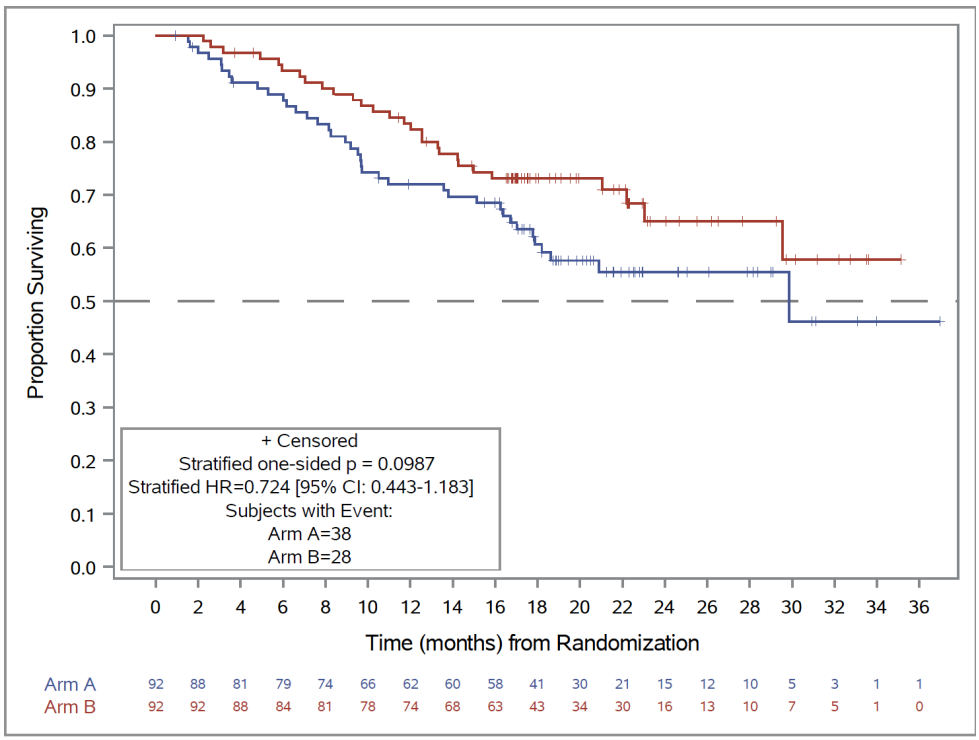


Figure 18. Kaplan-Meier Plot of Progression-free Survival based on IRC Assessment - ITT Principle (ITT Analysis Set)



Twenty-one (22.8%) subjects in the SOC arm had a CR and the median DoCR was 9.3 months (95% CI: 5.1, NE); 19 (20.7%) subjects were censored. Twenty-one (22.8%) subjects in the liso cel arm had a CR and the median DoCR was not evaluable (95% CI: NE, NE); 47 (51.1%) subjects were censored.

Figure 19. Kaplan-Meier Plot of Overall Survival based on IRC Assessment - ITT Principle (ITT Analysis Set)



The liso-cel arm did not demonstrate a statistically significant improvement in OS compared to the SOC arm, although a numerical trend in favor of the liso-cel arm was demonstrated. The nature of the study did not allow to adequately power the test for OS due to various factors including the limited number of events (i.e., deaths) available for analysis and the confounding effect of subjects crossing over from the SOC arm to receive liso-cel.

When adjusted for the confounding effect of subjects in the SOC arm crossing over to receive liso cel using the 2-stage Accelerated Failure Time Model, the results for OS are consistent with the ITT analysis and generate a HR = 0.415 (95% CI: 0.251, 0.686) favoring liso-cel over SOC.

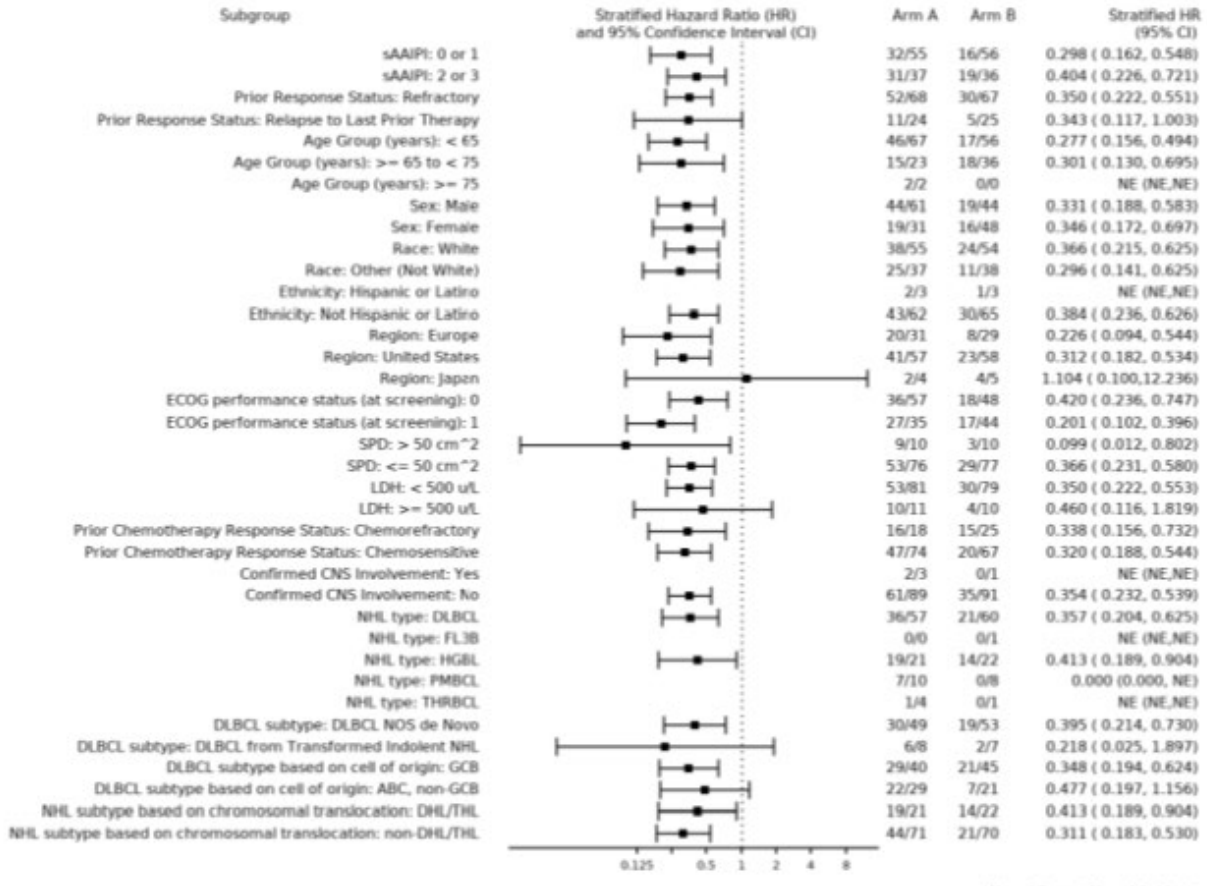
When adjusted for the confounding effect of subjects in the SOC arm crossing over to receive liso cel using the RPSFT model, the results for OS are consistent with the ITT principle and generate a HR = 0.279 (95% CI: 0.145, 0.537) favoring liso-cel over SOC.

Ancillary analyses

Subgroup analyses

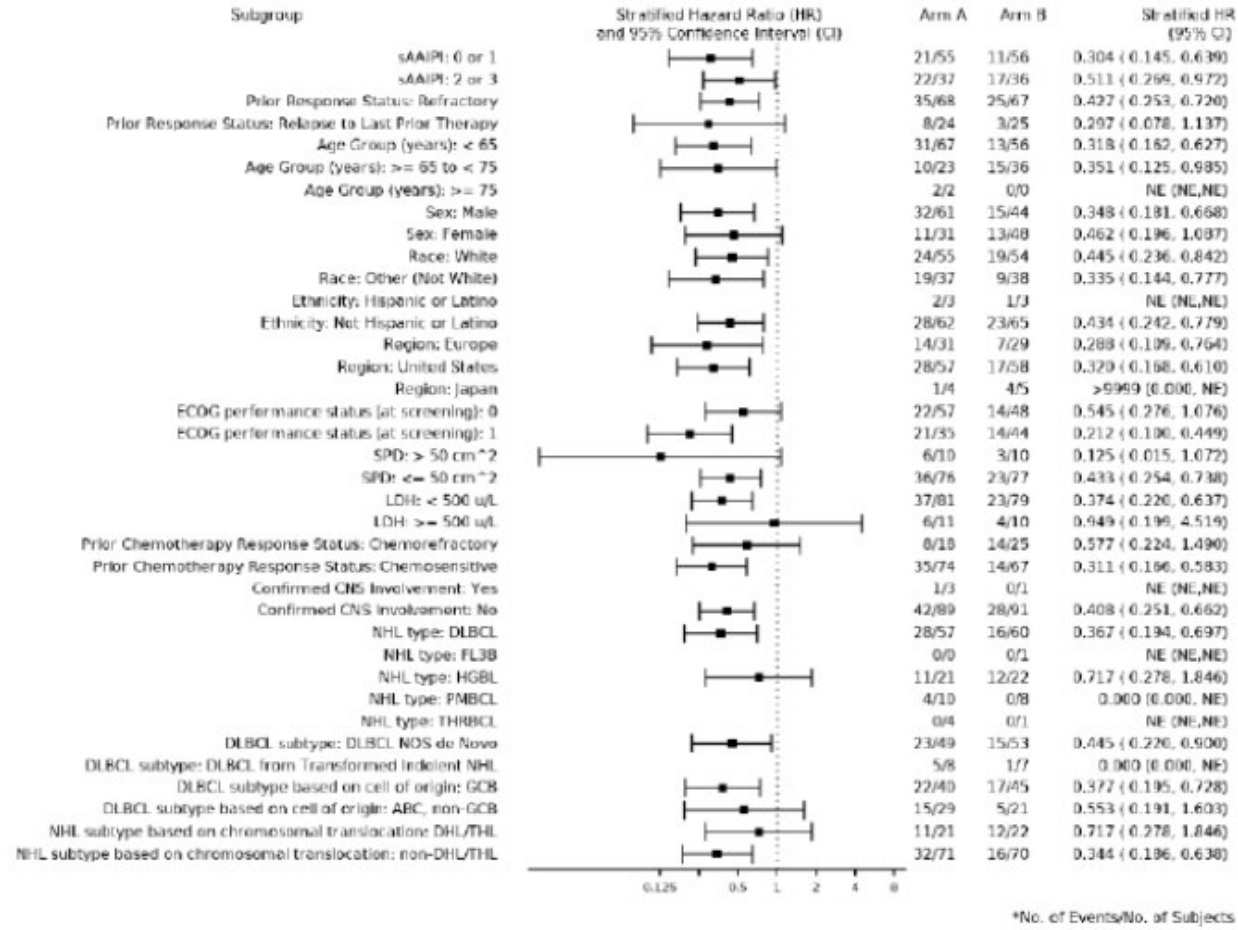
Results from subgroup analyses for EFS are summarised in Figure below.

Figure 20. Forest Plot of Event-Free Survival Based on IRC Assessment by Subgroup in Study BCM-003 (ITT Analysis Set)



Note: No subject had an SPD = 50 cm^2. Therefore, the 2 SPD subgroups are < 50 cm^2 versus > 50 cm^2.
Arm A = SOC arm; Arm B = liso-cel arm

Figure 21. Forest Plot of Progression-Free Survival Based on IRC Assessment by Subgroup in Study BCM-003 – ITT Principle (ITT Analysis Set)



Note: No subject had an SPD = 50 cm^2. Therefore, the 2 SPD subgroups are < 50 cm^2 versus > 50 cm^2.
Arm A = SOC arm; Arm B = liso-cel arm

Subgroup analyses for OS were inconclusive due to the limited number of deaths in each subgroup.

Correlations between one of the Two Drug Drug Product Component Quality Attribute and EFS

For the attribute ranges observed in Study-BCM-003, univariate statistical analyses revealed a correlative relationship between a T cell attribute in one of the two drug product component and EFS.

This attribute exhibited a relationship with EFS ($p= 2.985 \times 10^{-4}$) such that variation in this attribute secretion was associated with a different risk of hazard of progression, death, failure to achieve CR/PR by 9 weeks post randomization or start of a new anti-neoplastic therapy. A multivariate analysis correcting for other patient characteristics (i.e., age, sex, ECOG, relapsed or refractory disease status, sAAIPI score, LDH, and SPD) was also performed, confirming the univariate findings.

Quartile-based analyses confirmed a statistically significant relationship with EFS: equally split quartiles revealed a statistically significant relationship with EFS ($p = 0.0016$) in which the highest quartile of this attribute demonstrates a median EFS of 6.14 months compared to the other quartile groups (14.78 months or median not reached yet). Optimally split analyses reveal a statistically significant relationship with EFS ($p < 0.0001$) in which the higher attribute group ($x > 1789$ pg/mL) demonstrates a median EFS of 4.07 months compared to the lower attribute group (14.78 months, see Figure below).

Notably, in both instances, even the expressors of this attribute demonstrate improved benefit in median EFS in liso-cel arm over the standard-of-care arm in Study BCM-003 (i.e. 2.3 months median EFS).

As these associations were post-hoc and hypothesis generating, the precise biological and medical implications of these findings remain undetermined (see the Quality section above for additional details).

To investigate whether this attribute offers offers some prognostic value in the clinical setting of 2L TI patients in general, patients whose apheresis was processed to manufacture liso-cel drug product, but were ultimately randomized into the SOC arm (Arm A) and not treated with liso-cel , were analyzed for potential correlations between their clinical efficacy outcomes, with chemoimmunotherapy and transplant, and this T cell attribute

The presented analyses indicate no statistically significant relationships between this T cell attribute liso-cel drug product (manufactured for patients prior to randomization into the SOC Arm) and patient clinical efficacy outcomes upon their treatment with SOC.

Efficacy in subjects who underwent crossover

Fifty subjects were approved to crossover after IRC confirmation of a qualifying event. Of the 50 subjects approved to crossover, 46 received liso-cel; 1 received non-conforming product and 3 did not receive liso-cel. Of the 50 subjects approved to crossover, 10 had prior HSCT. For this interim analysis, the median follow-up (time from liso-cel infusion to the last date known alive) for subjects in the SOC arm who crossed-over to liso-cel was 4.14 months and the minimum follow-up was 0.4 months.

Results from the cross-over subset are summarised in Table below.

Table 42. Efficacy Endpoint in the Liso-cel-treated Analysis Set in Study BCM-003 (SOC Arm Post-crossover)

Parameter	SOC Arm Post-crossover (N = 46)
Event-free Survival Based on Investigator's Assessment	
Number of subjects with event, n (%)	22 (47.8)
Censored, n (%)	24 (52.2)
Median EFS (95% CI) (months)[a]	3.4 (2.8, 7.8)
Best Overall Response Based on Investigator's Assessment	
Complete Response, n (%)	18 (39.1)
Partial Response, n (%)	4 (8.7)
Stable Disease, n (%)	1 (2.2)
Progressive Disease, n (%)	16 (34.8)
Non-evaluable, n (%)	7 (15.2)
Complete Response Rate Based on Investigator's Assessment, n (%)	18 (39.1)
Two-sided 95% CI	25.1, 54.6
Overall Response Rate Based on Investigator's Assessment, n (%)	22 (47.8)
Two-sided 95% CI	32.9, 63.1
Progression-free Survival Based on Investigator's Assessment	
Number of subjects with event, n (%)	21 (45.7)
Censored, n (%)	25 (54.3)
Median PFS (95% CI) (months) [a]	3.4 (3.0, 7.8)
Overall Survival	
Death, n (%)	15 (32.6)
Censored, n (%)	31 (67.4)
Median OS (95% CI) (months) [a]	7.8 (6.1, 13.6)
Duration of Response Based on Investigator's Assessment	
Number of subjects with event, n (%)	4 (8.7)
Censored, n (%)	18 (39.1)
Median DoR (95% CI) (months) [a]	NE (4.0, NE)
Duration of Complete Response Based on Investigator's Assessment	
Number of subjects with event, n (%)	4 (8.7)
Censored, n (%)	14 (30.4)
Median DoCR (95% CI) (months) [a]	5.0 (2.3, NE)

[a] From Kaplan-Meier product-limit estimates.
CI = confidence interval; DoCR = duration of complete response; DoR = duration of response; EFS = event-free survival; NE = not evaluable; OS = overall survival; PFS = progression-free survival; SOC = standard of care.

Subjects who received liso-cel as 3L treatment in the crossover subgroup had lower response rates than those in 2L (liso-cel arm). However, the SOC arm post-crossover differed from the liso-cel arm in several ways: first, subjects in the SOC arm who received liso-cel post-crossover were subjects unable to achieve an adequate response to SOC 2L therapy, and these subjects received liso-cel as a third-line (3L) treatment. The patient populations also differ in that the SOC arm post-crossover contains subjects with rapidly progressive disease who may not have been able to wait to undergo leukapheresis, liso-cel manufacture, and subsequent administration. However, because they were enrolled in Study BCM-003,

liso-cel had already been manufactured after their enrolment in the study and was available immediately at time of approval to crossover.

Response assessments post-crossover in the SOC Arm were based on Investigator assessment only, while the response assessments from time of randomization in the liso-cel and SOC Arm were based on IRC assessments. In addition, the response assessment schedule was different: the assessments in the SOC arm post-crossover began when liso-cel was administered. After administration of liso-cel as crossover treatment, the only timepoints at which efficacy assessments were required were 3 months and 6 months post liso-cel infusion. Unless progressive disease was reported, evaluation of efficacy endpoints based on disease assessment for these subjects were consequentially impacted by censoring before completion of the 12-month follow up period post liso-cel infusion. As a result, a larger number of subjects were censored post-crossover as compared to the liso-cel arm or SOC arm before crossover.

Summary of main study

The following table summarise the efficacy results from the main study 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 43. Summary of Efficacy for trial JCAR017-BCM-003

Title: A global randomized multicenter Phase 3 trial to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell Non-Hodgkin Lymphomas (TRANSFORM)		
Study identifier	JCAR017-BCM-003	
Design	A randomized, open-label, parallel-group, multi-center, Phase 3 study to demonstrate the efficacy and safety of liso-cel versus standard of care (SOC) salvage therapies in subjects with aggressive B-cell non-Hodgkin lymphoma (NHL) (defined as diffuse large B-cel lymphoma [DLBCL] not otherwise specified [NOS], de novo or transformed indolent NHL), high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double-hit lymphoma[DHL]/triple-hit lymphoma [THL]), primary mediastinal large B-cell lymphoma (PMBCL), T cell rich/histiocyte rich large B-cell lymphoma [THRBCL] or follicular lymphoma Grade 3B (FL3B) who are refractory to front-line immunochemotherapy or have relapsed within 12 months after front-line immunochemotherapy and are eligible for high-dose chemotherapy (HDCT) and hematopoietic stem-cell transplant (HSCT). The time of relapse was calculated from the date of the first disease assessment confirming a complete response (CR) obtained with first-line treatment for disease under study, to the date of first assessment demonstrating a relapse	
	Duration of main phase:	Treatment period: Study Days 1 [+ 3 days]to 126 [± 7 days] Post-treatment period: follow-up visits at approximately Months 6 (± 10 days), 9, 12, 18, 24 and 36 (or end of study [EOS]) ± 14 days. Survival Follow-up: visits were scheduled every 3 months (± 30 days) until last subject last visit.
Hypothesis	Superiority of liso-cel to SOC in adults subjects with transplant-eligible relapsed or refractory LBCLs	

Treatments groups	Arm A (SOC)		Three 21-day cycles of salvage immune-chemotherapy (rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP], rituximab, ifosfamide, carboplatin and etoposide [R-ICE], or rituximab, gemcitabine, dexamethasone, and cisplatin [R GDP]), followed by HDCT and HSCT
	Arm B (liso-cel)		Bridging therapy, if needed, followed by lymphodepleting chemotherapy (LDC) with Fludarabine and Cyclophosphamide and liso-cel (100×10^6 CAR+ viable T cells on Day 29 [2 to 7 days after completion of LDC])
Endpoints and definitions	Primary endpoint	EFS by IRC	Event-free survival, defined as the time from randomization to death from any cause, progressive disease (PD), failure to achieve complete response (CR) or partial response (PR) by 9 weeks post-randomization, or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first
	Key secondary Endpoint	PFS by IRC	Progression-free survival, defined as the time from randomization to PD or death from any cause, whichever occurs first
	Key secondary Endpoint	OS	Overall survival, defined as the time from randomization to death due to any cause
	Key secondary Endpoint	CRR by IRC	Complete response rate, defined as the proportion of subjects achieving a CR from randomization up to 3 years post-randomization
Database lock	Data cutoff for interim analysis 08-Mar-2021 Data cutoff for primary analysis 13-May-2022		

Results and Analysis

Analysis description	**Interim and primary analyses**		
Analysis population and time point description	Intention to treat (ITT)		
80% information fraction inferential interim analysis			
Descriptive statistics and estimate variability	Treatment group	Arm A (SOC)	Arm B (liso-cel)
	Number of subject	N=92	N=92
	Median EFS (months)	2.3	10.1

	95%CI	2.2, 4.3	6.1, NE
	Median PFS (months)	5.7	14.8
	95%CI	3.9, 9.4	6.6, NE
	Median OS (months)	16.4	NE
	95%CI	11.0, NE	15.8, NE
	CRR (%)	39.1	66.3
	95%CI	29.1, 49.9	55.7, 75.8
Effect estimate per comparison	EFS by IRC	Comparison groups	SOC vs. liso-cel
		Stratified HR	0.349
		95%CI	0.229, 0.530
		P-value	<0.0001
	PFS by IRC	Comparison groups	SOC vs. liso-cel
		Stratified HR	0.406
		95%CI	0.250, 0.659
		P-value	0.0001
	OS	Comparison groups	SOC vs. liso-cel
		Stratified HR	0.509
		95%CI	0.258, 1.004
		P-value	0.0257
	CRR by IRC	Comparison groups	SOC vs. liso-cel
		P-value	<0.0001
Primary analysis			
Descriptive statistics and estimate variability	Treatment group	Arm A (SOC)	Arm B (liso-cel)
	Number of subject	N=92	N=92
	Median EFS (months)	2.4	NE
	95%CI	2.2, 4.9	9.5, NE
	Median PFS (months)	6.2	NE

	95%CI	4.3, 8.6	12.6, NE
	Median OS (months)	29.9	NE
	95%CI	17.9, NE	29.5, NE
	CRR (%)	43.5	73.9
	95%CI	33.2, 54.2	63.7, 82.5
Effect estimate per comparison	EFS by IRC	Comparison groups	SOC vs. liso-cel
		Stratified HR	0.356
		95%CI	0.243, 0.522
		P-value	<0.0001
	PFS by IRC	Comparison groups	SOC vs. liso-cel
		Stratified HR	0.400
		95%CI	0.261, 0.615
		P-value	<0.0001
	OS	Comparison groups	SOC vs. liso-cel
		Stratified HR	0.724
		95%CI	0.443, 1.184
		P-value	0.0987
	CRR by IRC	Comparison groups	SOC vs. liso-cel
		P-value	<0.0001
Notes	Median estimates of time to event is from a Kaplan-Meier product-limit estimate; CI = confidence interval; CRR = complete response rate; EFS = event-free survival; HR = hazard ratio; IRC=independent review committee; ITT = intent-to-treat; NE = not evaluable; OS = overall survival; PFS = progression-free survival; SOC = standard of care.		
Analysis description			

Supportive study(ies)

Study 017006 (TRASCEND PILOT)

Title of study: **A Phase 2 study of lisocabtagene maraleucel (JCAR017) as second-line therapy in adult patients with aggressive B-cell Non-Hodgkin's Lymphoma (TRANSCEND-PILOT-017006)**

Methods

Study 017006 was an open-label, single-arm, multicentre, Phase 2 study to determine the antitumor activity, PK, and safety of liso-cel in subjects who were ineligible for autologous hematopoietic stem cell

transplantation (ASCT) (i.e., transplant non-eligible [TNE]), and relapsed from, or are refractory to, front-line immunochemotherapy for large B-cell lymphoma (LBCL).

The primary and secondary objectives/endpoints are summarised in table below:

Table 44. Primary and Secondary Study Objectives and Endpoints

Objectives	Endpoints
Primary:	
Assess the antitumor activity of liso-cel in adult subjects with large B-cell lymphoma (LBCL) who are ineligible for hematopoietic stem cell transplantation (HSCT)	ORR (complete response [CR] + partial response [PR])
Secondary:	
To assess the complete response rate (CRR) and durability of antitumor activity of liso-cel	CRR, duration of response (DOR), and DOR if best overall response (BOR) is CR
To estimate the progression-free survival, (PFS), event-free survival (EFS), and overall survival (OS) of subjects treated with liso-cel	PFS, EFS, OS
To evaluate the safety of liso-cel	Type, frequency, and severity of adverse events (AEs) and laboratory abnormalities
To characterize the pharmacokinetics (PK) profile of liso-cel in this subject population	Cmax, Tmax, AUC and other relevant PK parameters of liso-cel in blood as assessed by qPCR
To assess health-related quality of life (HRQoL) and health economics and outcomes research	Measurement of HRQoL changes as assessed using the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life questionnaire (QLQ-C30), the FACT-Lym subscale, and the EuroQol instrument EQ-5D-5L
	Numbers of intensive care unit (ICU) inpatient days and non-ICU inpatient days and reasons for hospitalization

Abbreviations: AE = adverse event; AUC = area under the blood concentration-time curve; BOR = best overall response; Cmax = maximum observed blood concentration; CR = complete response; CRR = complete response rate; DOR = duration of response; EFS = event-free survival; EORTC = European Organization for Research and Treatment of Cancer; QLQ-C30 = Core Quality of Life questionnaire; FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma "Additional concerns" subscale; HSCT = hematopoietic stem cell transplantation; HRQoL = health-related quality of life; ICU = intensive care unit; LBCL = large B-cell lymphoma; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; qPCR = quantitative polymerase chain reaction; R/R = relapsed or refractory; Tmax = time of maximum observed blood concentration.

The study was divided into screening (1-2 weeks prior to leukapheresis), treatment, and post-treatment follow-up periods. 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. The post-treatment follow-up period was defined as Day 30 after liso-cel infusion to end of study (EOS). Post-treatment follow-up included safety and disease follow-up visits at approximately 2, 3, 6, 9, 12, 18, and 24 months after receiving liso-cel; 24 months was the EOS visit.

The study population included men and women (≥ 18 years old) with relapsed/refractory (R/R) LBCL of the following histologies at relapse: diffuse large B-Cell lymphoma (DLBCL) NOS (de novo or transformed from follicular lymphoma [tFL]), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple hit lymphoma [DHL/THL]), or Follicular lymphoma grade 3B (FL3B) per World Health Organization (WHO) 2016 classification. Study eligibility was based on local pathologic diagnosis. If sufficient tissue was available, central confirmation of disease histology at baseline was performed retrospectively by an independent pathology laboratory.

Eligible subjects were deemed ineligible for both high-dose chemotherapy and HSCT while also having adequate organ function for CAR T-cell treatment. Subjects must have met at least one of the following TNE criteria: age ≥ 70 years, Eastern Cooperative Oncology Group (ECOG) performance status = 2,

impaired pulmonary function defined by diffusing capacity of the lung for carbon monoxide [DLCO] ≤ 60% adjusted for gender-specific hemoglobin concentration, impaired cardiac function: left ventricular ejection fraction (LVEF) < 50% by echocardiogram or MUGA scan performed within 4 weeks of determination of eligibility, calculated creatinine clearance(CrCl) (Cockcroft and Gault) < 60 mL/min and/or aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 2 × upper limit of normal (ULN).

Subjects with central nervous system (CNS)-only involvement by malignancy, history of another primary malignancy that had not been in remission for at least 2 years, or previous treatment with CD-19-targeted therapy were excluded.

Following screening and enrolment, leukapheresis was performed on each subject. Low-intensity LDC regimen consisting of cyclophosphamide (300 mg/m^2/day × 3 days) combined with fludarabine (30 mg/m^2/day × 3 days), was administered prior to treatment with liso-cel. 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. All subjects were assigned to a single liso-cel dose of 100 × 10^6 CAR+ T cells (50 × 10^6 CD8+ CAR+ T cells and 50 × 10^6 CD4+ CAR+ T cells), administered intravenously (IV) on Day 1 (between 2 and 7 days following the completion of lymphodepleting chemotherapy [LDC]).

The primary analysis was initially planned to be performed on a pooled analysis set containing combined data from Study 017006 and BCM-001 Cohort 2. With Protocol Amendment 6 (16-Aug-2021, 62 subjects already treated), it was specified that the primary analyses and formal hypothesis testing was to be performed only on the Study 017006 dataset. The primary analysis was modified in order to be conducted after approximately 62 subjects were treated with liso-cel in study 017006, and these subjects were followed for at least 6 months after first response (either CR or PR), or until death, progressive disease (PD), or withdrawal from study. The sample size in the Liso-cel-treated Efficacy Analysis Set for Study 017006 was determined to provide at least 85% power to reject the null hypothesis of response rate less than 50% assuming the target response rate of 70% using an exact binomial test with 1-sided significance level 0.025. The null hypothesis of 50% ORR used to size the study is supported by a meta-analysis of second-line (2L) DLBCL studies with similar but not identical patient populations compared to the patient population to be enrolled in the current study. Assuming a 15% drop-out rate from leukapheresis prior to liso-cel infusion, it was anticipated that approximately 73 subjects would be leukapheresed in the study.

Results

Ninety-three subjects were screened, 80/93 were deemed eligible, 74/80 were leukapheresed, 12 of which did not receive liso-cel or nonconforming product for the following reasons: death of 5 (6.8%) subjects, no longer met eligibility criteria in 5 (6.8%) subjects, and disease-related complications and reason of "other" in 1 (1.4%) subject each. Sixty-three subjects received LDC, and 61 received liso-cel (1 received nonconforming product). Screening and enrolment for this study were ongoing when the WHO declared the COVID-19 outbreak to be global pandemic on 12-Mar-2020. As a result of the pandemic, the Sponsor temporarily suspended screening, enrolment, and apheresis in all cellular therapy trials, including Study 017006. There were 36 subjects treated with liso-cel as of Mar-2020 and an additional 26 subjects were treated between Apr- to Dec-2020. As such, the impact on the study conduct and results was minimal. As of the data cutoff date for this CSR (24-Sep-2021), both the study and the COVID-19 pandemic were still ongoing. As a result of the pandemic, completion of study enrolment was delayed by approximately 5 months. A small proportion (2/62 [3%] subjects) died due to COVID-19-related AEs.

Demographic characteristics were similar between the Leukapheresed Analysis Set and the Liso-cel-treated Analysis Set (see Table below).

Table 45 Demographic and Baseline Characteristics

Demographic Characteristics	Leukapheresed Analysis Set N = 74	Liso-cel-treated Analysis Set N = 61
Age at screening (years)		
n	74	61
Mean (StD)	72.8 (6.57)	73.1 (6.64)
Median	73.5	74.0
Q1, Q3	70.0, 77.0	70.0, 78.0
Min, Max	53, 84	53, 84
Age Group, n (%)		
< 65 years	8 (10.8)	6 (9.8)
≥ 65 to < 70 years	7 (9.5)	7 (11.5)
≥ 70 to < 75 years	27 (36.5)	20 (32.8)
≥ 75 years	32 (43.2)	28 (45.9)
Sex, n (%)		
Female	29 (39.2)	24 (39.3)
Male	45 (60.8)	37 (60.7)
Race Group, n (%)		
White	64 (86.5)	54 (88.5)
Other Races	4 (5.4)	3 (4.9)
Missing	6 (8.1)	4 (6.6)
Race, n (%)		
Asian	2 (2.7)	2 (3.3)
Black or African American	2 (2.7)	1 (1.6)
White	64 (86.5)	54 (88.5)
Unknown	6 (8.1)	4 (6.6)
Ethnicity, n (%)		
Hispanic or Latino	1 (1.4)	0
Not Hispanic or Latino	64 (86.5)	54 (88.5)
Unknown	9 (12.2)	7 (11.5)
Screening aaIPI, n (%)		
0	10 (13.5)	10 (16.4)
1	26 (35.1)	24 (39.3)
2	25 (33.8)	16 (26.2)
3	12 (16.2)	10 (16.4)
Missing	1 (1.4)	1 (1.6)
Pre-LDC ECOG score, n (%)[a]		
0	19 (25.7)	18 (29.5)
1	34 (45.9)	27 (44.3)
2	20 (27.0)	16 (26.2)
3	1 (1.4)	0

Demographic Characteristics	Leukapheresed Analysis Set N = 74	Liso-cel-treated Analysis Set N = 61
Pre-LDC CrCl, n (%)[b]		
< 50 mL/min	7 (10.6)	6 (9.8)
≥ 50 to < 60 mL/min	9 (13.6)	8 (13.1)
≥ 60 mL/min	50 (75.8)	47 (77.0)
Pre-LDC LDH (U/L)		
n	74	61
Mean (StD)	460.4 (480.46)	399.4 (390.78)
Median	289.0	286.0
Q1, Q3	201.0, 452.0	201.0, 355.0
Min, Max	124, 2333	124, 2068
< 500 U/L, n (%)[b]	57 (77.0)	50 (82.0)
≥ 500 U/L, n (%)[b]	17 (23.0)	11 (18.0)
Pre-LDC SPD per IRC (cm^2)		
n	73	61
Mean (StD)	33.242 (40.7788)	29.229 (36.1369)
Median	15.680	14.700
Q1, Q3	6.800, 44.640	6.300, 42.090
Min, Max	1.44, 177.00	1.53, 172.30
< 50 cm^2, n (%)[b]	58 (79.5)	51 (83.6)
≥ 50 cm^2, n (%)[b]	15 (20.5)	10 (16.4)
Baseline CRP (mg/L)[c]		
n	64	61
Mean (StD)	48.23 (92.200)	49.16 (94.276)
Median	15.00	14.00
Q1, Q3	5.70, 50.50	5.60, 49.00
Min, Max	0.5, 617.0	0.5, 617.0
< 20 mg/L, n (%)[b]	36 (56.3)	35 (57.4)
≥ 20 mg/L, n (%)[b]	28 (43.8)	26 (42.6)
Screening HCT-CI Total Score		
n	74	61
Mean (StD)	2.4 (2.29)	2.3 (2.38)
Median	2.0	2.0
Q1, Q3	0.0, 3.0	0.0, 3.0
Min, Max	0, 8	0, 8
0, n (%)[b]	22 (29.7)	21 (34.4)
1, n (%)[b]	9 (12.2)	7 (11.5)
2, n (%)[b]	8 (10.8)	6 (9.8)
≥ 3, n (%)[b]	35 (47.3)	27 (44.3)

Demographic Characteristics	Leukapheresed Analysis Set N = 74	Liso-cel-treated Analysis Set N = 61
Pre-LDC ECG Status, n (%)		
Normal	28 (37.8)	21 (34.4)
Abnormal, not clinically significant	46 (62.2)	40 (65.6)
Abnormal, clinically significant	0	0

Abbreviations: aaIPI = age-adjusted international prognosis index; CrCl = creatinine clearance; CRP=C-reactive protein; ECG = electrocardiogram; ECOG=Eastern Cooperative Oncology Group; HCT-CI = hematopoietic stem cell transplant-specific comorbidity index; IRC = Independent Review Committee; LDC=lymphodepleting chemotherapy; LDH=lactate dehydrogenase; N = number of subjects; Q1 = quartile 1; Q3 = quartile 3 ; SPD=sum of the products of the greatest diameters; StD = standard deviation.

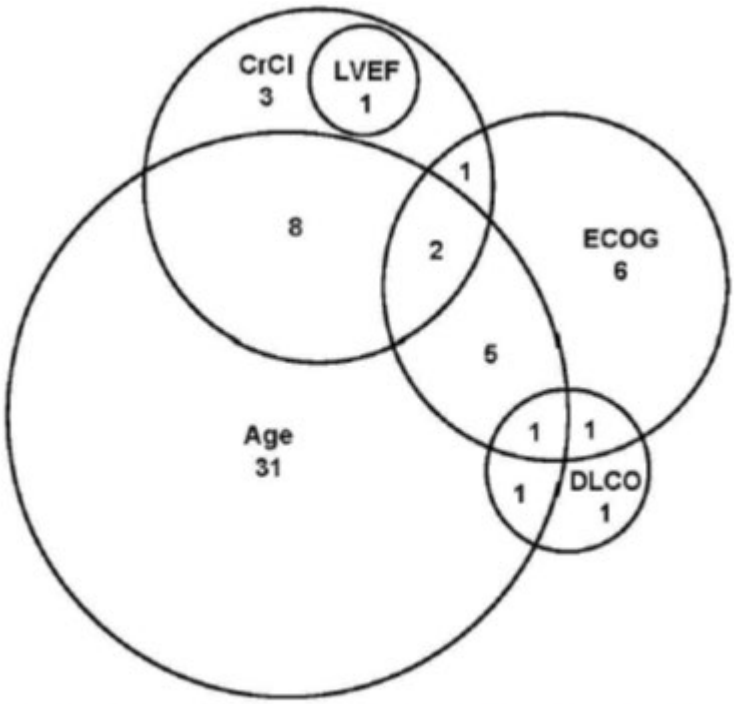
[a] Pre-LDC ECOG was the most recent ECOG score prior to the start of LDC

[b] Percentages were based on number of subjects with non-missing results.

[c] Baseline value was defined as the last value on or before the first dose of lis-cel is infused; if multiple values were present for the same date, the average of these values was used as the baseline. For subjects who were not treated, the baseline was the latest non-missing value.

In the Liso-cel-treated Analysis Set, of the 61 subjects in the liso-cel treated analysis set, 41 met 1 TNE criterion, 17 met 2 TNE criteria, and 3 met 3 TNE criteria. Of the 48 subjects in the Liso-cel-treated Analysis Set who met the age ≥ 70 criterion, 17 met at least one additional TNE criterion. Of the 31 subjects in the Liso-cel-treated Analysis Set who met only the age ≥ 70 criterion, the median age was 74 years (range: 70 to 84). Of these, 11/31 subjects had an aaIPI of 2 and 6/31 subjects had an aaIPI of 3 (see Figure below).

Figure 23. TNE Criteria Used for Eligibility in the Liso-cel-treated Analysis Set



Abbreviations: CrCl = creatinine clearance; DLCO = diffusing capacity of the lung for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; LVEF = left ventricular ejection fraction; TNE = transplant non-eligible.

Table 46. Baseline Disease Characteristics

Disease Characteristics	Leukapheresed Analysis Set N = 74	Liso-cel-treated Analysis Set N = 61
Type of B-cell non-Hodgkin Lymphoma, n (%)		
DLBCL, NOS	41 (55.4)	33 (54.1)
tFL	10 (13.5)	9 (14.8)
High grade lymphoma with DLBCL histology	22 (29.7)	18 (29.5)
FL3B	1 (1.4)	1 (1.6)
Double Hit or Triple Hit, n (%) [a]		
Yes	25 (33.8)	20 (32.8)
No	44 (59.5)	36 (59.0)
Missing	5 (6.8)	5 (8.2)
If DLBCL, cell of origin, n (%)		
GCB	33 (44.6)	26 (42.6)
ABC, non-GCB	20 (27.0)	18 (29.5)
Unknown	18 (24.3)	14 (23.0)
Missing	2 (2.7)	2 (3.3)
Refractory or Relapsed, n (%)		
Refractory	40 (54.1)	33 (54.1)
Relapsed	34 (45.9)	28 (45.9)
Relapsed ≤ 12 months	16 (21.6)	13 (21.3)
Relapsed > 12 months	18 (24.3)	15 (24.6)

Disease Characteristics	Leukapheresed Analysis Set N = 74	Liso-cel-treated Analysis Set N = 61
Active CNS disease at liso-cel infusion		
Yes	0	0
No	60 (81.1)	58 (95.1)
Unknown	4 (5.4)	3 (4.9)
Missing [b]	10 (13.5)	0
Best prior response to any prior therapies after diagnosis, n (%)		
CR	34 (45.9)	28 (45.9)
PR	17 (23.0)	15 (24.6)
SD	7 (9.5)	5 (8.2)
PD	16 (21.6)	13 (21.3)
Months from initial diagnosis to first liso-cel infusion		
n	62	61
Mean (StD)	27.00 (36.203)	26.61 (36.371)
Median	13.73	13.60
Q1, Q3	8.05, 22.47	8.05, 22.11
Min, Max	2.3, 183.4	2.3, 183.4

Abbreviations: ABC = activated B-cell; CNS = central nervous system; CR = complete response; DLBCL = diffuse large B-cell lymphoma; FL3B = follicular lymphoma grade 3B; GCB = germinal center B-cell; N = number of subjects; NOS = not otherwise specified; PD = progressive disease; PR = partial response; Q1 = quartile 1; Q3 = quartile 3; SD = stable disease; StD = standard deviation; tFL = transformed follicular lymphoma

[a] Double hit or triple hit are derived for subjects with high grade lymphoma or tFL

[b] Missing in Leukapheresed Analysis Set assessment at pre-treatment, not at screening

Efficacy outcomes in the Liso-cel-treated Analysis Set(N=61) are summarised in Table and Figure below:

Table 47. Summary of Primary and Secondary Efficacy Endpoints per IRC Assessemnt in the Liso-cel-treated Efficacy Analysis Set

Parameter	Total (N = 61)
Primary Efficacy Endpoint	
ORR per IRC Assessment	
BOR[a], n (%)	
CR	33 (54.1)
PR	16 (26.2)
SD	3 (4.9)
PD	8 (13.1)
NE	1 (1.6)
ORR, n (%)	
CR+PR	49 (80.3)
95% CI[b]	68.2, 89.4
P-value[c]	<0.0001
CRR, n (%)	
CR	33 (54.1)
95% CI[b]	40.8, 66.9
PR Rate n (%)	
PR	16 (26.2)
95% CI[b]	15.8, 39.1
Secondary Efficacy Endpoints	
DOR (months) per IRC Assessment	
Median (95% CI)[d]	12.09, 6.24-NR
Q1, Q3	3.29, NR
Min, Max	0.0, 23.0
Follow-up (months)	
Median (95% CI)[e]	15.51, 11.17-17.12
Min, Max	0.0, 23.0
PFS (months) per IRC Assessment	
Median (95% CI)[d]	9.03, 4.17-NR
Q1, Q3	2.89, NR
Min, Max	0.7, 23.9

Parameter	Total (N = 61)
Follow-up (months)	
Median (95% CI)[e]	12.98, 11.99-18.07
Min, Max	0.7, 23.9
EFS (months) per IRC Assessment	
Median (95% CI)[d]	7.23, 3.22-22.60
Q1, Q3	2.63, NR
Min, Max	0.7, 23.9
Follow-up (months)	
Median (95% CI)[e]	16.43, 12.09-18.07
Min, Max	0.7, 23.9
OS (months)	
Median (95% CI)[d]	NR, 17.28-NR
Q1, Q3	10.48, NR
Min, Max	1.2, 35.4
Follow-up (months)	
Median (95% CI)[e]	17.58, 12.39-18.63
Min, Max	1.2, 35.4

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; CRR = complete response rate; DOR = duration of response; EFS = event-free survival; IRC = independent review committee; Max = maximum; Min = minimum; NE = not evaluable; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; Q1 = quartile 1; Q3 = quartile 3; SD = stable disease.

[a] 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 subsequent anticancer therapy or liso-cel retreatment.

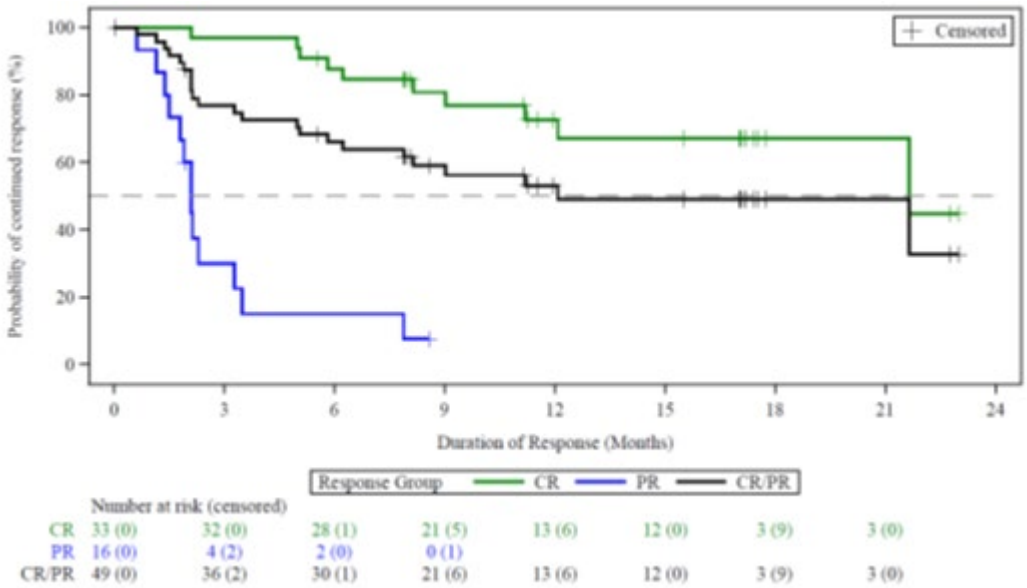
[b] 2-sided 95% exact Clopper-Pearson CI

[c] One sided P-value is calculated based on the null hypothesis ORR <= 50.2%. The reference rate of 50.2% is from the real-world data (RWD) cohort using the same inclusion/exclusion/TNE criteria of Study 017006.

[d] Kaplan-Meier (KM) method is used to obtain 2-sided 95% CI

[e] Reverse KM method is used to obtain the median follow-up and its 95% confidence intervals.

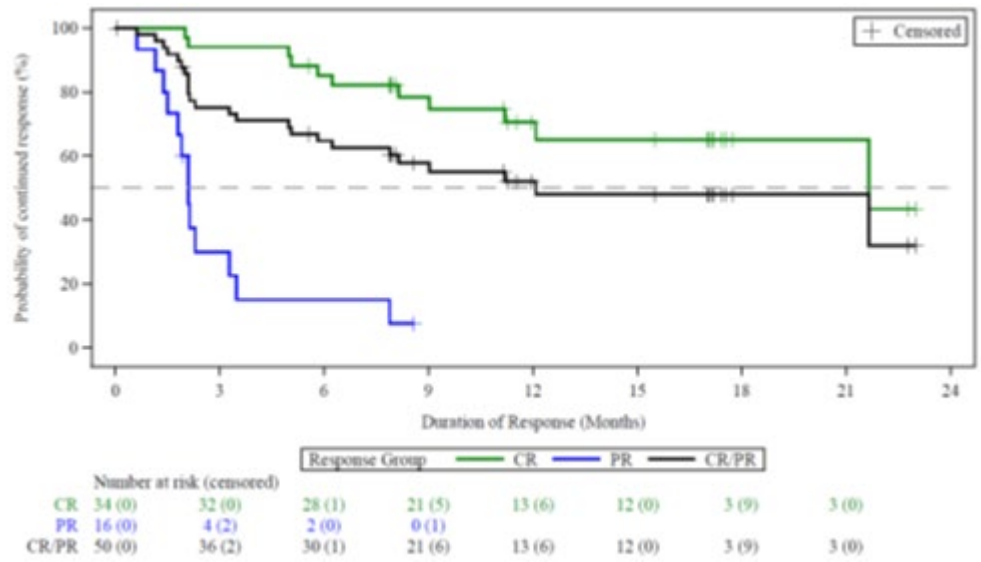
Figure 24. Duration of Response (DOR) – IRC Assessment JCAR017-treated Efficacy Analysis Set



Based on investigator's assessment in the Liso-cel-treated Efficacy Analysis Set, the ORR was 80.3% (95% CI: 68.2, 89.4), the CRR 55.7% (95% CI: 42.4, 68.5), the median DoR 12.09 months (95% CI: 5.82, NR), the median PFS 7.23 (95% CI: 3.02, 22.60) and the median EFS 7.23 months (95% CI: 3.02, 22.60) .

Based on IRC assessment in the Leukapheresed Analysis Set, the ORR was 67.6% (95% CI: 55.7, 78.0), the CRR 45.9% (95% CI: 34.3, 57.9), the median DoR 12.09 months (95% CI: 5.82, NR), the median PFS 10.48 months (95% CI: 5.13, 13.90) and the median EFS 8.15 months (95% CI: 4.37, 13.34). The KM estimate for the median OS in the Leukapheresed Analysis Set was NR (95% CI: 14.65, NR) and the median duration of follow-up for OS was 17.68 months (95% CI: 13.27, 19.15). Overall, 26 (35.1%) subjects in the Leukapheresed Analysis Set died. The survival rate at 3 months was 91.7% (95% CI: 82.4, 96.2) and it gradually declined until 24 months, where it was 56.7 (95% CI: 42.2, 68.8).

Figure 25. Duration of Response (DOR) – IRC Assessment Leukapheresed Analysis Set



The median DOR per EMA censoring criteria was 12.09 months (95% CI: 5.82, NR) in both the liso-cel-treated and all leukapheresed analysis sets. The median follow-up for subjects achieving response was 15.51 months (95% CI: 11.17, 17.12)

The median PFS per EMA censoring criteria was 8.80 months (95% CI: 3.22, 22.60). The median duration of follow-up for PFS was 16.43 months (95% CI: 12.09, 18.07).

Subgroup analyses for ORR and CRR in the liso-cel-treated efficacy set are summarised in Figures below:

Figure 26. Forest Plot of Overall Response rate (ORR) – IRC Assessment JCAR017-treated Efficacy Analysis Set

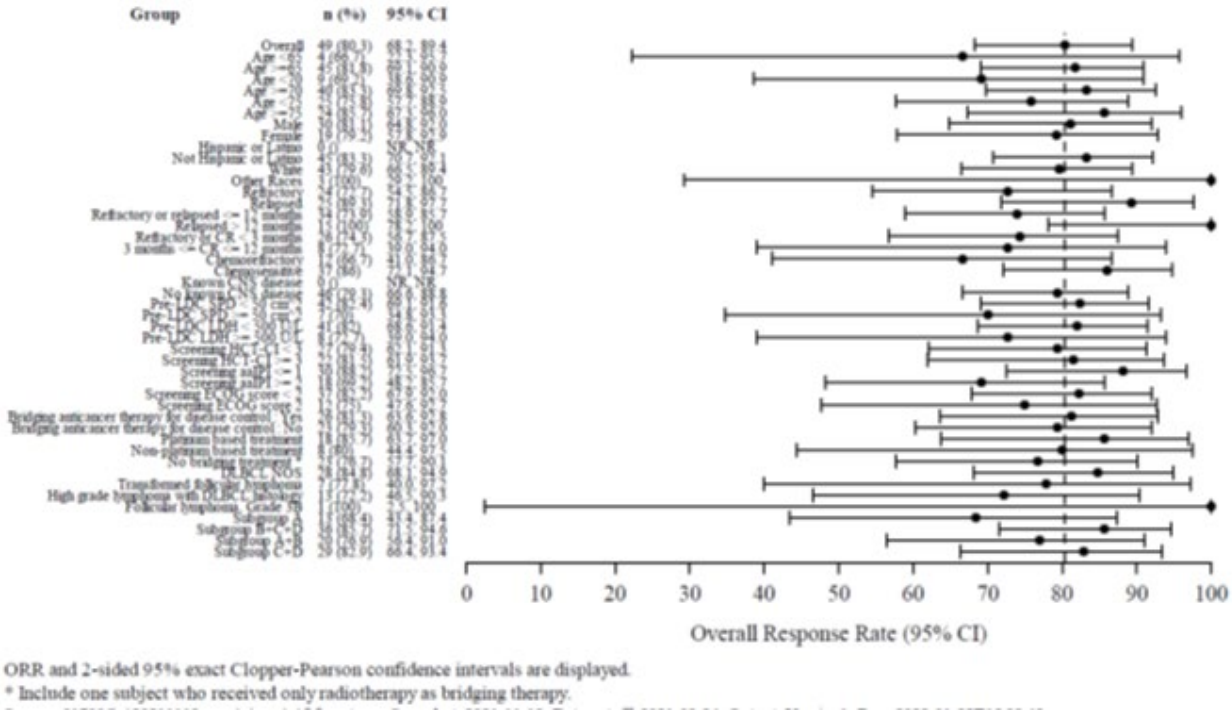
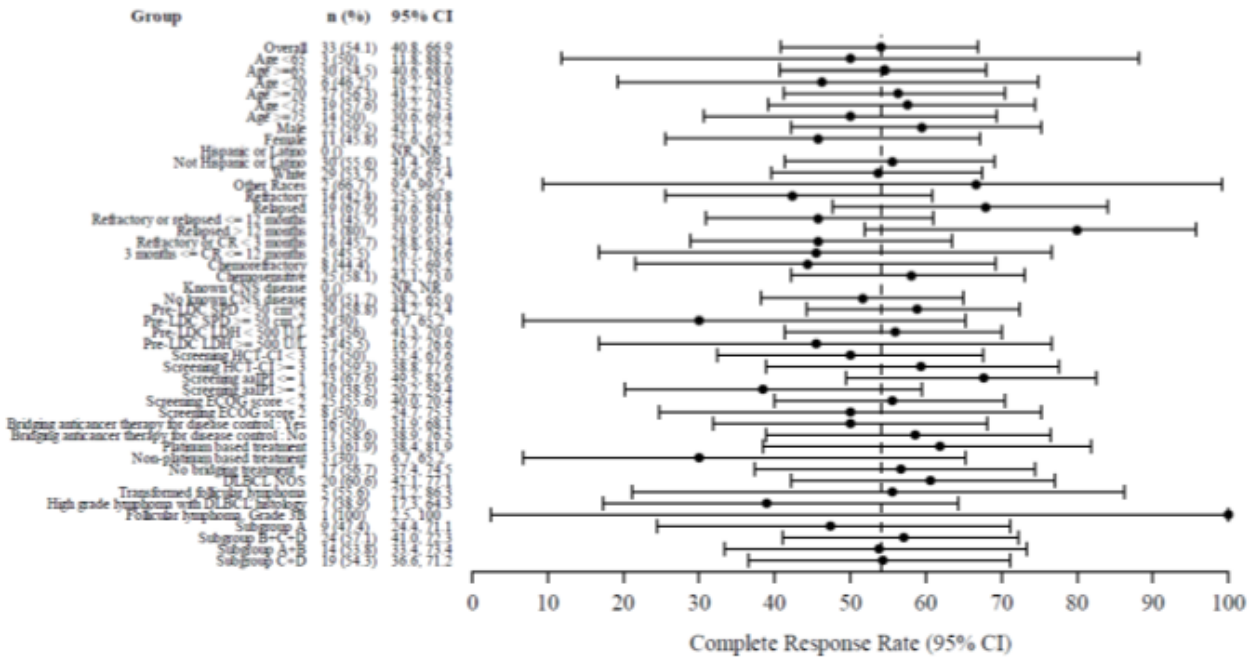


Figure 27. Forest Plot of Complete Response Rate – IRC Assessment JCAR017-treated Efficacy Analysis Set



CRR and 2-sided 95% exact Clopper-Pearson confidence intervals are displayed.
* Include one subject who received only radiotherapy as bridging therapy.

Study BCM-001 Cohort 2 (TRASCEND WORLD)

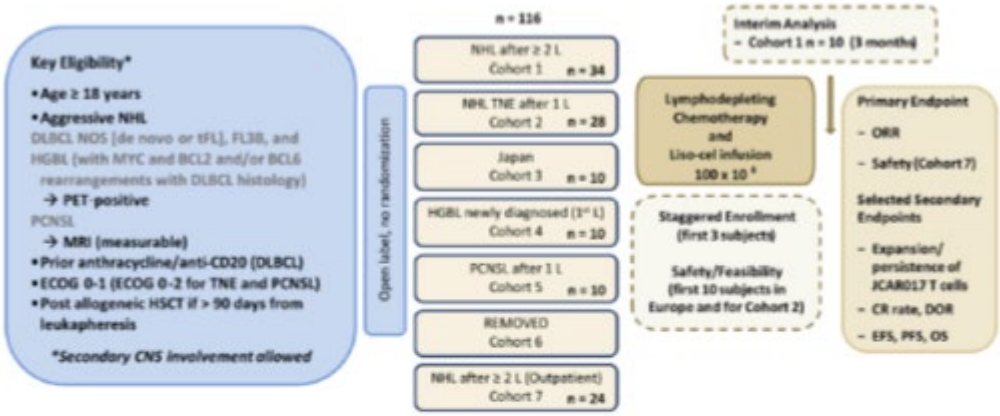
Title of study*: A Phase 2, Single-Arm, Multi-Cohort, Multi-Center Trial To Determine The Efficacy And Safety Of JCAR017 In Adult Subjects With Aggressive B-Cell Non-Hodgkin Lymphoma (Transcend World*)

Methods

Study JCAR017-BCM-001 is a single-arm, multi-cohort, multi-center, Phase 2 study to determine the efficacy and safety of lisocabtagene maraleucel (JCAR017; BMS-986387; liso-cel) as treatment in adult subjects with large B-cell non-Hodgkin lymphoma (LBCL). The current submission provides the preliminary efficacy results observed in Cohort 2 (transplant not eligible [TNE] adult subjects with LBCL, DCO date Nov 2021).

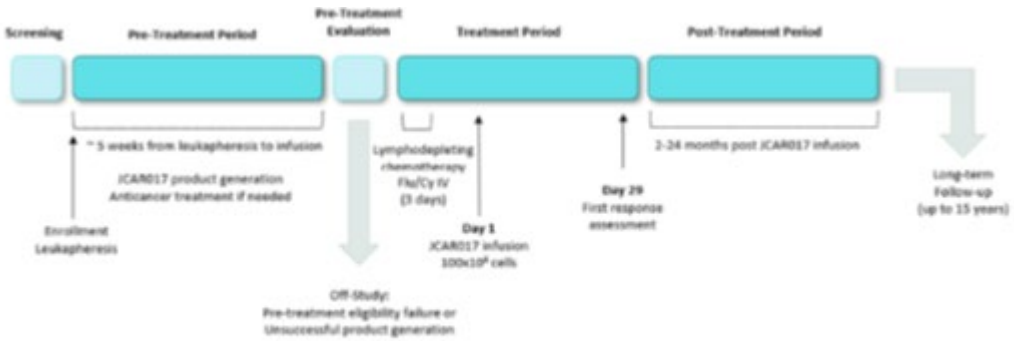
Study design is summarised in Figures below:

Figure 28. Overall Study Design



Abbreviations: CNS = central nervous system; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; FL3B = follicular lymphoma Grade 3B; HGBCL = High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology; HSCT = hematopoietic stem cell transplantation; L = line(s) of therapy; max= maximum; MRI = magnetic resonance imaging; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; ORR = overall response rate; OS = overall survival; PCNSL = primary central nervous system lymphoma; PET = positron emission tomography; PFS = progression-free survival; tFL = transformed follicular lymphoma; TNE = transplant not eligible.

Figure 29. Study Schematic



Abbreviations: Flu/Cy = fludarabine/cyclophosphamide; IV = intravenous
JCAR017 = liso-cel

The study primary and secondary objectives/endpoints are summarised in Table below:

Table 48. Study Objectives

Objectives
Primary To determine the efficacy, defined as overall response rate (ORR) of JCAR017 in subjects with aggressive B-cell non-Hodgkin lymphoma
Secondary To evaluate the safety and feasibility of administering JCAR017 (Cohort 2) To evaluate other measures of efficacy of JCAR017 (eg, complete response rate [CRR], event-free survival [EFS], progression-free survival [PFS], overall survival [OS], duration of response [DOR]) To characterize the pharmacokinetic (PK) profile of JCAR017 in the peripheral blood measured using qPCR detection for the JCAR017 vector sequence

The primary endpoint of Cohort 2 in the study is the IRC-reviewed ORR, defined as the proportion of subjects with a best overall response (BOR) of either CR or PR. The BOR was defined as 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. Secondary endpoints are: CRR, DoR (evaluated for subjects who achieved a response), PFS (when PFS analysis was conducted on the leukapheresed subjects the reference was the date of leukapheresis that was closest to the liso-cel infusion), EFS (when the EFS analysis was conducted on the leukapheresed subjects, the reference was the date of leukapheresis that was closest to the liso-cel infusion), and OS.

DoR, PFS and EFS were analysed following the censoring rules per FDA guideline. Supportive analysis was performed using censoring rules per EMA guideline.

The study population for Cohort 2 included TNE subjects aged ≥ 18 years with DLBCL NOS (de novo or transformed from follicular lymphoma [tFL]), high-grade B-cell lymphoma (HGBCL) and follicular lymphoma grade 3B (FL3B) per WHO 2016 classification, who failed first line therapy, including an anthracycline and rituximab (or other CD20-targeted agent). For subjects with transformed disease, the subject was required to have had 1 line of systemic therapy for his/her transformed disease (ie, DLBCL) to be eligible. Lines of therapy did not include those given for a previously indolent condition.

Transplant not eligible subjects included those who were not intended for high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT) due to age, performance status or comorbidity, while also having adequate organ function for CAR T-cell treatment. At the very least, subjects had to meet one of the following TNE criteria: age ≥ 70 years, ECOG performance status ≥ 2, diffusion capacity of carbon monoxide [DLCO] ≤ 60%, left ventricular ejection fraction [LVEF] < 50%, creatinine clearance [CrCl] < 60 mL/min, aspartate aminotransferase [AST] / alanine aminotransferase [ALT] > 2 x upper limit of normal [ULN], bilirubin ≥ 2 mg/dL or cirrhosis Child-Pugh B or C.

Liso-cel was infused at a single liso-cel dose of 100 × 10^6 CAR+ T cells (50 × 10^6 CD8+ CAR+ T cells and 50 × 10^6 CD4+ CAR+ T cells), administered IV on Day 1 (between 2 and 7 days following the completion of lymphodepleting chemotherapy [LDC]). The CD8+ and CD4+ components were thawed and administered consecutively by IV infusion. LDC was to be initiated to finish at least 2 days prior to liso-cel infusion. LDC could start 5 to 10 days prior to liso-cel infusion. LDC consisted of fludarabine intravenously (IV) (30 mg/m^2/day for 3 days) and cyclophosphamide IV (300 mg/m^2/day for 3 days).

For Cohort 2, following protocol amendment 5 (12-Aug-2021, subjects enrolled in Cohort 2 n=32) a sample size of approximately 28 subjects treated with liso-cel conforming product was selected to provide at least 80% power to reject the null hypothesis of response rate <40% assuming the target response rate of 70% using an exact binomial test with 2-sided significance level 0.05. The reference rate for null hypothesis testing for Cohort 2 was estimated from a Real-World Study (formal testing introduced with protocol amendment 5). For the purpose of this efficacy analyses, performed for health

authority submission, results were summarized descriptively: Cohort 2 was underpowered to test the revised ORR reference rate of 50.2% based on RWE 2L TNE LBCL data; with a final sample size of 27, the power was 55% to correctly reject the null hypothesis (50.2%) when the alternative hypothesis of 70% was true. At the time the decision was made to update the null hypothesis ORR to be based on RWE, enrolment in Cohort 2 had been completed and neither the actual RWE rate nor its effect on the power was known.

Results

Overall, 32 subjects underwent leukapheresis in Cohort 2, and 27 subjects were treated with liso-cel. Five subjects were leukapheresed, but did not proceed with LDC and liso-cel. Of these, 3 died, 1 did not proceed because Eastern Cooperative Oncology Group (ECOG) performance status score did not meet the inclusion criteria, and 1 was not yet infused at the time of data cut. During the Post-treatment Period, among the 25 (92.6%) liso-cel-treated subjects who continued the follow-up; 16 (59.3%) subjects were still ongoing, while 9 (33.3%) subjects had discontinued, most commonly due to death (25.9%).

Completion of study enrollment was delayed by approximately 4 months due to the COVID-19 pandemic. The impact of the pandemic's disruption on study conduct was considered to be minimal since there were no important protocol deviations due to COVID-19, no subjects discontinued the Post-treatment or Survival Follow-up Periods due to COVID-19, no subject was reported with any AEs related to COVID-19 and there was 1 death related to COVID-19 during the pre-treatment period that occurred prior to the initiation of LDC.

Baseline demographic and disease characteristics among the liso-cel-treated and leukapheresed subjects were similar (see Table below):

Table 49. Key Baseline Demographic and Disease Characteristics – Liso-cel-treated and Leukapheresed Subjects

Characteristic	Liso-cel-treated (n = 27)	Leukapheresed (n = 32)
Age (years)		
N	27	32
Median (Min, Max)	74.0 (49, 81)	74.0 (49, 81)
Q1, Q3	72.0, 76.0	71.5, 76.0
Sex – n (%)		
Female	12 (44.4)	13 (40.6)
Childbearing Potential	0	0
Nonchildbearing Potential	12 (44.4)	13 (40.6)
Male	15 (55.6)	19 (59.4)
Primary Race – n (%)		
American Indian or Alaska Native	0	0
Asian	2 (7.4)	3 (9.4)
Japanese	2 (7.4)	3 (9.4)
Other	0	0
Black or African American	0	0

Characteristic	Liso-cel-treated (n = 27)	Leukapheresed (n = 32)
Native Hawaiian or Other Pacific Islander	0	0
White	18 (66.7)	19 (59.4)
Not Collected or Reported	0	0
Other	0	0
Unknown	7 (25.9)	10 (31.3)
Weight (kg)		
N	27	32
Median (Min, Max)	64.30 (46.0, 113.5)	64.15 (46.0, 113.5)
Q1, Q3	55.0, 82.0	56.85, 80.15
ECOG Performance Status at Screening		
0	7 (25.9)	9 (28.1)
1	11 (40.7)	12 (37.5)
2	9 (33.3)	11 (34.4)
B-cell NHL Type per Local Analysis – n (%)		
DLBCL NOS	18 (66.7)	21 (65.6)
Transformed Follicular Lymphoma	0	1 (3.1)
HGBCL[a]	8 (29.6)	10 (31.3)
Follicular Lymphoma Grade 3B	1 (3.7)	1 (3.1)
Response Status to Last Prior Therapy[b] – n (%)		
Refractory	12 (44.4)	15 (46.9)
Relapsed	15 (55.6)	17 (53.1)
Relapsed ≤ 12 months	8 (29.6)	9 (28.1)
Relapsed > 12 months	7 (25.9)	8 (25.0)
Prior Hematopoietic Stem Cell Transplant		
Yes	0	0
No	27 (100.0)	32 (100.0)
LDH Prior to LDC, n (%)		
≥ 500 U/L	6 (22.2)	6 (18.8)
< 500 U/L	21 (77.8)	21 (65.6)

Characteristic	Liso-cel-treated (n = 27)	Leukapheresed (n = 32)
Missing	N/A	5 (15.6)
CRP prior to liso-cel, n (%)		
< 20 mg/L	17 (63.0)	17 (53.1)
≥ 20 mg/L	10 (37.0)	10 (31.3)
Missing	N/A	5 (15.6)
ALC Prior to Leukapheresis, n (%)		
$< 0.1 \times 10^9$/L	0	0
$\geq 0.1 \times 10^9$/L and $< 0.3 \times 10^9$/L	0	0
$\geq 0.3 \times 10^9$/L	27 (100.0)	32 (100.0)
International Prognostic Index at Screening – n (%)		
Low risk	2 (7.4)	2 (6.3)
Low-intermediate risk	5 (18.5)	6 (18.8)
High-intermediate risk	8 (29.6)	9 (28.1)
High risk	12 (44.4)	15 (46.9)
aaIPI[C] Score at Screening - n (%)		
0	2 (7.4)	2 (6.3)
1	10 (37.0)	11 (34.4)
2	8 (29.6)	10 (31.3)
3	7 (25.9)	9 (28.1)

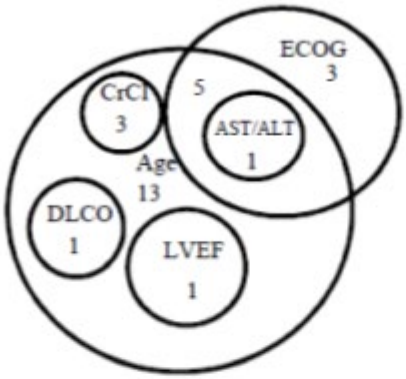
[B]High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology

[V]The status is refractory if a subject achieved less than a CR to last prior therapy; otherwise the status is relapsed.

[C]Age adjusted International Prognostic Index

The TNE criteria that were met by the liso-cel-treated subjects are shown in Figure below.

Figure 30. TNE Criteria Used for Eligibility in Liso-cel-treated subjects



[a] Age ≥ 70 years; screening ECOG performance status ≥ 2; impaired pulmonary function (screening DLCO ≤ 60%, adjusted for hemoglobin concentration using the Dinakara equation); impaired cardiac function (LVEF < 50%); impaired renal function (CrCl < 60 mL/min); impaired hepatic function (AST/ ALT > 2 x ULN, bilirubin ≥ 2 mg/dL or cirrhosis Child-Pugh B or C).

ALT= alanine transaminase; AST = aspartate aminotransferase; CrCl = Creatinine clearance; DLCO = Diffusing capacity of the lung for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; LVEF = left ventricular ejection fraction; N = number of subjects; TNE = Transplant non-eligible; ULN = upper limit of normal.

Of these 27 subjects, 16 met 1 TNE criterion, 10 met 2 TNE criteria, and met 3 TNE criteria. The most common criterion met was age ≥ 70 (24 [88.8%]) subjects) followed by ECOG PS = 2 (9 [33.3%] subjects) and creatine clearance < 60 mL/min (3 [11.1%] subjects).

The main efficacy outcomes are summarised in Table and Figure below:

Table 50. Summary of Primary and Secondary Efficacy Endpoints per IRC Assessment and Survival (Lios-cel-treated Subjects)

	Total N = 27
PRIMARY ENDPOINT	
ORR	
BOR, n (%)	
CR	13 (48.1)
PR	4 (14.8)
SD	3 (11.1)
PD	6 (22.2)
NE	1(3.7)
ND	0
ORR, n (%)	17 (63.0)
95% CI[a]	42.4, 80.6
p-value[b]	0.128
SECONDARY ENDPOINTS	
CRR	
n (%)	13 (48.1)
95% CI[a]	28.7, 68.1
DOR (months)	
Median, 95% CI[c]	12.12 (2.23, NE)
Q1, Q3[c]	2.23, NE
Min, Max	0.03, 23.26
Follow up (months)	
Median, 95% CI	11.10, 4.63-17.08
Min, Max	0.03+, 23.26
PFS (months)	
Median, 95% CI[c]	3.55 (1.97, 13.04)
Q1, Q3[c]	1.64, 13.04
Min, Max	0.66, 24.15
Follow up (months)	
Median, 95% CI	11.99, 6.57-18.04
Min, Max	0.66, 24.15

	Total N = 27
EFS (months)	
Median, 95% CI[c]	3.29 (1.97, 6.41)
Q1, Q3[c]	1.64, 13.04
Min, Max	0.66, 24.15
Follow up (months)	-
Median, 95% CI	-
Min, Max	-
OS (months)	
Median, 95% CI[c]	NE (4.27, NE)
Q1, Q3[c]	3.91, NE
Min, Max	1.5, 26.3
Follow up (months)	
Median, 95% CI	13.14, 12.02-20.57
Min, Max	1.51, 26.32

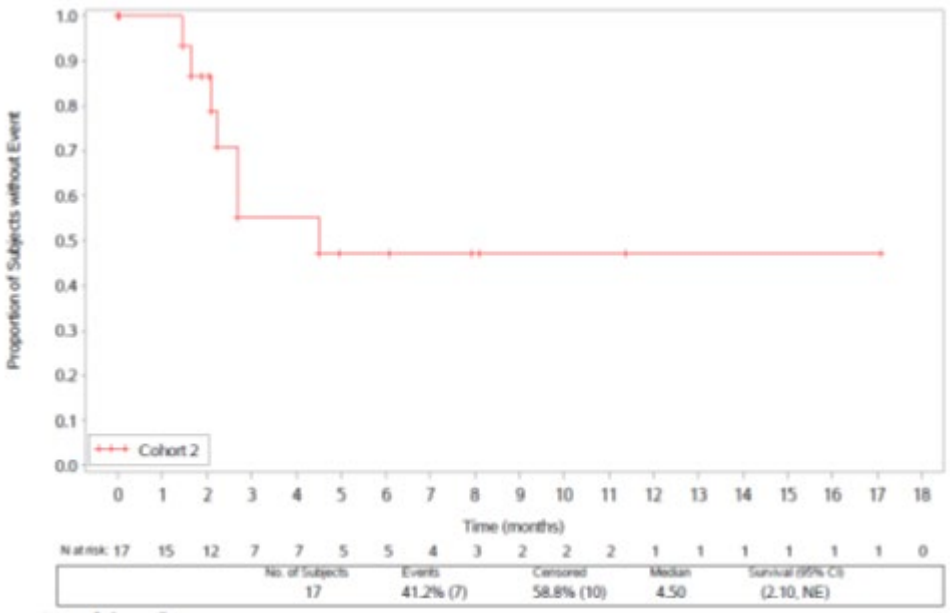
Abbreviations: BOR = best overall response; CI = confidence interval; CRR = complete response rate; DOR = duration of response; EFS = event-free survival; IRC = Independent Review Committee; Max = maximum; Min = minimum; NE = not evaluable; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; Q1 = quartile 1; Q3 = quartile 3; SD = stable disease.

[a] Two-sided 95% confidence interval based on exact Clopper-Pearson method

[b] ORR > 50.2% against the null hypothesis that the ORR <= 50.2%. Significance level is one-sided alpha=0.025.

[c] Median, Q1, Q3 are estimated from Kaplan-Meier product-limit estimates

Figure 31. Kaplan-Meier Plot of Duration of Response (DOR) by IRC Assessment using EMA Criteria Leukaphered Set



Based on IRC assessment in liso-cel-treated subjects, the median DOR among the 13 subjects achieving CR was 12.12 months (95% CI: 1.64, NE), whereas in the 4 subjects achieving PR, the median DOR was 2.69 months (95% CI: 2.10, 2.69).

Results in additional sensitivity analyses are as follows:

Based on investigator's assessment in liso-cel-treated subjects, the ORR was 74.1% (20/27 subjects; 95% CI: 53.7, 88.9), the CRR 37.0% (10/27 subjects; 95% CI: 19.4, 57.6). Based on Investigator

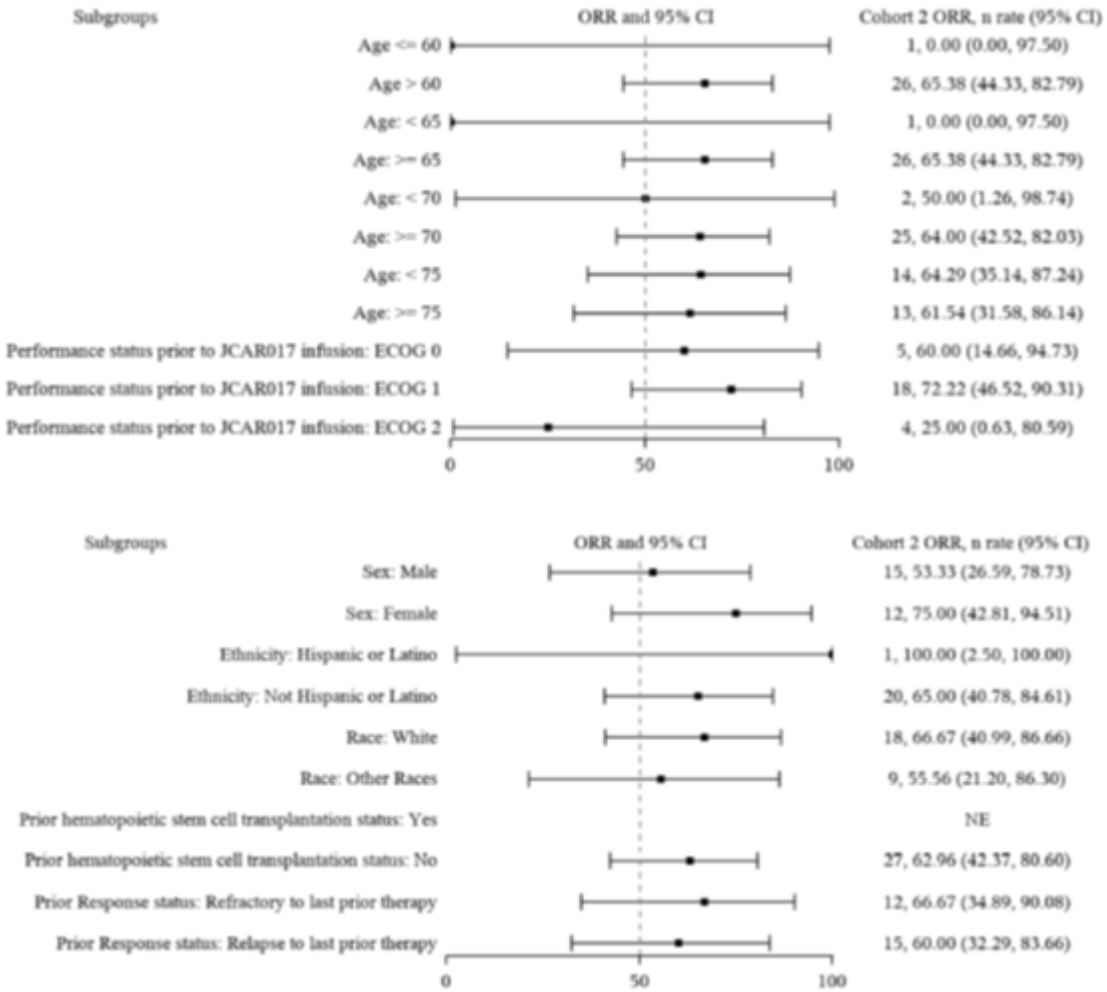
assessment in liso-cel-treated subjects using EMA censoring criteria, the median DOR was 2.69 months (95% CI: 1.87, NE), the median PFS 3.12 months (95% CI: 1.97, 5.78) and the median EFS 3.12 months (95% CI: 1.97, 5.78).

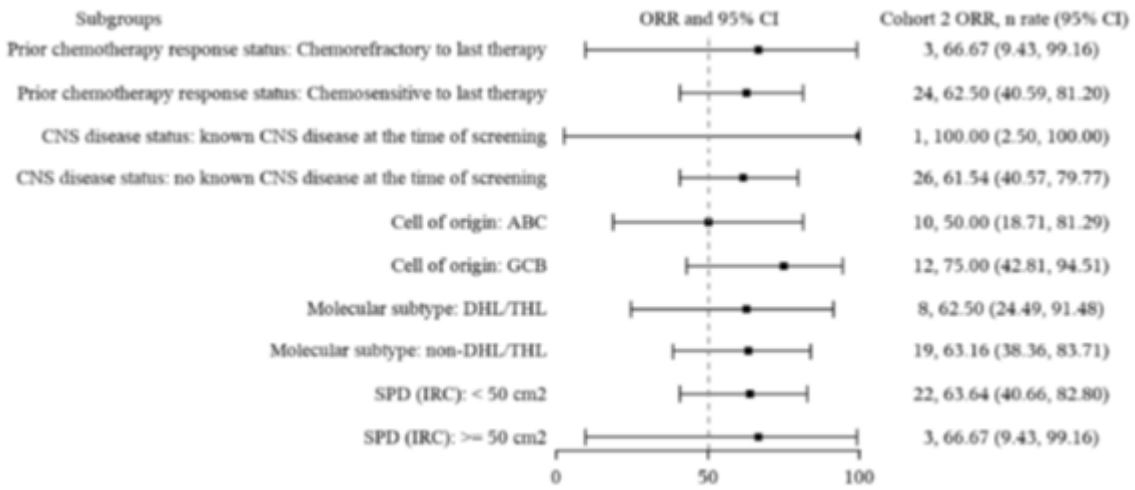
Based on IRC assessment in Leukapheresed subjects, the ORR was 53.1% (17/32 subjects; 95% CI: 34.7, 70.9), the CRR 37.5% (12/32 subjects; 95% CI: 21.1, 56.3). Based on IRC assessment in leukapheresed subjects using EMA censoring criteria, the median DOR was 4.50 months (95% CI: 2.10, NE), the median PFS 4.67 months (95% CI: 3.65, 7.75) and the median EFS 4.67 months (95% CI: 3.65, 7.23).

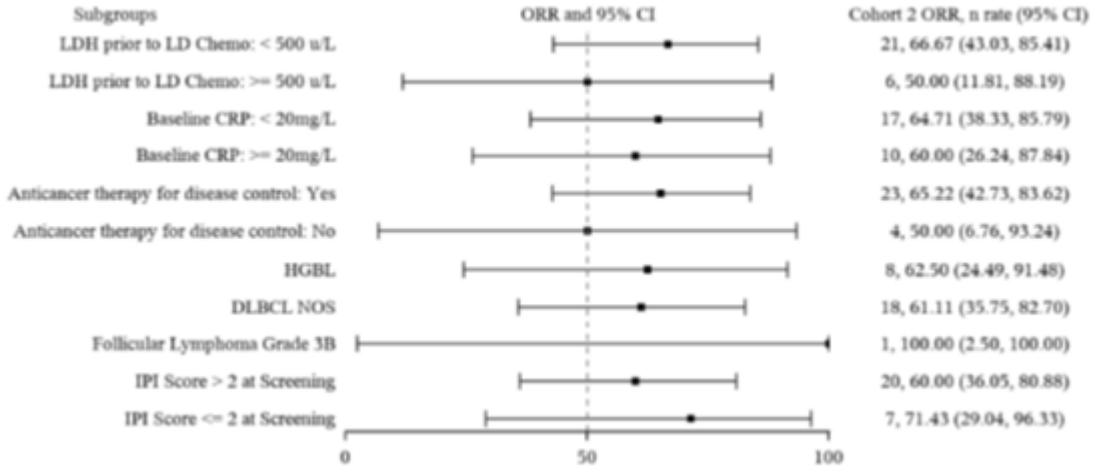
In the sensitivity analysis, the KM estimate for the median OS in leukapheresed subjects was 11.37 months (95% CI: 5.68, NE). The median follow-up time was 8.84 months (95% CI: 7.29, 12.91).

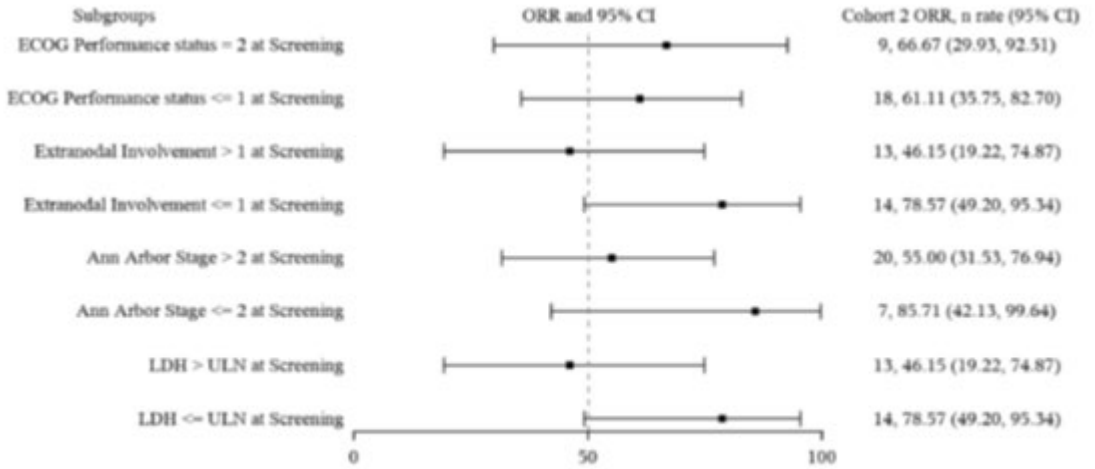
ORR results across subgroups in the liso-cel-treated subjects based on IRC assessment are summarised in Figure below:

Figure 32. Forest Plot of Overall Response rate – IRC Assessment Liso-cel-treated Subjects









*Vertical line at 50% is a visual guide only

2.5.3. Discussion on clinical efficacy

Based on the results from pivotal Phase III study JCAR017-BCM-003, the Marketing Authorisation Holder (MAH) requested an extension of the indication to include subjects who were refractory or had relapsed

within 12 months of initial therapy and were candidates for autologous haematopoietic stem cell transplant (HSCT). The finally agreed extended indication is:

Breyanzi is indicated 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.

Design and conduct of clinical studies

The study design of the pivotal study BCM-003 is overall compliant to the 2017 CHMP scientific advice (SA), although additional changes have been introduced to address further requests from. a health agency

Study participants

The study inclusion/exclusion criteria were adequate to define a study population that included adult subjects with large B-cell lymphomas who have failed standard frontline immunochemotherapy (i.e., R-CHOP or other combinations based on anthracycline and anti-CD20 monoclonal antibody) and are at higher risk of salvage treatment failure due to primary refractory disease or short-lasting response to frontline treatment.

The unmet medical need in the target population is recognised: despite salvage immunochemotherapy followed by high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT) has been demonstrated to result in long-term disease remission/cure in approximately 40% of 2nd line DLBCL patients (Philip T et al, 1995), the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study showed how subjects treated with rituximab-based first-line chemo-immunotherapies and either not achieving CR or experiencing early relapse (i.e. relapsed within 1 year of initial diagnosis) still had a higher risk of salvage failure (3-year PFS ~20%,. Gisselbrecht C et al, 2010; Hamadani M et al,. 2014, Van Den Neste E et al, 2016).

In line with the CHMP SA, subjects with several different LBCL histologies (as per the revised 2016 WHO classification of lymphoid neoplasms; Swerdlow SH et al, 2016) were deemed eligible; following FDA request, study eligibility was further broadened to specifically include subjects with PMBCL and T cell/histiocyte rich B-cell lymphoma (THRBCL). The inclusion of PMBCL is not controversial, being already considered in the approved 3rd line indication. THRBCL is a rare (1-3%) variant of DLBCL characterised by atypical histology (i.e., fewer than 10% malignant B cell in the setting of polyclonal T cells +/- histiocytes), frequent extranodal involvement and aggressive clinical course. Preliminary data suggested that primary resistance to CD19-directed CAR T-cell therapy in THRBCL might not be uncommon (Trujillo JA et al, 2021).

The limited information with Breyanzi in subjects with CD19-negative disease has been reflected in section 4.4 of the SmPC. Considering this aspect, further characterisation of the correlation between liso-cel efficacy and CD19 expression (as assessed by either flow cytometry or IHC at the time of relapse) is considered needed and data will be collected post approval of the new indication. Subjects with secondary CNS involvement could be enrolled in study BCM-003 if the individual patient B/R was considered positive by the Investigator. Eventually, only 4 subjects with CNS involvement were treated in the pivotal study, and specific B/R evaluations were, therefore, hampered by the reduced sample size. A warning on the limited clinical experience of use of Breyanzi for secondary CNS lymphoma is already included in section 4.4 of the SmPC.

Autologous transplant was mandatory in the control arm of study BCM-003, hence participation in the pivotal trial was restricted to higher risk 2nd line patients with large B cell lymphomas (LBCLs) who were

deemed fit for ASCT. The claimed indication was also initially worded to reflect ASCT-fitness as a requirement. The CAT noted, however, that such wording was ambiguous, since patients eligible to Breyanzi were not actually intended to undergo ASCT in real-world clinical practice. Moreover, the very use of ASCT eligibility criteria to identify patients fit for CAR T-cell treatment was questioned: ASCT eligibility assessment is known to be a complex, not standardised evaluation that incorporates multiple variables (e.g., functional status, organ function, comorbid conditions, psychosocial issues, disease status, local access to transplant procedures, patient preferences etc.), so that ASCT fitness criteria can vary significantly between institutions. Most importantly, the safety profiles of anti-CD19 CAR T-cell ATMPs and ASCT are different (see the Safety section below) and since eligibility to Breyanzi is expected to be based on a specific clinical reasoning, it cannot be excluded that some non-transplant eligible (NTE) subjects could still benefit from treatment with Breyanzi. With the support of data from studies 017006 and BCM-001 Cohort 2 (see below), the indication wording has been reworded to avoid reference to ASCT eligibility.

Treatment

Subjects in study BCM-003 were randomised either to SOC (Arm A) or liso-cel (Arm B).

Liso-cel was administered in accordance with the current recommendations in the SmPC.

The SOC arm is considered representative of the current standard of care in the target population (Tilly H et al, 2015] and NCCN v. 5.2022 guidelines): transplant-eligible LBCL patients who have failed frontline immunochemotherapy are usually managed with non-cross resistant "salvage" immunotherapy combinations (e.g., regimens including gemcitabine, cytarabine and/or platinum), with the main aim to reduce disease bulk and (re-)induce remission. Response to salvage immunochemotherapy is a sign of residual chemosensitivity and represents an independent prognostic factor for long-term benefit with HDCT and ASCT. Subjects in study BCM-003 could receive 3 cycles of R-DHAP, R-ICE or R-GDP, as per physician preference: this is acceptable, since the three SOC regimens are frequently used in clinical practice and randomized studies have not shown any clear evidence supporting the superiority of one regimen over another. The choice to allow for multiple SOC combinations in the control arm of study BCM-003 is endorsed to enhance results generalisability, since in real world practice salvage regimens are often selected taking into consideration differences in the safety profile. In case of toxicity or lack of satisfactory response to the selected SOC regimen, a switch within the 3 defined SOC regimen was allowed: this is also acceptable to further enhance adherence to clinical practice.

Subjects who were able to achieve disease remission/response (i.e., CR or PR evaluated by PET/CT) with salvage immunochemotherapy could proceed to HDCT and ASCT. The BEAM combination was selected as conditioning regimen, as per current guidelines recommendations (Tilly H et al, 2015).

Cross-over from SOC to liso-cel was allowed. In principle, the introduction of a one-way cross-over to liso-cel might result in OS evaluations being confounded. On the other hand, it is recognised that anti-CD19 CAR T-cell products are the current 3rd line efficacy standard and introducing the possibility for "in study" cross-over allowed for a better control of subsequent treatments in the control arm. This could, theoretically, also provide some insight in terms of better treatment sequence (i.e., liso-cel in 2nd line vs. SOC followed by liso-cel in non-responders).

Objectives and endpoints

The primary objective of study BCM-003 was to compare the efficacy of liso-cel vs. SOC in the target population in terms of event-free survival (EFS). Response to treatment was assessed according to the Lugano criteria (Cheson et al, 2014) by the IRC: this is in line with current clinical standards and acceptable.

EFS is a composite time-to-event endpoint that has been frequently used in curative settings of blood diseases in order to speed approvals. EFS is usually defined in such a way to capture clinical benefit in terms of optimal conditions to achieve long-term disease control in a specific setting. The choice of EFS as primary endpoint in study BCM-003 was considered acceptable by the CHMP in the 2017 SA.

EFS was defined in the pivotal trial as the time from randomisation to death from any cause, PD, failure to achieve CR/PR by 9 weeks post-randomisation and start of any anti-neoplastic therapy due to efficacy concerns, whichever occurred first. It should be noted that this definition was introduced with Amendment 1 and differed from the one endorsed by the CHMP in the SA (i.e., the time from randomisation to death, PD or start of any anti-neoplastic therapy, whichever occurred first). Failure to achieve CR/PR at the end of 3 cycles of salvage chemotherapy or 5 weeks after liso-cel infusion was introduced as an event to enhance adherence to clinical practice: reaching disease remission before ASCT is, in fact, considered a sign of residual chemosensitivity, an independent prognostic factor for long-term disease control and a pre-requisite to proceed to ASCT consolidation. In clinical practice, subjects failing to achieve response to 2nd line salvage regimens are candidate for 3rd line approaches, including anti-CD19 CAR T cell products. Therefore, the changes introduced in the EFS definition since the 2017 CHMP SA can be considered in line with current guidelines recommendations and overall acceptable. The timing for pre-transplant response assessment (i.e., 9 weeks post-randomisation) allowed for the completion of salvage chemotherapy and was adequate to evaluate response in the experimental arm, since the median time to first CR/PR in the Breyanzi registrational study was 0.95 months. It should be taken into consideration, however, that when EFS has been selected as primary endpoint in other acute hematologic conditions, it was shown that median EFS estimates differed considerably based on the timing of the response assessment in defining induction failure, with the magnitude of difference being large enough in some cases to impact conclusions (Yin J et al, 2019). Consistent results in the key secondary endpoint PFS (not including failure to achieve CR/PR as an event) and OS are, therefore, also considered key in supporting the clinical benefit conclusions.

The proposed sensitivity analyses for the primary endpoints are considered of relevance and acceptable. Although the study was not formally designed under an "estimand" framework, intercurrent events in the primary endpoint analysis were dealt with a mixed strategy: response to bridging therapy in the experimental arm and manufacturing issues preventing the infusion of liso-cel were addressed under a strict "treatment policy strategy", since they were considered to reflect clinical practice in the real-world setting. This is in line with the ITT principle and agreed.

PD events in unscheduled visits were addressed under a "composite" strategy: this is in principle agreed, since in the current treatment paradigm for R/R LBCL, residual sensitivity to chemoimmunotherapy (as indicated by achieving CR with salvage regimens) is a necessary pre-requisite to proceed to ASCT. In study BCM-003, the first efficacy assessment to confirm CR in the SOC arm was planned to be performed at Day 64 (i.e., approximately after 3 cycles of SOC, corresponding to 5 weeks after liso-cel infusion). However, in RW clinical practice salvage therapy failure is usually assessed as early as possible in order to switch to alternative options and save the patient unneeded toxicity. Early unscheduled PD assessments were, therefore, expected to be systematically more frequent in the SOC arm compared to liso-cel. The data provided by the MAH confirmed that early unscheduled PD assessments (i.e., before Day 64) were significantly more common in the SOC arm (n=21) compared to the experimental arm (n=3). Although this imbalance might have theoretically favoured the experimental arm, it is agreed that early assessment of PD does not have the same value in the context of conventional therapy and CAR T-cell therapy. While progression during immunochemotherapy is the sign of chemoresistance and precludes access to transplantation, determining the failure of the salvage treatment strategy, evidence of PD occurring in the time between leukapheresis and CAR T-cells administration has no significant impact on the final outcomes with CAR T-cell products, except for those patients whose worsening clinical conditions would not allow for CAR T-cells infusion. This is confirmed by the fact that although 83.9% of

subjects who received bridging chemotherapy in the liso-cel arm of study BCM-003 were PET/CT-positive before LDC, PD was reported only in 5/89 at the first disease status assessment post liso-cel infusion (Day 64). The observed imbalance in the frequency of unscheduled early PD assessment across treatment arms can be considered, therefore, in line with current clinical practice and unavoidable.

The (key) secondary and exploratory efficacy endpoints in study BCM-003 are considered, overall, adequate to further characterise the clinical benefit with liso-cel in the target population.

Statistical methods and conduct of the study

Sample size calculations were driven by the number of required EFS events and based on the assumption of a median EFS (mEFS) of 3 months in the control arm vs. ~5.5 months in the experimental arms (HR 0.55). Overall, 119 EFS events were required to provide at least 90% power with a one-sided significance level of 0.025, resulting in a minimum of 182 subjects to be randomised. The clinical assumptions are considered justified when the limited evidence at the time of study initiation is taken into account. The observed mEFS in the control arm was actually shorter (2.3 months) than expected, yet the 95%CI (2.2, 4.3) still included the assumed value (i.e. 3 months). Conversely, the mEFS observed in the experimental arm was significantly longer than assumed (mEFS 10.1 months, 95%CI 6.1, NE), increasing the already elevated study power. When the magnitude of the observed effect and its clinical value are taken into account, however (see the Efficacy data section below), the possible consequences of such overpowering are considered of limited relevance. The Applicant pre-planned an adaptive strategy for increasing the number of patients based on the Bayesian predictive probabilities approach: although sample size reassessment in ongoing, open-label studies is in principle discouraged, no sample-size increase was eventually required in the pivotal study since the pre-defined criteria for superiority of liso-cel were met at the time of the second IA.

All subjects were randomised at a 1:1 ratio to SOC or liso-cel using a permuted-blocks methodology: this is acceptable, as well as the selected stratification factors (refractory vs. relapsed and sAAIPI 0/1 vs. 2/3). Due the significant differences in treatment strategies across study arms, the unfeasibility of blinding can be acknowledged, and additional measures to maintain study integrity (e.g. the Applicant and the IRC were blinded to the treatment arm, and an independent DSMB was in charge of safety oversight) were anyway put in place. This is acceptable.

Overall, the statistical methods used for time-to-event and binary endpoints are standard and acceptable, including the approach based on Schoenfeld residuals to evaluate the proportional hazards assumption.

The hierarchical testing strategy to control multiplicity across endpoints and the O'Brien-Fleming approach to allocate Type I error rate across IAs were considered methodologically appropriate. The futility analysis was conducted on November 2019: no formal statistical testing occurred and the DSMB recommended to continue the study without modifications. The pre-specified superiority IA was conducted on November 2020 at 63% information fraction and the DSMB confirmed that the pre-defined criteria to claim superiority were met. Health agency recommendations, however, were to continue the study without modification and to conduct another IA at 80% information fraction for regulatory purposes. In principle, the introduction of new IAs in ongoing, open-label studies could raise concerns on study integrity. From a regulatory perspective, however, when the limited number of events at the time of the 60% information fraction IA (n=75) are taken into consideration, the health agency concerns about the overall data maturity and results representativeness can be shared. Further, the requested additional IA was also in line with the 2017 CHMP SA, in which the need for sufficient data maturity was stressed. Overall, the impact of this" Interim analysis on study integrity is considered limited: study BCM-003 had already met his primary objective at the 60% information fraction IA, and the only purpose of the new IA was to increase data maturity. Furthermore, to reduce the risk of bias, an independent

external statistical group was responsible for the additional IA, and the O'Brien-Fleming spending function was updated to maintain the overall type I error control across the IAs and primary analysis. This is considered overall acceptable.

At the data cut-off date for the 80% IA, the crossover rate from SOC arm to liso-cel arm was about 54.3%, leading to a possible underestimation of the true survival benefit with liso-cel in the conventional ITT analysis.

The statistical analyses proposed for Quality of Life (QoL) are also considered in principle acceptable. The open-label nature of the study and the lack of control of multiplicity hampered, however, the possibility for HR-QoL-based claims.

Overall, only 2 major amendments were issued during study conduct. Theoretically the impact of amendment 1 ongoing changes on study integrity cannot be considered negligible. On the other hand, as highlighted by the MAH, when Amendment 1 was issued, only 1 patient had been enrolled, thus the overall impact of the introduced changes on study integrity is considered minor. Changes in Amendment 2 were of less clinical/methodological relevance, with one exception: pseudo-progression was specified not being an event for EFS. Overall, only 7 cases of pseudoprogression were reported in study BCM-003, 3 (3.3%) in the SOC arm and 4 (4.3%) in the liso-cel arm. When the different nature of liso-cel and immunochemotherapy is considered, the observed similar incidence of pseudoprogression in the SOC and liso-cel arms was unexpected. Additional information on the "pseudoprogression" events reported in the control arm showed that all the events in subjects who received salvage therapy in study BCM-003 occurred, in the absence of severe leukopenia, at the time of the interim PET/CT scan (i.e. approximately 2 weeks after the last dose of salvage immunochemotherapy), or shortly after ASCT (i.e. approximately 3 months post ASCT). Adams HJA et al. (2016) have described how false-positive PET/CT scans during or shortly after completion of anti-lymphoma treatment are far from uncommon, ranging between 7.7% and 90.5% of all biopsied FDG-avid lesions, and mainly result from treatment-related inflammatory changes in existing tumour masses. The transient PET/CT positivity events observed in the SOC arms are, therefore, likely to reflect post-chemotherapy reactive inflammation rather than immunotherapy-related "pseudoprogression"; the very use of the term "pseudoprogression" to describe such events, although in line with the study IRC charter, cannot be considered fully appropriate. Due to very limited numbers, the impact of such events on efficacy results is, anyway, negligible

Overall, an equal number of subjects reported at least one important protocol deviation (IPD) in the experimental (n=9; 9.8%) and control arms (n=9; 9.8%) of study BCM-003. Most IPD were related to failure to report SUSARs and their impact on study efficacy is considered limited. Due to the COVID-19 pandemic, study enrolment was delayed by ~4 months, yet no IPD involved COVID-19, no subject had missed response assessments, discontinued, or delayed treatment because of COVID-19. Out of window visits due to COVID-19 were limited (0.5%), as well as the number of subjects with COVID-19 related AEs or deaths (see the Safety section below). Overall, the impact of the COVID-19 pandemic on study conduct is considered limited.

Supportive studies 017006 and BCM-001 Cohort 2

In the initial submission limited data were available on the efficacy of Breyanzi in 2nd line non-transplant eligible (NTE) high-risk patients. To further characterise the clinical benefit with liso-cel in this frailer subset, the MAH submitted efficacy data from studies 017006 and BCM-001 Cohort 2 that investigated the efficacy and safety of Breyanzi in NTE subjects with R/R LBCLs.

Results from supportive study 017006 and study BCM-001 Cohort 2 are only seen as descriptive in the context of this extension indication application.

Efficacy data and additional analyses

The proportion of subjects who discontinued during the treatment phase of study BCM-003 was significantly higher in the SOC (~60%) compared to the liso-cel arm (~12%). This is not unexpected when the significant differences in ORR and CRR across treatment arms are taken into account, especially considering that only subjects achieving a PR/CR with salvage chemotherapy could proceed to ASCT in the SOC arm.

Only one patient in the liso-cel arm did not receive the planned treatment due to manufacturing failure, and two subjects (1 in the liso-cel arm and 1 in the cross-over subset) received a non-conforming product: these data support the overall robustness of the manufacturing process.

Baseline and disease characteristics in study BCM-003 were overall balanced across treatment arms and representative of the target population. As expected, since ASCT was part of the treatment strategy in the SOC arm, the vast majority of patients were medically fit (ECOG PS score ≤1 in ~98% of patients and median HCT-CI score 1.0). A slight increase in the prevalence of male subjects was observed (57.1%), in line with the known epidemiology of most LGBCLs; however, male subjects were more frequent in the SOC (66.3%) compared to the liso-cel arm (47.8%): male gender has been associated with a poor prognosis in DLBCL patients treated with rituximab-containing regimens (Yldirim M et al, 2015), thus a possible impact on study results, although hardly quantifiable, cannot be excluded.

Rarer LGBL subtypes were poorly represented (e.g., FL3B 0.5%, THRBCL 2.7%), hampering the possibility for dedicated B/R evaluations. The MAH has committed to update the PASS (Study JCAR017-BCM-005) protocol to collect further data on 2nd line LBCL patients with rare histologies. Such changes will be applied and reflected in the protocol of the PASS study upon approval of this extension of indication procedure. As already discussed in the original submission for Breyanzi, extrapolation of clinical activity to FL3B can be accepted, based on clinical and biological similarities with DLBCL and transformed FL (see the Breyanzi EPAR). With respect to THRBCL, the MAH specified that only 5 subjects with THRBCL were treated in study BCM-003, and only 2/5 received liso-cel (1 subject in the liso-cel arm and 1 subject in the control arm after cross-over to liso-cel. Although 1 subject with THRBCL who received liso-cel experienced sustained CR, reliable conclusions on the efficacy and tolerability of liso-cel in the THRBCL population were hampered by limited numbers. No claim for the treatment of THRBCL has been included in the proposed indication.

The results submitted to support the claimed extension of indication for Breyanzi are based on an IA at 80% information fraction (data cut-off date 08 Mar 2021).In line with historical data, approximately half (~46%) of the subjects who received salvage immunochemotherapy in the SOC arm were able to proceed to HDCT and ASCT; the HDCT-ASCT rates reported in literature with the SOC regimens (but also including lower-risk patients) were in the range 51-55%, supporting the external validity of study results (Gisselbrecht C et al, 2010; Kuruvilla J et al, 2015).

With a median survival follow-up of 6 months and 53% of subjects with an event at the data cut-off date for the inferential 80% IA, study BCM-003 met its primary objective: the median **EFS by IRC** was 2.3 months (95%CI 2.2, 4.3) with SOC and 10.1 months (95%CI 6.1, NE) with liso-cel, resulting in a EFS HR of 0.349 (95%CI 0.229, 0.530; p<0.0001). The 6-month EFS rates were 33.4% and 63.3%, in the SOC and liso-cel arms, respectively, with the KM curves diverging early to remain clearly separated. The KM curve tails were, however, poorly informative due to the reduced number of subjects at risk.

The results from all the pre-specified sensitivity analyses for EFS were consistent with the primary analysis, including EFS not adjusting for stratification factors (HR 0.376, 95%CI 0.248, 0.569), EFS by Investigator's assessment (HR 0.343, 95%CI 0.225, 0.522), EFS using the stricter "FDA imaging interpretation rules" (HR 0.383, 95%CI 0.254, 0.576), and EFS censoring for RT (HR 0.344, 95%CI

0.266, 0.523) or not including subjects who were PET/TC negative after bridging chemotherapy (HR 0.353, 95%CI 0.209, 0.595).

The submitted updated efficacy data from the primary analysis of study BCM-003 (data cut-off date 13 May 2022) covered a longer follow-up (mFU 17.53 and 17.49 months, in the liso-cel and SOC arm, respectively) and a higher number of events (38% and 68.5% in the liso-cel and SOC arm, respectively) showing that the **updated EFS analysis by IRC** was consistent with the results observed in the interim analysis (IA) at 80% information fraction: the updated HR for EFS based on IRC assessment was 0.356 (95%CI 0.243, 0.522), the mEFS was not reached in the experimental arm (NE, 95%CI 9.5, NE) vs. 2.4 months (95%CI 2.2, 4.9) in the control arm. The updated KM curves for EFS started diverging from time 0 to remain clearly separated until the end, and a plateau phase could be identified from approximately month 12 onwards in both treatment arms, suggesting a possible improvement in terms of cure/long-term disease control rate with liso-cel compared to SOC.

Failure to achieve PR/CR with salvage treatments is known to negatively impact on long-term outcomes, yet a subset of patients who fail to achieve disease remission in 2nd line might still benefit from HDCT and ASCT. In this regard, PFS analysis (which does not consider the failure to achieve CR/PR as an event) is considered of value to further characterise clinical benefit with liso-cel. With 39% of subjects in study BCM-003 who had an event, the key secondary endpoint PFS was met: **mPFS by IRC** was 5.7 months (95%CI 3.9, 9.4) in the SOC arm and 14.8 months (95%CI 6.6, NE) in the liso-cel arm, respectively. The PFS HR was 0.406 (95%CI 0.250, 0.659, p=0.0001), with the KM curves showing a trend similar to those observed in the primary EFS analysis. PFS2 data were also provided, and results were consistent with the PFS analysis (HR 0.494, 95%CI 0.321, 0.760); data immaturity (only 4 subjects had a second progression event reported), however, did not allow for definitive conclusions.

The **updated PFS by IRC** data from the primary efficacy analysis of study BCM-003 were consistent with the EFS analysis and with data previously submitted at the time of the 80% IA: the updated HR was 0.400 (95%CI 0.261, 0.615) and the updated KM curves for PFS showed a consistent trend towards clinical benefit with liso-cel.

Subgroup analyses for EFS and PFS must be interpreted with caution, due to the limited sample size in several subgroups. The observed treatment effect was, overall, consistent across the most relevant subsets, including subgroups defined by sAAIPI, refractoriness to frontline treatment and prior chemotherapy response status, age (with the caveat that no subject aged ≥75 years received liso-cel in study BCM-003), sex and region. No significant differences in EFS could be observed in subgroups defined by histology subtypes. Although numbers were limited, the observed homogeneity of response and the consistent pattern of expression of CD19 across all subgroups are considered sufficient to extrapolate that a similar clinical benefit with Breyanzi vs. SOC can be expected across all these conditions. The very limited number of subjects (n=1) in the FL3B subgroup cannot be considered sufficient, however, to support specific B/R evaluations. FL3B is a rare form of aggressive B-cell lymphoma whose clinical behaviour and treatment paradigm do not differ significantly from DLBCL (Barraclough A et al, 2021, Swerdlow SH et al, 2008 WHO classification of Tumours of Haematopoietic and Lymphoid Tissues, Katzenberger OG et al, 2002; Koch K et al, 2016; Kikkeri NN et al, 2007). In the original MAA of Breyanzi, 6 subjects with FL3B were treated with Breyanzi across all the registrational studies: long-lasting remissions were observed, despite failure of multiple prior lines of chemotherapy, in all patients, suggesting that the efficacy of Breyanzi in FL3B was at least similar to that observed in DLBCL. Considering the biological and clinical similarities between DLBCL and FL3B and the rarity of FL3B, the available 3rd+ line data were considered sufficient to support the extrapolation of a positive B/R also to FL3B. In this respect, all the arguments supporting the extrapolation of the efficacy of Breyanzi in DLBCL to FL3B in 3rd+ line are equally acceptable in 2nd line, since no deviating outcomes are expected (e.g., the only subject with FL3B who received Breyanzi in study BCM-003 achieved a response that was still

ongoing at the time of the data cut-off date). The inclusion of FL3B in the proposed 2nd line indication is, considered therefore, acceptable.

In contrast to what observed in 3rd+ line LBCL in registrational studies 017001 and BCM-001, high baseline LDH serum levels and SPD did not appear to have a negative impact on liso-cel EFS in 2nd line. A reduced treatment effect in PFS could be observed, however, in subjects with high baseline LDH serum levels (HR 0.949) and HGBL (HR 0.717): the actual relevance of these results is of difficult evaluation due to sample size constraints. It was shown by univariate and multivariate analyses (see the Quality section above) that a relationship could be observed a T cell attribute in one of the two cell components of liso-cel and clinical efficacy. The MAH specified that >93% of the variance in this T cell attribute in 2L LBCL patients was due to patient-intrinsic factors which is not unexpected due to the autologous nature of the product. Point estimates for mEFS still hinted to a persistent benefit with liso-cel, even when the highest quartile of this product attribute or optimal splitting values were considered. The effect of this attribute in both cell components on patient outcomes was investigated also in the control arm. The results did not show any significant correlation, suggesting that this T cell attribute had no general prognostic value in this high-risk 2nd line setting. It was, therefore, confirmed that the effect of this attribute could only be observed in the liso-cel arm, supporting a possible predictive value for liso-cel in this specific indication. However, the biological/clinical rationale of this correlation is unclear, and further validation would be needed to conclude on its possible predictive value. However, it is noted that a consistent trend towards clinical benefit with liso-cel vs. SOC could still be observed across the full range of values for this T cell attribute. This attribute is considered to deserve further characterisation in the setting of the 2L treatment with Breyanzi (see the Quality section).

OS data are considered of value to understand the real benefit of early administration of liso-cel vs. SOC in the targeted 2nd line high risk setting, especially considering the availability of anti-CD19 CAR T cell products in 3rd line. The provided OS data at the time of the 80% IA were, however, not sufficiently mature. With a median survival follow-up of 6 months, only 37/184 (20%) subjects had an event in study BCM-001. The KM curves for OS started diverging after approximately 3 months to remain separated; their informativeness after month 6 was, however, severely limited by elevated censoring. **Updated OS data** were submitted from the primary analysis of study BCM-003 and no statistically significant effect could still be observed (the updated HR was 0.725 [95%CI 0.443, 1.183]). Study BCM-003 was not, however, sufficiently powered to test for OS superiority; moreover, the impact of the limited number of events observed at the time of the data cut-off date (26% and 14% in the SOC and liso-cel arm, respectively) and of the high rate of cross-over from the control arm to liso-cel on survival analyses was not negligible. With the limits of the "post-hoc" nature of such exercises, the MAH also submitted additional sensitivity analyses adjusted for the confounding effect of subjects crossing over from SOC to liso-cel using the Accelerated Failure Time Model and the RPSFT model. Both models showed a significant and potentially clinically relevant effect of liso-cel on OS (HR 0.415 and 0.279, respectively). The actual value of these analyses is, however, limited, and their interpretation not straightforward when the availability in the EU clinical practice of anti-CD19 CAR T-cell products from the 3rd line onwards is taken into consideration. Based on these considerations, the available OS data must be interpreted with caution, yet it can be noted that no clear detrimental effect was observed with liso-cel. Conversely, a trend towards a possible OS benefit is described: this might be of relevance when the high rates of cross-over to liso-cel are taken into consideration, and would support the importance of an earlier (i.e., 2nd line) introduction of anti-CD19 CAR T cell products in the treatment of high-risk R/R LBCLs. More mature data are needed, however, to draw definitive conclusions and the company has agreed to provide the final study report and the longer OS follow up for study JCAR017-BCM-003 in the post opinion setting.

The analysis in the key secondary endpoint **CRR by IRC** highlighted how liso-cel was significantly more effective in inducing remission compared to SOC. A similar but somehow less remarkable effect was also observed in the CRR analysis by Investigator. ORR data were consistent with the CRR analysis, with an

ORR by IRC of 47.8% and 85.9% in the SOC and liso-cel arms, respectively. Duration of CR data did not show significant differences across study arms, confirming the importance of achieving disease remission to aim for long-term clinical benefit. Similar results could be observed in the **DoR by IRC** analysis (HR 0.782, 95%CI 0.406, 1.505).

Compared to the 80% IA, the **updated CRR** from the primary analysis of study BMC-003 was improved both in the SOC (CRR 43.5%) and liso-cel arms (73.9%): this is not unexpected since time might be needed in same cases to reach the best metabolic response. The **updated median DoCR** was 9.3 months (95%CI 5.1, NE) in the control arm vs. NE (95%CI NE, NE) in the liso-cel arm.

Results from the planned **HR-QoL** analyses were also submitted. The available data were restricted to the first 6 months of treatment since time points with less than 10 available PRO assessments were not evaluable. Median scores on the EORTC QLQ-C30 primary domains of interest and on the FACT-LymS at baseline were generally similar across treatment arms and in line with those reported in the general population (whenever available). Mean changes from baseline in the group-level analysis pointed towards a favourable trend with liso-cel, in particular in terms of GH/QoL, cognitive functioning and fatigue. A similar case could also be observed in the individual-level analysis, showing a trend towards a greater improvement with liso-cel vs. SOC in the fatigue, pain, cognitive functioning and GH/QoL domains of the EORTC QLQ-C30 tool and in the FACT-LymS. The reliability of these data is, however, reduced by the limited overall compliance rates (~40%), the lack of blinding and the absence of multiplicity control.

In line with the CAT/CHMP recommendations at the time of the initial MA for Breyanzi (i.e. to further characterise the efficacy and safety of Breyanzi in 3rd line), the MAH has also submitted efficacy data from subjects who crossed over to liso-cel after failing conventional salvage treatment in the SOC arm. Overall, response rates were lower and response duration shorter in the "cross-over" subgroup of study BCM-003 when compared to 3rd+ line data with liso-cel in registrational study 017001 (ORR 72.7%, CRR 53.2%, mDoR 20.2 months, as reported in section 5.1 of the Breyanzi SmPC). This could be a reflection, however, of differences in study populations (e.g., enrolment in study BCM-003 was limited to high-risk patients, and rapidly progressing disease did not result in patient exclusion since liso-cel was already manufactured and available at the time of cross-over) and response assessment schedule.

Efficacy results in non-transplant eligible (NTE) 2nd line patients from supportive studies 017006 and BCM-001 Cohort 2

Eighty patients were deemed eligible to liso-cel in study 017006, 74/80 underwent leukapheresis and 61 received liso-cel.. Baseline characteristics were still similar between the leukapheresed (n=74) and the treated (n=61) analysis sets, suggesting that the risk of selection bias was reduced.

The median age in the overall population was 73.5 years (74 years in the treated set), with approximately 43% of patients aged ≥75 years, as expected in the NTE setting. Although 27% of patients had a baseline ECOG score 2, ~24% had a reduced renal function (CrCl <60 ml/min) and approximately 47% of subjects had a HCT-CI score ≥3, which is predictive of a higher risk of non-relapse mortality in the allogeneic transplant setting, it is noted that 41/61 (67%) of subjects enrolled in study 017006 met 1 single protocol NTE criterion, and approximately 50% of subjects were included based on the sole age criterion. Further, only 28% and 5% of subjects in study 017006 met 2 or 3 NTE criteria, respectively, suggesting that the overall comorbidity burden still played a significant role in determining eligibility to CAR T-cell treatment in the NTE setting. To what extent the population enrolled in study 017006 could be considered representative of the overall NTE R/R LBCL population was uncertain, since the clinical and logistic requirements of anti-CD19 CAR T-cell therapy likely resulted in the selection of "fitter" NTE subjects, at the same time confirming, however, that the eligibility to CAR T-cell products is specific and distinct from ASCT eligibility.

With respect to disease characteristics, DLBCL NOS and HGBCL were the most prevalent histologies (~55% and 30%, respectively). Although the study was not designed to explore liso-cel activity in the specific higher risk 2nd line setting targeted by this extension of indication, it is noted that refractory and early relapsed (i.e. <12 months) patients comprised ~75% of the whole population.

Efficacy data were overall encouraging: treatment with liso-cel in study 017006 resulted in a clinically relevant anti-tumour activity. Subgroup analyses showed that the ORRs in the subsets of patients with refractory or early relapsed (≤12 months) disease that are targeted by this extension of the indication were overall consistent with the primary analysis, although these data should be interpreted with caution due to the limited sample size. Deep and durable responses could be observed in study 017006. Overall, these data suggested the possibility of long-term disease control in a subset of responders. In the absence of a randomised control, PFS, EFS and OS data from study 017006 were of difficult interpretation.

Although in absolute terms the point estimations for ORR and CRR were lower compared to those observed in pivotal study BCM-003 (85.9% and 66.3%, respectively), they were in line or ameliorative compared to those reported with liso-cel in the approved ≥3rd line indication (i.e., the ORR and CRR in the leukapheresed analysis set of pivotal study 017001 were 60.1% and 43%, respectively, as reported in the currently approved Breyanzi SmPC). Differences in study populations and median follow-up hampered indirect comparisons with other products/combinations approved in NTE R/R LBCLs, yet the magnitude, depth and duration of response observed in study 017006 (especially in subjects who achieved a CR) could still be considered of relevance when contextualized in the current treatment framework.

Overall, 32 subjects underwent leukapheresis and 27 (~84%) received liso-cel in study BCM-001 Cohort 2; Baseline characteristics were similar between the leukapheresed (n=32) and liso-cel treated (n=27) analysis sets, indicating a limited risk of selection bias.

Consistently with study 017006, the median age in Cohort 2 was 74 years (min. 49, max 81 years), and a slight prevalence of male patients could be observed. Although approximately 33% of patients had an ECOG PS score of 2, most patients (59%) met 1 single NTE protocol criterion (most commonly age: 48%). As per study 017006, it is uncertain whether or to what extent patients in Cohort 2 could be considered representative of the overall NTE R/R LBCL population. With respect to disease characteristics, DLBCL NOS and HGBCL were the most prevalent histologies (~66% and 30% of the study population, respectively), most patients (60%) had high aaIPI score at screening, and approximately 75% of subjects were primary refractory or experienced early (≤12 months) relapse after frontline immunochemotherapy. Overall, it can be agreed that the patients treated in study BCM-001 Cohort 2 were representative of a higher risk 2nd line setting.

Efficacy results in Cohort 2 were generally less favourable, yet still in line with those observed in study 017006, as indicated by the largely overlapping confidence intervals. Subgroup analyses were hampered by limited numbers. Due to the short follow-up (11.1 months), duration of response data had to be interpreted with caution, and an initial plateau in the KM plots suggested the possibility of long-term disease control in a subgroup. The interpretation of survival data from study BCM-001 Cohort 2 was hampered by the limited follow-up and by the absence of a randomised control.

Overall, results from supportive studies 017006 and BCM-001 Cohort 2 provided supplementary evidence of the activity of Breyanzi in NTE patients. Short follow-up did not allow, however, for the characterisation of long-term efficacy in this setting. The MAH agreed to submit updated data from the final CSR of studies 017006 and BCM-001 Cohort 2 post approval.

2.5.4. Conclusions on the clinical efficacy

The current salvage strategy in 2nd line LBCLs is aimed at achieving high remission rates to maximize clinical benefit from HDCT and ASCT, especially in terms of long-term disease control. The available efficacy data from pivotal study BCM-003 showed how, in the targeted high-risk (yet still curative) setting, liso-cel was able to induce a higher CRR compared to SOC, which resulted in a clinically relevant and statistically significant prolongation of EFS and PFS.

No significant differences in terms of treatment effects were observed across the LBCL histologies included in the claimed indication. Although low numbers did not allow specific efficacy evaluations in rarer subgroups (e.g. PMBCL, FL3B), homogeneity in treatment response and consistent CD19 expression across all the considered histologies support the extrapolation of a similar clinical benefit with Breyanzi in the broad claimed indication. Further data in rare LBCL variants will be collected in the post-approval setting.

A consistent high anti-tumour activity could also be observed across supportive studies, indicating the possibility to achieve deep and durable responses also in a frailer (NTE), high risk patient population that received Breyanzi as second line treatment, and further supporting the broad claimed indication. More mature data from studies 017006 and BCM-001 Cohort 2 will be provided post approval.

The efficacy of Breyanzi in the target population is considered demonstrated.

2.6. Clinical safety

Introduction

On 04-Apr-2022, the European Commission (EC) granted a marketing authorization for Breyanzi (liso-cel; JCAR017) for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy. With respect to safety, Breyanzi was generally well tolerated in patients with 3L+ large B-cell lymphoma, with an overall toxicity profile in line with that of the approved anti-CD19 CAR T-cell products. The important identified risks and the potential risks identified for Breyanzi were similar to those identified for this product class. Adverse events of CRS and NT were generally low-grade and resolved. Importantly, low rate of ≥ Grade 3 CRS occurred in the context of overall use of tocilizumab and/or corticosteroid in less than one-quarter of all patients treated with JCAR017. Despite evidence was limited for some less common large B-cell lymphoma subtypes including R/R FL3B and R/R PMBCL, as well as for other clinically relevant subgroups (ECOG PS ≥2; secondary CNS lymphoma; DLBCL post-allo HSCT), due to the small number of patients included, overall the JCAR017 activity was consistent across these subgroups. Data from Study BCM-001 were considered of particular relevance for EU patients, due to the same manufacturing process as proposed for commercial use in the EU. When additional patients were enrolled in Study BCM-001 (n= 36, Cohort 1), more comparable baseline characteristics were observed across the pivotal studies. Overall, the incidence of AEs and AESIs in the treatment-emergent (Day 1 to Day 90) and post-treatment emergent (Day 91 to end of Study) periods was generally similar, despite higher Grade ≥ 3 liso-cel-related TEAEs in Study BCM-001 compared with Study 017001, mainly driven by higher incidences of neutropenia, anemia and febrile neutropenia, and no notable difference in the incidence of individual AESIs.

For this proposed indication, the safety evaluation is primarily based on the studies included in the table below:

Table 51. Summary of Clinical Studies in the Liso-cel Clinical Development Program - Safety Populations Included in the Pooled and the Modified Pooled Safety Analyses

Study/Phase/Arm	Study Population	Trial Design	Target Dose	Region	Number of Subjects Treated with Liso-cel[a] included in the Pooled Safety Analyses	Number of Subjects Treated with Liso-cel[b] included in the Modified Pooled Safety Analyses	Data Cutoff Date
JCAR017-BCM-003 (TRANSFORM); Phase 3 Liso-cel arm 2L TI LBCL	Adult 2L CD19+ large B-cell lymphoma (DLBCL NOS Including transformed indolent NHL, HGBCL, FL3B, PMBCL, THRBCL)	Randomized, open-label, parallel-group, multi-site trial	100×10^6 CAR+ T cells	US, Europe, Japan	89	89	13-May-2022
017006 (TRANSCEND-PILOT-017006); Phase 2 2L TNI LBCL	Adult 2L CD19+ large B-cell lymphoma (DLBCL NOS including transformed follicular lymphoma NHL, HGL, FL3B)	Open-label, single-arm, multi-site trial	100×10^6 CAR+ T cells	US	61	61	24-Sep-2021
JCAR017-BCM-001 (TRANSCEND World); Phase 2 Cohort 2 2L TNI LBCL	Adult 2L CD19+ large B-cell lymphoma (DLBCL NOS including transformed follicular lymphoma NHL, HGL, FL3B)	Open-label, single-arm, multi-cohort, multi-site trial	100×10^6 CAR+ T cells	Europe, Japan	27	27	02-Mar-2022
JCAR017-BCM-001 (TRANSCEND World); Phase 2 Cohorts 1, 3 and 7 3L+ DLBCL	Adult 3L+ CD19+ large B-cell lymphoma (NOS including transformed follicular lymphoma, HGL, FL3B)	Open-label, single-arm, multi-cohort, multi-site trial	100×10^6 CAR+ T cells	Europe, Japan	Cohort 1: 36 Cohort 3: 10 Cohort 7: 6	Cohort 1: 36 Cohort 3: 10 Cohort 7: 6	02-Mar-2022

Study/Phase/Arm	Study Population	Trial Design	Target Dose	Region	Number of Subjects Treated with Liso-cel[a] included in the Pooled Safety Analyses	Number of Subjects Treated with Liso-cel[b] included in the Modified Pooled Safety Analyses	Data Cutoff Date
017001 (TRANSCEND NHL-001); Phase 1 3L+ DLBCL Cohort	Adult 3L+ CD19+ large B-cell lymphoma (DLBCL NOS including transformed indolent NHL, HGL, FL3B, PMBCL)	Open-label, single-arm, multi-cohort, multi-site trial	50×10^6 CAR+ T cells 100×10^6 CAR+ T cells 150×10^6 CAR+ T cells	US	270	229	04-Jan-2021
017007 (OUTREACH); Phase 2 3L+ DLBCL	Adult 3L+ CD19+ large B-cell lymphoma (DLBCL NOS including transformed indolent NHL, HGL, FL3B, PMBCL)	Open-label, single-arm multi-site trial	100×10^6 CAR+ T cells	US	80	78	24-Sep-2021

Study/Phase/Arm	Study Population	Trial Design	Target Dose	Region	Number of Subjects Treated with Liso-cel[a] included in the Pooled Safety Analyses	Number of Subjects Treated with Liso-cel[b] included in the Modified Pooled Safety Analyses	Data Cutoff Date
JCAR017-BCM-002[c] (PLATFORM); Phase 1/2 3L+ DLBCL	Adult 3L+ CD19+ large B-cell lymphoma (DLBCL NOS, FL3B, tFL, and other subtypes)	Open-label, single-arm, multi-cohort, multi-site combination therapy trial	Arm A Cohort 1A: 50×10^6 CAR+ T cells + durvalumab (up to 1500mg) from Day 29 Cohort 1B: 100×10^6 CAR+ T cells + durvalumab (up to 1500mg) from Day 29 Arm B Cohort 1A: 100×10^6 CAR+ T cells + CC-122 (2mg) from Day 29	US	Phase 1: 26	Phase 1: 22	01-Aug-2019

[a] Number represents the number of subjects treated with liso-cel as of the data cutoff dates in respective studies.

[b] Number represents the number of subjects treated with liso-cel within dose range of 44 to 120 x 10^6 cells as of the data cutoff dates in respective studies.

[c] Study BCM-002 only presented the arms and cohorts with no combination agent started before 1 month post liso-cel infusion and with treated subjects at the time of the data cutoff date of 01-Aug-2019, the same data cutoff to support the 3L+ LBCL application. Since then, no additional subjects had been treated in this study without a combination agent starting at least 1 month after liso-cel infusion. Adverse events (AEs) from liso-cel infusion up to the start of any combination therapy (Day 29) or up to 90 days after liso-cel infusion if no combination therapy is administered are included as TEAEs.

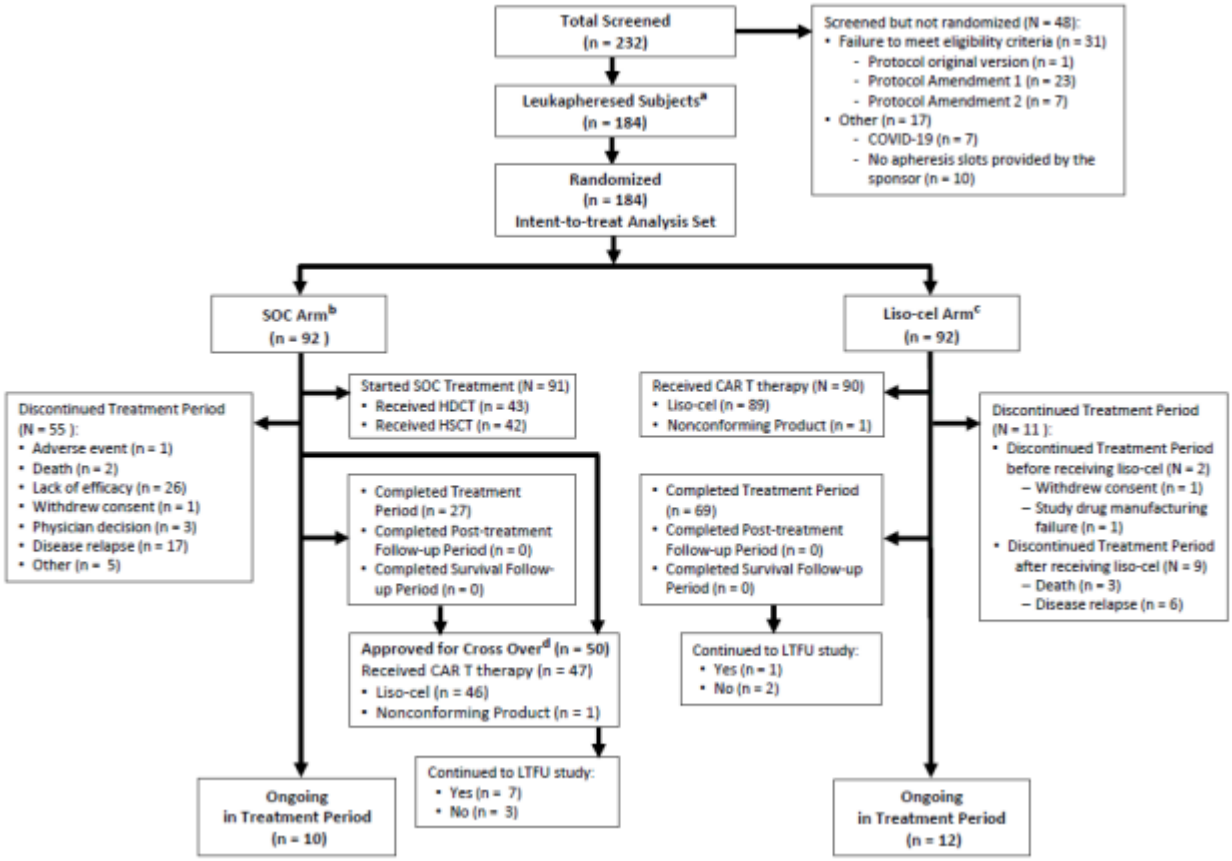
Abbreviations: 2L = second-line; 3L = third-line; 3L+ = third-line and greater; CAR = chimeric antigen receptor; DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; FL3B = follicular lymphoma Grade 3B; HGL, HGBCL = high grade B cell lymphoma; LBCL = large B-cell lymphoma; LTFU = long-term follow up; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal B cell lymphoma; TI = transplant intended; THRBCL = T cell/histiocyte-rich large B-cell lymphoma; TNI = transplant not-intended; US = United States.

Patient exposure

Overall Subject Disposition

For BCM-003 Study, a summary of overall subject disposition for subjects in the ITT analysis set, up to the end of the treatment period, is shown in the figure below.

Figure 33. Subject Disposition



Study BCM-003

Study BCM-003 is an ongoing randomized, open-label, parallel-group, Phase 3 multicenter trial to determine the efficacy and safety of liso-cel in adult subjects with LBCL after failure of anti-CD20 antibody and anthracycline containing first-line (1L) immunochemotherapy, compared with the salvage immunochemotherapy strategy. Approximately 184 subjects with high risk DLBCL, HGBCL, PMBCL, T cell/histiocyte-rich large B-cell lymphoma (THRBCL), and FL3B were - randomized to receive either:

Arm A (SOC arm, n=92): 3 cycles of salvage immunochemotherapy. Responding subjects were expected to proceed to HDCT and autologous HSCT. (1/92 subjects in the SOC arm withdrew consent before receiving treatment and was not included in the safety analysis set)

Arm B (liso-cel arm, n= 92): LDC followed by liso-cel infusion (where LDC was preceded by bridging therapy, if needed). Of the 92 randomized subjects in the liso-cel arm, 89 subjects received liso-cel infusion (Table 52).

Table 52. Analysis Populations - Study BCM-003

Population	SOC Arm n (%)	Liso-cel Arm n (%)	Total [a] n (%)
Intent-to-treat Analysis Set [a]	92 (100)	92 (100)	184 (100)
Safety Analysis Set [b]	91 (98.9)	92 (100)	183 (99.5)
Liso-cel-treated Analysis Set [c]	-	89 (96.7)	-

ITT = intent-to-treat; n (%) = number (percentage) of subjects; SOC = standard of care.
[a] All subjects randomized to a treatment arm.
[b] All subjects who have taken at least one dose of study treatment.
[c] All subjects who have received liso-cel.
Source: Table 17 of Study BCM-003 CSR. See Section 1.3.1 for detailed subject disposition in Study BCM-003.

Study Therapy

- **Arm A (SOC arm)**

Standard of Care Salvage Therapy

Among the 91 treated subjects in the SOC arm, the most frequently used starting regimen of SOC salvage therapy regimen was rituximab-ifosphamide, carboplatin and etoposide regimen (R-ICE) (63.7%). Twelve (13.2%) subjects switched SOC salvage therapy. The most frequently reported reason to switch SOC salvage therapy was suboptimal response (5 subjects [5.5%]) followed by AE (4 subjects [4.4%]). Of the 91 subjects who received SOC salvage therapy, 50 (54.9%) met the criteria for crossover and were approved to crossover to receive liso-cel.

High Dose Chemotherapy and HSCT

Out of 91 subjects who received SOC salvage therapy, 48 (52.7%) discontinued treatment before starting HDCT. Of those, 40 discontinued before starting HDCT because they were approved to crossover to liso-cel before HDCT: 5 after completion of SOC Cycle 1, 13 after completion of SOC Cycle 2, and 22 after completion of SOC Cycle 3. All 43 subjects who started HDCT went on to receive all HDCT agents (Table 3). A total of 42 (46.2%) subjects in the SOC arm received HSCT after HDCT. Additionally, one subject received the last dose of HDCT on the date of the cut-off for the study and was expected to go on to receive HSCT after the data cut-off.

Table 53. Summary of Exposure to High Dose Chemotherapy in SOC Arm (Safety Analysis Set)

	SOC Arm		
Parameter Group	**Non-crossover (N = 41) n (%)**	**Crossover (N = 50) n (%)**	**Total (N = 91) n (%)**
Subjects who Discontinued Before Starting HDCT	8 (19.5)	40 (80.0)	48 (52.7)
Subjects who Received All HDCT Agents	33 (80.5)	10 (20.0)	43 (47.3)
Subjects who Did Not Receive All HDCT Agents	0	0	0

HDCT = high dose chemotherapy; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; SOC = standard of care.
Source: Table 14.3.1.1.1.5.2.

- **Arm B (liso-cel arm)**

Bridging Therapy

A total of 58 (63.0%) subjects received bridging therapy to stabilize their disease during liso-cel manufacturing: 28 (30.4%) received it due to high tumor burden and 23 (25.0%) due to rapid progression. The most frequently used bridging therapy was R-ICE (Table 54). Five patients received additional cycles of bridging therapy due to delays related to the contamination issue (4 subjects) and due to rapid disease progression (1 subject). Nine subjects were PET-negative after receiving bridging therapy at pre-LDC assessment.

Table 54. Summary of Exposure to Bridging Therapy in Liso-cel Arm (Safety Analysis Set)

Parameter Group	Liso-cel Arm (N = 92) n (%)
Subjects who Received Bridging Therapy	58 (63.0)
High Tumor Burden	28 (30.4)
Rapid Progression	23 (25.0)
Other	7 (7.6)
Subjects who Did Not Receive Bridging Therapy	34 (37.0)
Low Tumor Burden	13 (14.1)
Slow Progression	12 (13.0)
Other	9 (9.8)
Regimen of Bridging Therapy	
R-DHAP	13 (14.1)
R-ICE	29 (31.5)
R-GDP	16 (17.4)

N = number of subjects in analysis set; n (%) = number (percentage) of subjects; R-DHAP = rituximab - dexamethasone, high dose cytarabine (AraC), and cisplatin; R-GDP = rituximab - gemcitabine, dexamethasone, and cisplatin; R-ICE = rituximab - ifosfamide, carboplatin, and etoposide.
Source: Table 14.3.1.1.1.1.2

Lymphodepleting Chemotherapy

Two subjects in the Safety Analysis Set discontinued before starting LDC. All 90 subjects in the Safety Analysis Set who received LDC received all LDC agents (cyclophosphamide and fludarabine); 89 (96.7%) went on to receive liso-cel and 1 (1.1%) received a nonconforming product. The median time from the last dose of LDC to liso-cel infusion was 4.0 days.

Liso-cel

A total of 89 (96.7%) subjects in the Safety Analysis Set received liso-cel. The median total liso-cel dose was 99.92 x 10^6 cells; the median CD8 and CD4 doses were 49.97 $\times$ 10^6 cells and 49.89 $\times$ 10^6 cells, respectively (Table 55). One (1.1%) subject received a nonconforming product because the CD4 component purity was out of specifications (OOS).

Table 55. Exposure to Liso-cel in Liso-cel Arm (Safety Analysis Set)

Parameter Statistic Group	Liso-cel Arm (N = 92)
Subjects who Discontinued Before Liso-cel Infusion - n (%)	2 (2.2)
Subjects who Received CAR T-cell Therapy – n (%)	90 (97.8)
Subjects who Received Liso-cel– n (%)	89 (96.7)
Subjects who Received Nonconforming product – n (%)	1 (1.1)
Reason: CD4:Nonconforming - Purity OOS	1 (1.1)
Total median number of Liso-cel CD4+ plus CD8+ Cells Infused (10^6)	99.92
Min, Max	97.1, 102.5
Total median number of Liso-cel CD8+ Cells Infused (10^6)	49.97
Min, Max	48.0, 51.8
Total median number of Liso-cel CD4+ Cells Infused (10^6)	49.89
Min, Max	48.1, 51.5
Time from Randomization to Liso-cel Infusion (days)[b]	
n	90
Median	34.0
Q1, Q3	31.0, 36.0
Min, Max	24, 104[a]
Time from Last Dose of LDC to Liso-cel Infusion (days)[b]	
n	90
Median	4.0
Q1, Q3	4.0, 5.0
Min, Max	3, 12
Time from Leukapheresis to Liso-cel infusion (days)[b]	
n	90
Median	36.0
Q1, Q3	34.0, 41.0
Min, Max	25, 91

CAR = chimeric antigen receptor; LDC = lymphodepleting chemotherapy; Max = maximum; Min = minimum; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; OOS = out of specifications; Q1 = first quartile; Q3 = third quartile.

Subjects who Crossed Over to Liso-cel

Of the 47 subjects who were approved to crossover by the Medical Monitor after IRC confirmation of a qualifying event and included in the safety analysis set, 46 (97.9%) received liso-cel and 1 (2.1%) received a nonconforming product. Among these subjects, the median total liso-cel dose was 99.88 x 10^6 cells. One subject received a nonconforming product because the CD4 component purity was OOS.

Manufacturing Time and Manufacturing Failure (Intent-to-treat Analysis Set)

The median time from leukapheresis to liso-cel product availability was 26.0 days (range: 19 to 84 days) (Table 56).

Table 56. Manufacturing Time (Intent-to-treat Analysis Set)

Parameter Statistic	Liso-cel Arm (N=92)
Time from Informed Consent to Leukapheresis (days)	
n	92
Mean	14.8
StD	6.97
Median	14.5
Q1, Q3	9.5, 19.0
Min, Max	3, 50
Time from Leukapheresis to liso-cel Product Availability (days)	
n	91
Mean	28.5
StD	10.68
Median	26.0
Q1, Q3	22.0, 30.0
Min, Max	19, 84
Time from liso-cel Product Availability to First Dose of LD Chemotherapy (days)	
n	90
Mean	5.4
StD	3.97
Median	5.0
Q1, Q3	2.0, 8.0
Min, Max	-4, 18

LD = lymphodepleting; Max = maximum; Min = minimum; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; Q1 = first quartile; Q3 = third quartile; StD = standard deviation.
Source: Table 14.3.1.1.1.3.4

While most subjects received liso-cel within this time period, 4 subjects in the liso-cel arm had delayed liso-cel product availability due to a contamination issue.

There were 4 manufacturing failures in total: 2 in the liso-cel arm and 2 in the SOC arm post crossover:

- One subject each in the liso-cel arm and the SOC arm post-crossover received liso-cel product that was determined to be nonconforming because the purity of the CD4 component was OOS
- The third subject was randomized to the liso-cel arm but never received liso-cel. The subject discontinued treatment on Day 26 due to study drug manufacturing failure
- The fourth subject was randomized to the SOC arm and was found to have a complete response 64 days after randomization and subsequently went on to receive HDCT. While the subject never requested to crossover to liso-cel, the contamination issue described above did affect the subject's apheresis material but no repeated leukapheresis was done due to the subject's death on Day 94.

On study follow up time

In the liso-cel-treated analysis set of Study BCM-003, median on-study follow up time was 5.32 months (range 1.0, 18.0 months). Among the 89 liso-cel-treated subjects of Study BCM-003, 38 (42.7%) subjects had ≥ 6 months of follow-up, 32 (36.0%) subjects had ≥ 9 months follow-up, 14 (15.7%) subjects had ≥ 12 months of follow up, and no subjects had ≥ 24 months of follow-up. Total on study follow up time was 54.2 patient years by the data cut-off. For this interim analysis, the median follow-up (time from liso-cel infusion to the last date known alive) for subjects in the SOC arm who crossed-over to liso-cel was 4.14 months and the minimum follow-up was 0.4 months.

In the Pooled 2L Treated Set and Pooled 3L+ LBCL Treated Set, median on-study follow up time was 7.10 months (range 1.0, 26.5 months) and 11.55 months (range 0.2, 45.2 months), respectively.

As requested, additional follow-up is now available from Study BCM-003 (data cut-off date of 13-May-2022) and BCM-001 (2L LBCL Cohort 2 and 3L+ LBCL Cohorts 1, 3, and 7) (data cut-off date of

02-Mar-2022). The follow-up time for Study BCM-003 increased from a median of 5.32 months to a median of 16.43 months, whereas the median follow-up for 2L total and 3L+ total was 15.64 and 11.40 months, respectively.

Demographic and Other Characteristics of Study Population in Study BCM-003

For details on demographic and other characteristics of Study Population see the Efficacy section above.

Pooled Safety Analyses in 2L and 3L+ Populations

Safety data from time of liso-cel infusion to liso-cel-treated 2L LBCL subjects from Study BCM-003 liso-cel arm as well as other 2L studies (Study 017006, and Study BCM-001 [Cohort 2]) **(Pooled 2L LBCL Treated Set, n=177)** and the marketed indication of 3L+ LBCL (Study 017001 [DLBCL Cohort], Study BCM-001 [Cohorts 1, 3, and 7], Study 017007, and Study BCM-002) **(Pooled 3L+ LBCL Treated Set, n=428)** were pooled to allow for a side-by-side comparison.

Additional pooled safety analyses from time of liso-cel infusion were conducted for the subset of subjects who received a dose of liso-cel within the dose range of 44 to 120 × 10^6 CAR+ viable T cells in the Pooled 2L and Pooled 3L+ LBCL Treated Sets **(i.e., the Modified Pooled 2L LBCL Treated Set [n= 177]** and **Modified Pooled 3L+ LBCL Treated Set [n= 381], respectively).**

Adverse events

Summary of adverse events

The overall incidences of TEAEs and SAEs were similar for subjects in the liso-cel and SOC arms, however the AE profiles were different but in line with the respective mechanism of action for liso-cel and SOC.

Table 57. Overall Summary of Safety - Study BCM-003 (Safety Analysis Set)

Safety Parameters	No. of Subjects (%)			
	SOC Arm (N = 91)		Liso-cel Arm (N = 92)	
All SAEs	**44 (48.4)**		**44 (47.8)**	
All Treatment-emergent SAEs (related to any drug)	**34 (37.4)**		**31 (33.7)**	
All-causality AEs leading to Withdrawal of any Study Drug	**4 (4.4)**		**0**	
	Any Grade	**Grade 3/4**	**Any Grade**	**Grade 3/4**
TEAEs	**90 (98.9)**	**79 (86.8)**	**92 (100)**	**85 (92.4)**
Most frequently reported AEs (≥ 20% of any grade in either treatment group)				
Neutropenia	49 (53.8)	46 (50.5)	75 (81.5)	74 (80.4)
Anaemia	58 (63.7)	45 (49.5)	58 (63.0)	45 (48.9)
Thrombocytopenia	62 (68.1)	58 (63.7)	53 (57.6)	45 (48.9)
Nausea	52 (57.1)	3 (3.3)	49 (53.3)	3 (3.3)
Fatigue	35 (38.5)	2 (2.2)	36 (39.1)	0
Diarrhoea	38 (41.8)	3 (3.3)	23 (25.0)	0
Headache	20 (22.0)	1 (1.1)	39 (42.4)	4 (4.3)
Constipation	22 (24.2)	0	31 (33.7)	2 (2.2)
Decreased appetite	28 (30.8)	3 (3.3)	21 (22.8)	1 (1.1)
Pyrexia	21 (23.1)	0	27 (29.3)	0
Cytokine release syndrome	0	0	45 (48.9)	1 (1.1)
Vomiting	23 (25.3)	2 (2.2)	18 (19.6)	1 (1.1)
Hypokalaemia	20 (22.0)	4 (4.4)	19 (20.7)	4 (4.3)
Febrile neutropenia	22 (24.2)	19 (20.9)	14 (15.2)	11 (12.0)
Lymphopenia	10 (11.0)	8 (8.8)	25 (27.2)	23 (25.0)
Dizziness	13 (14.3)	0	20 (21.7)	0
Hypomagnesaemia	19 (20.9)	1 (1.1)	13 (14.1)	0
Insomnia	11 (12.1)	0	19 (20.7)	0
Hypotension	4 (4.4)	0	19 (20.7)	3 (3.3)

Safety Parameters	No. of Subjects (%)			
	SOC Arm (N = 91)		Liso-cel Arm (N = 92)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Febrile neutropenia	22 (24.2)	19 (20.9)	14 (15.2)	11 (12.0)
Lymphopenia	10 (11.0)	8 (8.8)	25 (27.2)	23 (25.0)
Dizziness	13 (14.3)	0	20 (21.7)	0
Hypomagnesaemia	19 (20.9)	1 (1.1)	13 (14.1)	0
Insomnia	11 (12.1)	0	19 (20.7)	0
Hypotension	4 (4.4)	0	19 (20.7)	3 (3.3)
TEAEs (related to any study drug)	**84 (92.3)**	**71 (78.0)**	**88 (95.7)**	**82 (89.1)**
Most frequently reported AEs (≥ 20% of any grade in either treatment group)				
Neutropenia	47 (51.6)	43 (47.3)	72 (78.3)	71 (77.2)
Thrombocytopenia	56 (61.5)	52 (57.1)	50 (54.3)	43 (46.7)
Anaemia	53 (58.2)	43 (47.3)	51 (55.4)	40 (43.5)
Lymphopenia	9 (9.9)	8 (8.8)	24 (26.1)	23 (25.0)
Febrile neutropenia	21 (23.1)	18 (19.8)	11 (12.0)	10 (10.9)
Nausea	46 (50.5)	3 (3.3)	42 (45.7)	1 (1.1)
Diarrhea	30 (33.0)	3 (3.3)	14 (15.2)	0
Fatigue	25 (27.5)	2 (2.2)	25 (27.2)	0
Pyrexia	11 (12.1)	0	19 (20.7)	0
Decreased appetite	23 (25.3)	2 (2.2)	13 (14.1)	1 (1.1)
Cytokine release syndrome	0	0	45 (48.9)	1 (1.1)
Treatment-emergent AESIs	**68 (74.7)**	**25 (27.5)**	**83 (90.2)**	**51 (55.4)**
Neurological toxicity	58 (63.7)	6 (6.6)	59 (64.1)	12 (13.0)
iiNT	N/A	N/A	11 (12.0)	4 (4.3)
Cytokine Release Syndrome	0	0	45 (48.9)	1 (1.1)
Prolonged cytopenia	3 (3.3)	3 (3.3)	40 (43.5)	40 (43.5)
Severe Infections (Grade ≥ 3)	19 (20.9)	19 (20.9)	14 (15.2)	14 (15.2)
Hypogammaglobulinaemia	2 (2.2)	0	8 (8.7)	1 (1.1)
Infusion-related Reaction (IRR)	3 (3.3)	0	6 (6.5)	2 (2.2)
Tumor Lysis Syndrome (TLS)	2 (2.2)	1 (1.1)	0	0
Macrophage Activation Syndrome (MAS)	0	0	1 (1.1)	0
Second Primary Malignancy	0	0	0	0

Safety Parameters	No. of Subjects (%)			
	SOC Arm (N = 91)		Liso-cel Arm (N = 92)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
AESI Leading to Death[a]	**1 (1.1)**	**N/A**	**0**	**N/A**
AESI Leading to Withdrawal of Any Study Drug[b]	**2 (2.2)**	**N/A**	**0**	**N/A**

AE = adverse event; AESI = adverse event of special interest; CRS = cytokine release syndrome; iiNT = investigator-identified neurologic toxicity; MedDRA = Medical Dictionary for Regulatory Activities; N/A = not applicable; SAE = serious adverse event; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.

TEAE are AEs occurring or worsening on or after the date of randomization and within 90 days after last dose of chemotherapy (SOC arm), or within 90 days after the infusion of liso-cel (liso-cel arm or subjects in SOC arm crossing over to liso-cel) or start of new antineoplastic therapy, whichever occurs first as well as those AEs made known to the investigator at any time thereafter that are suspected of being related to study treatment.

AESI categories used either MedDRA v23.0 SMQ or sub-SMQ or system organ class or high-level term or list of preferred terms. A subject is counted only once for multiple events within each AESI category.

Graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. CRS was graded according to the Lee criteria.[3]

iiNT events could be reported only in subjects who had received liso-cel.

[a] One subject in the SOC arm experienced an AESI of sepsis leading to death. The event was considered not related to any study drug

[b] Two subjects in the SOC arm experienced AESIs of confusional state and substance-induced psychotic disorder leading to withdrawal of ifosfamide. The events were considered related to ifosfamide.

Source: Table 36 of Study BCM-003 CSR

Treatment-emergent Adverse Events (TEAEs)

A TEAE was defined as an AE that started any time from initiation of JCAR017 administration through and including 90 days following the final cycle (i.e., final infusion) of JCAR017 (or occurring within 90 days after last dose of immunochemotherapy or HDCT in SOC arm). Any AE occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment was not considered as a TEAE.

The overall frequency of any grade TEAEs reported in the liso-cel arm (92 [100%] subjects) was comparable to that reported in the SOC arm (90 [98.9%] subjects).

Table 58. TEAEs by System Organ Class and Preferred Term Occurring in ≥ 10% of Subjects in Liso-cel Arm or SOC Arm (Safety Analysis Set) - Study BCM-003

	No. of Subjects (%)				
	SOC Arm				
System Organ Class Preferred Term [a]	Non-crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) n (%)	Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
Subjects with at Least One TEAE	41 (100)	49 (98.0)	90 (98.9)	92 (100)	44 (93.6)
Blood and lymphatic system disorders	36 (87.8)	39 (78.0)	75 (82.4)	84 (91.3)	33 (70.2)
Neutropenia	20 (48.8)	29 (58.0)	49 (53.8)	75 (81.5)	20 (42.6)
Anaemia	24 (58.5)	34 (68.0)	58 (63.7)	58 (63.0)	18 (38.3)
Thrombocytopenia	28 (68.3)	34 (68.0)	62 (68.1)	53 (57.6)	16 (34.0)
Febrile neutropenia	15 (36.6)	7 (14.0)	22 (24.2)	14 (15.2)	4 (8.5)
Lymphopenia	5 (12.2)	5 (10.0)	10 (11.0)	25 (27.2)	5 (10.6)

	No. of Subjects (%)				
	SOC Arm				
System Organ Class Preferred Term [a]	Non-crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) n (%)	Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
Leukopenia	9 (22.0)	4 (8.0)	13 (14.3)	14 (15.2)	5 (10.6)
Gastrointestinal disorders	35 (85.4)	39 (78.0)	74 (81.3)	73 (79.3)	25 (53.2)
Nausea	25 (61.0)	27 (54.0)	52 (57.1)	49 (53.3)	10 (21.3)
Diarrhoea	21 (51.2)	17 (34.0)	38 (41.8)	23 (25.0)	6 (12.8)
Constipation	8 (19.5)	14 (28.0)	22 (24.2)	31 (33.7)	9 (19.1)
Vomiting	13 (31.7)	10 (20.0)	23 (25.3)	18 (19.6)	6 (12.8)
Abdominal pain	6 (14.6)	6 (12.0)	12 (13.2)	13 (14.1)	4 (8.5)
Dyspepsia	5 (12.2)	5 (10.0)	10 (11.0)	5 (5.4)	1 (2.1)
Stomatitis	6 (14.6)	4 (8.0)	10 (11.0)	5 (5.4)	0
General disorders and administration site conditions	28 (68.3)	37 (74.0)	65 (71.4)	67 (72.8)	23 (48.9)
Fatigue	16 (39.0)	19 (38.0)	35 (38.5)	36 (39.1)	7 (14.9)
Pyrexia	8 (19.5)	13 (26.0)	21 (23.1)	27 (29.3)	6 (12.8)
Oedema peripheral	7 (17.1)	9 (18.0)	16 (17.6)	15 (16.3)	5 (10.6)
Asthenia	4 (9.8)	4 (8.0)	8 (8.8)	10 (10.9)	3 (6.4)
Mucosal inflammation	9 (22.0)	3 (6.0)	12 (13.2)	4 (4.3)	0
Metabolism and nutrition disorders	35 (85.4)	28 (56.0)	63 (69.2)	45 (48.9)	21 (44.7)
Decreased appetite	18 (43.9)	10 (20.0)	28 (30.8)	21 (22.8)	7 (14.9)
Hypokalaemia	15 (36.6)	5 (10.0)	20 (22.0)	19 (20.7)	7 (14.9)
Hypomagnesaemia	13 (31.7)	6 (12.0)	19 (20.9)	13 (14.1)	4 (8.5)
Hypophosphataemia	8 (19.5)	4 (8.0)	12 (13.2)	6 (6.5)	3 (6.4)
Nervous system disorders	21 (51.2)	24 (48.0)	45 (49.5)	53 (57.6)	25 (53.2)
Headache	13 (31.7)	7 (14.0)	20 (22.0)	39 (42.4)	10 (21.3)
Dizziness	6 (14.6)	7 (14.0)	13 (14.3)	20 (21.7)	5 (10.6)
Peripheral sensory neuropathy	3 (7.3)	8 (16.0)	11 (12.1)	7 (7.6)	2 (4.3)
Tremor	0	0	0	11 (12.0)	7 (14.9)
Musculoskeletal and connective tissue disorders	16 (39.0)	27 (54.0)	43 (47.3)	51 (55.4)	19 (40.4)
Back pain	3 (7.3)	13 (26.0)	16 (17.6)	15 (16.3)	4 (8.5)
Arthralgia	4 (9.8)	5 (10.0)	9 (9.9)	13 (14.1)	2 (4.3)
Bone pain	4 (9.8)	5 (10.0)	9 (9.9)	12 (13.0)	2 (4.3)
Myalgia	2 (4.9)	2 (4.0)	4 (4.4)	11 (12.0)	3 (6.4)
Respiratory, thoracic and mediastinal disorders	20 (48.8)	19 (38.0)	39 (42.9)	41 (44.6)	16 (34.0)
Cough	3 (7.3)	5 (10.0)	8 (8.8)	13 (14.1)	2 (4.3)
Dyspnoea	4 (9.8)	4 (8.0)	8 (8.8)	13 (14.1)	2 (4.3)

	No. of Subjects (%)				
	SOC Arm				
System Organ Class Preferred Term [a]	Non-crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) n (%)	Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
Infections and infestations	18 (43.9)	18 (36.0)	36 (39.6)	39 (42.4)	9 (19.1)
Skin and subcutaneous tissue disorders	15 (36.6)	17 (34.0)	32 (35.2)	32 (34.8)	9 (19.1)
Investigations	13 (31.7)	14 (28.0)	27 (29.7)	36 (39.1)	11 (23.4)
Vascular disorders	13 (31.7)	11 (22.0)	24 (26.4)	35 (38.0)	10 (21.3)
Hypotension	3 (7.3)	1 (2.0)	4 (4.4)	19 (20.7)	5 (10.6)
Hypertension	4 (9.8)	3 (6.0)	7 (7.7)	10 (10.9)	5 (10.6)
Immune system disorders	3 (7.3)	4 (8.0)	7 (7.7)	50 (54.3)	24 (51.1)
Cytokine release syndrome	0	0	0	45 (48.9)	23 (48.9)
Psychiatric disorders	9 (22.0)	11 (22.0)	20 (22.0)	30 (32.6)	12 (25.5)
Insomnia	6 (14.6)	5 (10.0)	11 (12.1)	19 (20.7)	4 (8.5)
Cardiac disorders	11 (26.8)	7 (14.0)	18 (19.8)	21 (22.8)	5 (10.6)
Tachycardia	7 (17.1)	3 (6.0)	10 (11.0)	9 (9.8)	1 (2.1)
Renal and urinary disorders	9 (22.0)	10 (20.0)	19 (20.9)	16 (17.4)	6 (12.8)
Injury, poisoning and procedural complications	8 (19.5)	10 (20.0)	18 (19.8)	15 (16.3)	1 (2.1)
Eye disorders	3 (7.3)	4 (8.0)	7 (7.7)	17 (18.5)	3 (6.4)
Ear and labyrinth disorders	2 (4.9)	4 (8.0)	6 (6.6)	13 (14.1)	2 (4.3)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; SOC = standard of care; TEAE = treatment-emergent adverse event.
TEAEs are AEs that occurred or worsened on or after the date of randomization and within 90 days after last dose of chemotherapy (SOC arm), or within 90 days after the infusion of liso-cel (Liso-cel arm or subjects in the SOC arm who crossed over to liso-cel) or start of new antineoplastic therapy, whichever occurred first as well as those AEs made known to the investigator at any time thereafter that were suspected of being related to study treatment.
Frequencies are listed in descending order for total SOC arm + liso-cel arm.
[a] Coded using MedDRA Version 23.0. A subject is counted only once for multiple events within preferred term/system organ class.
Source: Table 14.3.1.3

Table 59. TEAEs by Treatment and Decreasing Frequency of Preferred Term Occurring in ≥ 10% of Subjects in Liso-cel Arm or Total SOC Arm (Safety Analysis Set)

	Number of Subjects (%)				
	SOC Arm				
Preferred Term [a]	Non-crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) n (%)	Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
Subjects with at Least One TEAE	41 (100)	49 (98.0)	90 (98.9)	92 (100)	44 (93.6)
Neutropenia	20 (48.8)	29 (58.0)	49 (53.8)	75 (81.5)	20 (42.6)
Anaemia	24 (58.5)	34 (68.0)	58 (63.7)	58 (63.0)	18 (38.3)
Thrombocytopenia	28 (68.3)	34 (68.0)	62 (68.1)	53 (57.6)	16 (34.0)
Nausea	25 (61.0)	27 (54.0)	52 (57.1)	49 (53.3)	10 (21.3)
Cytokine release syndrome	0	0	0	45 (48.9)	23 (48.9)
Headache	13 (31.7)	7 (14.0)	20 (22.0)	39 (42.4)	10 (21.3)
Fatigue	16 (39.0)	19 (38.0)	35 (38.5)	36 (39.1)	7 (14.9)
Constipation	8 (19.5)	14 (28.0)	22 (24.2)	31 (33.7)	9 (19.1)
Pyrexia	8 (19.5)	13 (26.0)	21 (23.1)	27 (29.3)	6 (12.8)
Lymphopenia	5 (12.2)	5 (10.0)	10 (11.0)	25 (27.2)	5 (10.6)
Diarrhoea	21 (51.2)	17 (34.0)	38 (41.8)	23 (25.0)	6 (12.8)
Decreased appetite	18 (43.9)	10 (20.0)	28 (30.8)	21 (22.8)	7 (14.9)
Dizziness	6 (14.6)	7 (14.0)	13 (14.3)	20 (21.7)	5 (10.6)
Hypokalaemia	15 (36.6)	5 (10.0)	20 (22.0)	19 (20.7)	7 (14.9)
Hypotension	3 (7.3)	1 (2.0)	4 (4.4)	19 (20.7)	5 (10.6)
Insomnia	6 (14.6)	5 (10.0)	11 (12.1)	19 (20.7)	4 (8.5)
Vomiting	13 (31.7)	10 (20.0)	23 (25.3)	18 (19.6)	6 (12.8)
Back pain	3 (7.3)	13 (26.0)	16 (17.6)	15 (16.3)	4 (8.5)
Oedema peripheral	7 (17.1)	9 (18.0)	16 (17.6)	15 (16.3)	5 (10.6)
Febrile neutropenia	15 (36.6)	7 (14.0)	22 (24.2)	14 (15.2)	4 (8.5)
Leukopenia	9 (22.0)	4 (8.0)	13 (14.3)	14 (15.2)	5 (10.6)
Hypomagnesaemia	13 (31.7)	6 (12.0)	19 (20.9)	13 (14.1)	4 (8.5)
Abdominal pain	6 (14.6)	6 (12.0)	12 (13.2)	13 (14.1)	4 (8.5)
Arthralgia	4 (9.8)	5 (10.0)	9 (9.9)	13 (14.1)	2 (4.3)
Cough	3 (7.3)	5 (10.0)	8 (8.8)	13 (14.1)	2 (4.3)
Dyspnoea	4 (9.8)	4 (8.0)	8 (8.8)	13 (14.1)	2 (4.3)
Bone pain	4 (9.8)	5 (10.0)	9 (9.9)	12 (13.0)	2 (4.3)
Myalgia	2 (4.9)	2 (4.0)	4 (4.4)	11 (12.0)	3 (6.4)
Tremor	0	0	0	11 (12.0)	7 (14.9)
Asthenia	4 (9.8)	4 (8.0)	8 (8.8)	10 (10.9)	3 (6.4)
Hypertension	4 (9.8)	3 (6.0)	7 (7.7)	10 (10.9)	5 (10.6)
Tachycardia	7 (17.1)	3 (6.0)	10 (11.0)	9 (9.8)	1 (2.1)
Peripheral sensory neuropathy	3 (7.3)	8 (16.0)	11 (12.1)	7 (7.6)	2 (4.3)
Hypophosphataemia	8 (19.5)	4 (8.0)	12 (13.2)	6 (6.5)	3 (6.4)
Dyspepsia	5 (12.2)	5 (10.0)	10 (11.0)	5 (5.4)	1 (2.1)
Stomatitis	6 (14.6)	4 (8.0)	10 (11.0)	5 (5.4)	0
Mucosal inflammation	9 (22.0)	3 (6.0)	12 (13.2)	4 (4.3)	0

MedDRA = Medical Dictionary for Regulatory Activities; SOC = standard of care; TEAE = treatment-emergent adverse event.

TEAEs are AEs that occurred or worsened on or after the date of randomization and within 90 days after last dose of chemotherapy (SOC arm), or within 90 days after the infusion of liso-cel (Liso-cel arm or subjects in the SOC arm who crossed over to liso-cel) or start of new antineoplastic therapy, whichever occurred first as well as those AEs made known to the investigator at any time thereafter that were suspected of being related to study treatment.

Frequencies are listed in descending order for total SOC arm + liso-cel arm.

[a] Coded using MedDRA Version 23.0. A subject is counted only once for multiple events within preferred term.

Source: Table 14.3.1.8

Grade 3 or 4 TEAEs

In the liso-cel arm, 85 (92.4%) subjects experienced at least 1 Grade 3-4 TEAE with the most frequently occurring Grade 3-4 TEAEs reported in the Blood and lymphatic system disorders system organ class. Similarly, in the SOC arm, 79 (86.8%) subjects experienced at least 1 Grade 3-4 TEAE.

Table 60. Grade 3/4 TEAEs Occurring in ≥ 2% of Subjects in Liso-cel Arm or Total SOC Arm by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term[a]	Number of Subjects (%)				
	SOC Arm			Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
	Non-Crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) (n %)		
Subjects with ≥ 1 Grade 3/4 TEAE[b]	36 (87.8)	43 (86.0)	79 (86.8)	85 (92.4)	32 (68.1)
Blood and lymphatic system disorders	32 (78.0)	39 (78.0)	71 (78.0)	82 (89.1)	31 (66.0)
Neutropenia	20 (48.8)	26 (52.0)	46 (50.5)	74 (80.4)	18 (38.3)
Thrombocytopenia	26 (63.4)	32 (64.0)	58 (63.7)	45 (48.9)	14 (29.8)
Anaemia	19 (46.3)	26 (52.0)	45 (49.5)	45 (48.9)	13 (27.7)
Lymphopenia	5 (12.2)	3 (6.0)	8 (8.8)	23 (25.0)	5 (10.6)
Febrile neutropenia	12 (29.3)	7 (14.0)	19 (20.9)	11 (12.0)	4 (8.5)
Leukopenia	8 (19.5)	3 (6.0)	11 (12.1)	14 (15.2)	5 (10.6)
Bone marrow failure	0	0	0	2 (2.2)	1 (2.1)
Infections and infestations	11 (26.8)	8 (16.0)	19 (20.9)	14 (15.2)	3 (6.4)
Sepsis	1 (2.4)	2 (4.0)	3 (3.3)	2 (2.2)	1 (2.1)
Escherichia sepsis	1 (2.4)	2 (4.0)	3 (3.3)	0	0
Pneumonia	2 (4.9)	0	2 (2.2)	1 (1.1)	1 (2.1)
Urinary tract infection	0	2 (4.0)	2 (2.2)	1 (1.1)	1 (2.1)
Metabolism and nutrition disorders	12 (29.3)	6 (12.0)	18 (19.8)	12 (13.0)	4 (8.5)
Hypophosphataemia	5 (12.2)	1 (2.0)	6 (6.6)	3 (3.3)	2 (4.3)
Hypokalaemia	4 (9.8)	0	4 (4.4)	4 (4.3)	0
Hyponatraemia	0	2 (4.0)	2 (2.2)	3 (3.3)	0
Decreased appetite	2 (4.9)	1 (2.0)	3 (3.3)	1 (1.1)	0
Electrolyte imbalance	1 (2.4)	1 (2.0)	2 (2.2)	0	0
Hyperglycaemia	0	0	0	2 (2.2)	1 (2.1)

System Organ Class Preferred Term[a]	Number of Subjects (%)				
	SOC Arm			Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
	Non-Crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) (n %)		
Investigations	5 (12.2)	4 (8.0)	9 (9.9)	13 (14.1)	4 (8.5)
Platelet count decreased	1 (2.4)	1 (2.0)	2 (2.2)	6 (6.5)	1 (2.1)
Neutrophil count decreased	0	0	0	4 (4.3)	1 (2.1)
Alanine aminotransferase increased	1 (2.4)	1 (2.0)	2 (2.2)	1 (1.1)	0
White blood cell count decreased	0	0	0	3 (3.3)	0
Gastrointestinal disorders	9 (22.0)	3 (6.0)	12 (13.2)	8 (8.7)	3 (6.4)
Nausea	2 (4.9)	1 (2.0)	3 (3.3)	3 (3.3)	1 (2.1)
Abdominal pain	0	1 (2.0)	1 (1.1)	3 (3.3)	1 (2.1)
Diarrhoea	2 (4.9)	1 (2.0)	3 (3.3)	0	0
Vomiting	2 (4.9)	0	2 (2.2)	1 (1.1)	0
Constipation	0	0	0	2 (2.2)	0
Stomatitis	1 (2.4)	1 (2.0)	2 (2.2)	0	0
General disorders and administration site conditions	5 (12.2)	4 (8.0)	9 (9.9)	5 (5.4)	0
Mucosal inflammation	3 (7.3)	0	3 (3.3)	0	0
Fatigue	1 (2.4)	1 (2.0)	2 (2.2)	0	0
Pain	0	2 (4.0)	2 (2.2)	0	0
Peripheral swelling	0	0	0	2 (2.2)	0
Nervous system disorders	2 (4.9)	2 (4.0)	4 (4.4)	10 (10.9)	6 (12.8)
Headache	1 (2.4)	0	1 (1.1)	4 (4.3)	0
Aphasia	0	0	0	2 (2.2)	1 (2.1)
Syncope	0	0	0	2 (2.2)	2 (4.3)
Vascular disorders	2 (4.9)	3 (6.0)	5 (5.5)	8 (8.7)	3 (6.4)
Hypertension	0	1 (2.0)	1 (1.1)	4 (4.3)	2 (4.3)
Deep vein thrombosis	1 (2.4)	1 (2.0)	2 (2.2)	1 (1.1)	0
Hypotension	0	0	0	3 (3.3)	1 (2.1)

System Organ Class Preferred Term[a]	Number of Subjects (%)				
	SOC Arm			Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
	Non-Crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) (n %)		
Musculoskeletal and connective tissue disorders	2 (4.9)	3 (6.0)	5 (5.5)	6 (6.5)	4 (8.5)
Back pain	0	2 (4.0)	2 (2.2)	1 (1.1)	2 (4.3)
Muscular weakness	0	0	0	3 (3.3)	0
Pain in extremity	2 (4.9)	0	2 (2.2)	1 (1.1)	0
Renal and urinary disorders	3 (7.3)	4 (8.0)	7 (7.7)	2 (2.2)	2 (4.3)
Acute kidney injury	2 (4.9)	2 (4.0)	4 (4.4)	1 (1.1)	2 (4.3)
Respiratory, thoracic and mediastinal disorders	2 (4.9)	2 (4.0)	4 (4.4)	5 (5.4)	3 (6.4)
Pulmonary embolism	0	1 (2.0)	1 (1.1)	2 (2.2)	0
Injury, poisoning and procedural complications	0	2 (4.0)	2 (2.2)	3 (3.3)	0
Infusion-related reaction	0	0	0	2 (2.2)	0
Psychiatric disorders	2 (4.9)	0	2 (2.2)	3 (3.3)	2 (4.3)
Confusional state	2 (4.9)	0	2 (2.2)	1 (1.1)	2 (4.3)
Cardiac disorders	2 (4.9)	0	2 (2.2)	2 (2.2)	2 (4.3)
Immune system disorders	1 (2.4)	1 (2.0)	2 (2.2)	2 (2.2)	2 (4.3)
Hepatobiliary disorders	1 (2.4)	1 (2.0)	2 (2.2)	1 (1.1)	0
Skin and subcutaneous tissue disorders	0	0	0	2 (2.2)	0

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; SOC = standard of care; TEAE = treatment-emergent adverse event.

[a] Coded using MedDRA Version 23.0. A subject is counted only once for multiple events within preferred term/system organ class.

[b] Graded using Common Terminology Criteria for Adverse Events Version 4.03. CRS was graded according to the Lee criteria (Lee, 2014).

TEAEs are AEs that occurred or worsened on or after the date of randomization and within 90 days after last dose of chemotherapy (SOC arm), or within 90 days after the infusion of liso-cel (Liso-cel arm or subjects in the SOC arm who crossed over to liso-cel) or start of new antineoplastic therapy, whichever occurred first as well as those AEs made known to the investigator at any time thereafter that were suspected of being related to study treatment.

Source: Table 14.3.1.5.1

Treatment-emergent AEs related to Study Treatment

Overall, the pattern of treatment-related TEAEs reported in the liso-cel arm was similar to that reported in the SOC arm with the exception of the system organ class categories of Metabolism and nutrition disorders, Immune system disorders, and Investigations.

Table 61. TEAEs Related to Study Treatment Occurring in ≥ 10% of Subjects in Liso-cel Arm or Total SOC Arm by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term[a]	Number of Subjects (%)				
	SOC Arm			Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
	Non-Crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) (n %)		
Subjects with ≥ 1 TEAE Related to Any Study Drug	37 (90.2)	47 (94.0)	84 (92.3)	88 (95.7)	42 (89.4)
Blood and lymphatic system disorders	34 (82.9)	37 (74.0)	71 (78.0)	81 (88.0)	31 (66.0)
Neutropenia	19 (46.3)	28 (56.0)	47 (51.6)	72 (78.3)	20 (42.6)
Thrombocytopenia	25 (61.0)	31 (62.0)	56 (61.5)	50 (54.3)	15 (31.9)
Anaemia	22 (53.7)	31 (62.0)	53 (58.2)	51 (55.4)	17 (36.2)
Lymphopenia	5 (12.2)	4 (8.0)	9 (9.9)	24 (26.1)	5 (10.6)
Febrile neutropenia	14 (34.1)	7 (14.0)	21 (23.1)	11 (12.0)	4 (8.5)
Leukopenia	8 (19.5)	3 (6.0)	11 (12.1)	14 (15.2)	5 (10.6)

System Organ Class Preferred Term[a]	Number of Subjects (%)				
	SOC Arm			Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
	Non-Crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) (n %)		
Gastrointestinal disorders	30 (73.2)	33 (66.0)	63 (69.2)	56 (60.9)	10 (21.3)
Nausea	22 (53.7)	24 (48.0)	46 (50.5)	42 (45.7)	4 (8.5)
Diarrhoea	17 (41.5)	13 (26.0)	30 (33.0)	14 (15.2)	4 (8.5)
Vomiting	7 (17.1)	9 (18.0)	16 (17.6)	13 (14.1)	2 (4.3)
Constipation	4 (9.8)	6 (12.0)	10 (11.0)	8 (8.7)	1 (2.1)
Stomatitis	6 (14.6)	4 (8.0)	10 (11.0)	5 (5.4)	0
General disorders and administration site conditions	22 (53.7)	24 (48.0)	46 (50.5)	44 (47.8)	13 (27.7)
Fatigue	12 (29.3)	13 (26.0)	25 (27.5)	25 (27.2)	6 (12.8)
Pyrexia	3 (7.3)	8 (16.0)	11 (12.1)	19 (20.7)	5 (10.6)
Mucosal inflammation	9 (22.0)	3 (6.0)	12 (13.2)	3 (3.3)	0
Metabolism and nutrition disorders	27 (65.9)	22 (44.0)	49 (53.8)	24 (26.1)	9 (19.1)
Decreased appetite	14 (34.1)	9 (18.0)	23 (25.3)	13 (14.1)	7 (14.9)
Hypomagnesaemia	9 (22.0)	4 (8.0)	13 (14.3)	6 (6.5)	0
Nervous system disorders	10 (24.4)	13 (26.0)	23 (25.3)	29 (31.5)	16 (34.0)
Headache	2 (4.9)	1 (2.0)	3 (3.3)	16 (17.4)	5 (10.6)
Immune system disorders	1 (2.4)	1 (2.0)	2 (2.2)	47 (51.1)	24 (51.1)
Cytokine release syndrome	0	0	0	45 (48.9)	23 (48.9)
Investigations	8 (19.5)	8 (16.0)	16 (17.6)	29 (31.5)	6 (12.8)
Infections and infestations	12 (29.3)	10 (20.0)	22 (24.2)	19 (20.7)	5 (10.6)
Respiratory, thoracic and mediastinal disorders	9 (22.0)	10 (20.0)	19 (20.9)	16 (17.4)	7 (14.9)
Skin and subcutaneous tissue disorders	9 (22.0)	5 (10.0)	14 (15.4)	16 (17.4)	2 (4.3)
Musculoskeletal and connective tissue disorders	5 (12.2)	7 (14.0)	12 (13.2)	15 (16.3)	7 (14.9)
Vascular disorders	3 (7.3)	3 (6.0)	6 (6.6)	10 (10.9)	5 (10.6)

Serious adverse event/deaths/other significant events

Death

The majority of deaths, including those in the SOC arm after crossover, were due to disease progression.

Table 62. Summary of Deaths and Causes by Treatment (Safety Analysis Set)

Primary Cause Group	SOC Arm (N = 91) n (%)	Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
Overall Number of Deaths	**8 (8.8)**	**13 (14.1)**	**16 (34.0)**
Cause of Death Category			
Death from malignant disease under study, or complication due to malignant disease under study	4 (4.4)	7 (7.6)	9 (19.1)
Death from adverse event (not otherwise specified)	4 (4.4)	2 (2.2)	0
Other	0	3 (3.3)	3 (6.4)
Unknown	0	1 (1.1)	4 (8.5)
Death			
On Treatment	2 (2.2)	3 (3.3)	0
Acute respiratory distress syndrome	1 (1.1)	0	0
COVID-19	0	1 (1.1)	0
Failure to thrive	0	1 (1.1)	0
Non-Hodgkin's lymphoma progression	0	1 (1.1)	0
Sepsis	1 (1.1)	0	0
During Post-Treatment Follow-up	6 (6.6)	9 (9.8)	12 (25.5)
During Survival Follow-up	0	1 (1.1)	4 (8.5)

COVID-19 = coronavirus disease 2019; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; SOC = standard of care.
Frequencies are listed in descending order for total SOC arm + liso-cel arm.
Treatment period is defined as the period from randomization to completion (ie, week 18) or discontinuation of the treatment.
Source: Table 14.3.2.7

Table 63. Subjects with Grade 5 TEAEs (Safety Analysis Set)

Treatment Arm	Grade 5 AE Preferred Term(s)	AE Start Day[a]	AE End Day[a]	Prior Therapy to or on the Start of AE	NCI CTCAE Grade
SOC Arm	Sepsis	83	95	R-ICE	4
		95 (death)	95	R-ICE	5
	Acute Respiratory Distress Syndrome	94	94	R-ICE, BEAM	5
Liso-cel Arm	Failure to Thrive	79	79	R-GDP, liso-cel	5

AE = adverse event; BEAM = carmustine, etoposide, cytarabine, melphalan; NCI CTCAE = National Cancer Institute Common terminology criteria for adverse events; R-GDP = rituximab - gemcitabine, dexamethasone, and cisplatin; R-ICE = rituximab - ifosfamide, carboplatin, and etoposide

[a] Study Day is relative to the date of randomization.
Source: Table 14.3.2.3 (TEAEs leading to death) and Listing 16.2.7.6.1 (Safety)

Serious Adverse Events

The frequencies and types of SAEs and treatment-related SAEs reported in the liso-cel arm were similar to the SOC arm for all causalities and related to any study treatment.

Table 64. Treatment-emergent Serious Adverse Events Reported in ≥ 2% of Subjects in the SOC and Liso-cel Arms by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term [a]	SOC Arm Non-crossover (N = 41) n (%)	SOC Arm Crossover (N = 50) n (%)	SOC Arm Total (N = 91) n (%)	Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
Subjects With at Least One Serious TEAE	24 (58.5)	20 (40.0)	44 (48.4)	44 (47.8)	13 (27.7)
Blood and lymphatic system disorders	9 (22.0)	5 (10.0)	14 (15.4)	15 (16.3)	4 (8.5)
Febrile neutropenia	5 (12.2)	4 (8.0)	9 (9.9)	7 (7.6)	3 (6.4)
Neutropenia	4 (9.8)	0	4 (4.4)	7 (7.6)	1 (2.1)
Thrombocytopenia	1 (2.4)	0	1 (1.1)	4 (4.3)	1 (2.1)
Anaemia	1 (2.4)	1 (2.0)	2 (2.2)	2 (2.2)	1 (2.1)
Infections and infestations	8 (19.5)	5 (10.0)	13 (14.3)	12 (13.0)	3 (6.4)
Pneumonia	2 (4.9)	0	2 (2.2)	1 (1.1)	0
Sepsis	1 (2.4)	0	1 (1.1)	2 (2.2)	0
COVID-19	0	0	0	2 (2.2)	0
Escherichia sepsis	0	2 (4.0)	2 (2.2)	0	0
General disorders and administration site conditions	7 (17.1)	6 (12.0)	13 (14.3)	8 (8.7)	1 (2.1)
Pyrexia	2 (4.9)	5 (10.0)	7 (7.7)	6 (6.5)	0
Peripheral swelling	0	0	0	2 (2.2)	0
Immune system disorders	1 (2.4)	1 (2.0)	2 (2.2)	12 (13.0)	4 (8.5)
Cytokine release syndrome	0	0	0	12 (13.0)	4 (8.5)
Renal and urinary disorders	3 (7.3)	4 (8.0)	7 (7.7)	1 (1.1)	1 (2.1)
Acute kidney injury	3 (7.3)	2 (4.0)	5 (5.5)	0	1 (2.1)
Nervous system disorders	1 (2.4)	1 (2.0)	2 (2.2)	5 (5.4)	3 (6.4)
Headache	1 (2.4)	0	1 (1.1)	2 (2.2)	0
Aphasia	0	0	0	2 (2.2)	1 (2.1)
Respiratory, thoracic and mediastinal disorders	2 (4.9)	0	2 (2.2)	3 (3.3)	2 (4.3)
Pulmonary embolism	0	0	0	2 (2.2)	0
Psychiatric disorders	2 (4.9)	0	2 (2.2)	0	2 (4.3)
Confusional state	2 (4.9)	0	2 (2.2)	0	1 (2.1)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; SOC = standard of care; TEAE = treatment-emergent adverse event.
Frequencies are listed in descending order for total SOC arm + liso-cel arm.
TEAE are AEs occurring or worsening on or after the date of randomization and within 90 days after last dose of chemotherapy (SOC arm), or within 90 days after the infusion of liso-cel (liso-cel arm or subjects in the SOC arm crossing over to lico-cel) or start of new antineoplastic therapy, whichever occurs first as well as those AEs made known to the investigator at any time thereafter that are suspected of being related to study treatment.
[a] Coded using MedDRA Version 23.0. A subject is counted only once for multiple events within preferred term/system organ class.
Source: Table 14.3.2.1

Table 65. Treatment-emergent Serious Adverse Events Related to Study Drug by Reported in ≥ 2% of Subjects in the SOC and Liso-cel Arms System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term [a]	SOC Arm Non-crossover (N = 41) n (%)	SOC Arm Crossover (N = 50) n (%)	SOC Arm Total (N = 91) n (%)	Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
Subjects With at Least One Serious TEAE Related to Any Study Drug	19 (46.3)	15 (30.0)	34 (37.4)	31 (33.7)	9 (19.1)
Blood and lymphatic system disorders	9 (22.0)	4 (8.0)	13 (14.3)	15 (16.3)	4 (8.5)
Febrile neutropenia	5 (12.2)	4 (8.0)	9 (9.9)	6 (6.5)	3 (6.4)
Neutropenia	4 (9.8)	0	4 (4.4)	7 (7.6)	1 (2.1)
Thrombocytopenia	1 (2.4)	0	1 (1.1)	4 (4.3)	1 (2.1)
Anaemia	1 (2.4)	0	1 (1.1)	2 (2.2)	1 (2.1)
Infections and infestations	7 (17.1)	3 (6.0)	10 (11.0)	5 (5.4)	2 (4.3)
Escherichia sepsis	0	2 (4.0)	2 (2.2)	0	0

General disorders and administration site conditions	5 (12.2)	5 (10.0)	10 (11.0)	4 (4.3)	0
Pyrexia	1 (2.4)	5 (10.0)	6 (6.6)	4 (4.3)	0
Immune system disorders	0	0	0	12 (13.0)	4 (8.5)
Cytokine release syndrome	0	0	0	12 (13.0)	4 (8.5)
Nervous system disorders	0	1 (2.0)	1 (1.1)	4 (4.3)	3 (6.4)
Aphasia	0	0	0	2 (2.2)	1 (2.1)
Renal and urinary disorders	1 (2.4)	2 (4.0)	3 (3.3)	0	0
Acute kidney injury	1 (2.4)	2 (4.0)	3 (3.3)	0	0
Psychiatric disorders	2 (4.9)	0	2 (2.2)	0	1 (2.1)
Confusional state	2 (4.9)	0	2 (2.2)	0	1 (2.1)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; SOC = standard of care; TEAE = treatment-emergent adverse event.
Frequencies are listed in descending order for total SOC arm + liso-cel arm.
TEAE are AEs occurring or worsening on or after the date of randomization and within 90 days after last dose of chemotherapy (SOC arm), or within 90 days after the infusion of liso-cel (liso-cel arm or subjects in the SOC arm crossing over to liso-cel) or start of new antineoplastic therapy, whichever occurs first as well as those AEs made known to the investigator at any time thereafter that are suspected of being related to study treatment.
[a] Coded using MedDRA version 23.0. A subject is counted only once for multiple events within preferred term/system organ class.
[b] In Japan ranimustine was used at the same dosage and schedule as carmustine.
Source: Table 14.3.2.2

Adverse Events of Special Interest (AESI)

AESIs included the following categories: CRS, neurologic toxicity immune effector cell-associated events (ie, iiNT), cytopenia and prolonged cytopenia, TLS, MAS, Grade ≥ 3 infection, and second primary malignancies. As expected, the frequency of AESIs was greater in the liso-cel arm than in the SOC arm.

Table 66. Treatment-emergent Adverse Events of Special Interest/Selected Adverse Events by Category (Safety Analysis Set)

	SOC Arm				
AESI Category [a] Preferred Term [b]	Non-crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) n (%)	Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
Subjects With at Least One AESI	33 (80.5)	35 (70.0)	68 (74.7)	83 (90.2)	40 (85.1)
Neurologic Toxicity	27 (65.9)	31 (62.0)	58 (63.7)	59 (64.1)	26 (55.3)
iiNT	N/A	N/A	N/A	11 (12.0)	8 (17.0)
Cytokine Release Syndrome	0	0	0	45 (48.9)	23 (48.9)
Prolonged cytopenia	0	3 (6.0)	3 (3.3)	40 (43.5)	22 (46.8)
Severe Infections	11 (26.8)	8 (16.0)	19 (20.9)	14 (15.2)	3 (6.4)
Hypogammaglobulinaemia	2 (4.9)	0	2 (2.2)	8 (8.7)	3 (6.4)
Infusion Related Reaction (IRR)	1 (2.4)	2 (4.0)	3 (3.3)	6 (6.5)	1 (2.1)
Tumor Lysis Syndrome (TLS)	1 (2.4)	1 (2.0)	2 (2.2)	0	1 (2.1)
Macrophage Activation Syndrome (MAS)	0	0	0	1 (1.1)	1 (2.1)
Second Primary Malignancy	0	0	0	0	1 (2.1)

AE = adverse event; AESI = adverse event of special interest; iiNT = investigator-identified neurologic toxicity; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; N/A = not applicable: SMQ = standardized MedDRA query; SOC = standard of care; TEAE = treatment-emergent adverse event.
[a] AESI categories used either MedDRA v23.0 SMQ or sub-SMQ or system organ class or high level term or list of preferred terms.
A subject is counted only once for multiple events within each AESI category.
[b] Coded using MedDRA version 23.0. A subject is counted only once for multiple events within preferred term/AESI category.
TEAE are AEs occurring or worsening on or after the date of randomization and within 90 days after last dose of chemotherapy (SOC arm), or within 90 days after the infusion of liso-cel (liso-cel arm or subjects in SOC arm crossing over to liso-cel) or start of new antineoplastic therapy, whichever occurs first as well as those AEs made known to the investigator at any time thereafter that are suspected of being related to study treatment.
A preferred term may be seen in multiple AESI categories.
iiNT events could be reported only in subjects who had received liso-cel.
Source: Table 14.3.2.11.2 (AESI) and Table 14.3.2.11.20.1 (iiNT.

Cytokine Release Syndrome

In the liso-cel arm, 45 (48.9%) subjects experienced at least one event of cytokine release syndrome with a median time to onset of 5.0 days (range 1 to 63 days) (Table 67). The median time to resolution as of the data cut-off date of 4.0 days (range 1 to 16 days). No subject had ongoing CRS at time of death. Only 1 subject in the liso-cel arm reported Grade ≥ 3 CRS, graded according to the Lee criteria (Lee, 2014), with a reported symptom of hypertransaminasaemia (Grade 3) with onset 9.0 days after the start of liso-cel infusion and resolution within 2.0 days. No CRS events of Grade 4 or 5 were reported. In the liso-cel arm, the 3 most frequently reported symptoms of CRS were pyrexia (44 [47.8%] subjects), hypotension (9 [9.8%] subjects), and chills and headache (both reported in 4 [4.3%] subjects)

(CRS Study BCM-003, data not shown). Similar results were observed for subjects in the SOC arm post-crossover.

Table 67. Summary of Cytokine Release Syndrome by Maximum Toxicity Grade and Time to Resolution (Safety Analysis Set)

Parameter Statistic/Group	Liso-cel Arm (N = 92)	SOC Arm Post-crossover (N = 47)
Subjects With at Least One CRS Event - n (%)	45 (48.9)	23 (48.9)
Overall Duration of CRS Episode (days)[a]		
n	45	23
Mean	4.8	5.6
StD	3.15	3.47
Median	4.0	6.0
Q1, Q3	2.0, 6.0	3.0, 7.0
Min, Max	1, 16	1, 14
Maximum Toxicity Grade - n (%)[b]		
Grade 1	34 (37.0)	16 (34.0)
Grade 2	10 (10.9)	6 (12.8)
Grade 3	1 (1.1)	0
Grade 4	0	1 (2.1)
Grade 5	0	0
Time From liso-cel Infusion to Onset of First CRS Event (days)		
n	45	23
Mean	6.9	3.7
StD	9.31	1.74
Median	5.0	3.0
Q1, Q3	3.0, 8.0	3.0, 5.0
Min, Max	1, 63	1, 8
Time From liso-cel infusion to onset of first Grade >= 3 CRS Event (days)		
n	1	1
Mean	9.0	6.0
StD	-	-
Median	9.0	6.0
Q1, Q3	9.0, 9.0	6.0, 6.0
Min, Max	9, 9	6, 6
Time From Onset to Resolution of First CRS Event (days)[c]		
n	45	23
Mean	4.7	5.6
StD	3.11	3.47
Median	4.0	6.0
Q1, Q3	2.0, 5.0	3.0, 7.0
Min, Max	1, 16	1, 14
Time From Onset to Downgrade of First Grade >= 3 to Grade <= 2 CRS Event (days) [d]		
n	0	0

Time From Onset to Resolution of First Grade >= 3 CRS Event (days)[e]		
n	1	1
Mean	2.0	6.0
StD		
Median	2.0	6.0
Q1, Q3	2.0, 2.0	6.0, 6.0
Min, Max	2, 2	6, 6
Time from Onset of First Grade 1/2 CRS to Progression to Grade >= 3 CRS Event (days)		
n	1	0
Mean	3.0	
StD		
Median	3.0	
Q1, Q3	3.0, 3.0	
Min, Max	3, 3	

CRS = cytokine release syndrome; Max = maximum; Min = minimum; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; Q1 = first quartile;Q3 = third quartile; SOC = standard of care; StD = standard deviation.
Multiple CRS events occurring close to each other (e.g., if the start date of one event is within 7 days of the end date of an earlier event) are to be considered as an episode of events.
Duration of CRS events is calculated based on each CRS episode. Time to resolution of CRS event is defined when the last CRS event of the episode ends.
[a] Derived as [(stop date of the event/cutoff date - start date of the event) + 1].
[b] CRS was graded according to the Lee criteria (Lee, 2014)
[c] Derived as [(resolution date - start date of the event + 1)]
[d] Derived as [(start date of the grade 1/2 event - start date of the grade ≥ 3 event +1)]
[e] Derived as [(resolution date - start date of the grade ≥ 3 event +1)]
Any CRS events stop/start within 7 days (start date-stop date <= 7) will be considered in a single episode. Time to resolution of CRS is defined when the last CRS event of the first episode end. Subjects with an unresolved event in the episode are excluded from the summary.

Source: Table 14.3.2.11.19.1

Investigator-identified Neurologic Toxicity (iiNT)

Of the 92 subjects in the liso-cel arm, 11 (12%) subjects experienced iiNT.

Table 68. Summary of Investigator-identified Neurologic Toxicity Maximum Toxicity Grade and Time to Resolution (Safety Analysis Set)

Parameter Statistic/Group	Liso-cel Arm (N = 92)	SOC Arm Post-crossover (N = 47)
Subjects With at Least One NT Immune Effector Cell-associated Event - n (%)	11 (12.0)	8 (17.0)
Overall Duration of NT Immune Effector Cell-associated Episode (days)		
n	11	8
Mean	9.4	46.3
StD	9.78	62.66
Median	6.0	16.5
Q1, Q3	2.0, 19.0	6.0, 71.0
Min, Max	1, 30	2, 181
Maximum Toxicity Grade - n (%)		
Grade 1	5 (5.4)	3 (6.4)
Grade 2	2 (2.2)	3 (6.4)
Grade 3	4 (4.3)	1 (2.1)
Grade 4	0	1 (2.1)
Grade 5	0	0
Time From Liso-cel Infusion to Onset of First NT Immune Effector Cell-associated Event (days)		
n	11	8
Mean	12.7	10.3
StD	5.20	4.77
Median	11.0	8.5
Q1, Q3	10.0, 17.0	7.5, 11.5
Min, Max	7, 25	6, 21
Time From Liso-cel Infusion to Onset of First Grade >= 3 NT Immune Effector Cell-associated Event (days)		
n	4	2
Mean	10.8	9.0
StD	3.20	0.00
Median	10.5	9.0
Q1, Q3	8.0, 13.5	9.0, 9.0
Min, Max	8, 14	9, 9
Time From Onset to Resolution of First NT Immune Effector Cell-associated Event (days)		
n	11	7
Mean	9.4	16.0
StD	9.78	15.81
Median	6.0	11.0
Q1, Q3	2.0, 19.0	3.0, 22.0
Min, Max	1, 30	2, 48
Time From Onset to Downgrade of First Grade >= 3 to Grade <= 2 NT Immune Effector Cell-associated Event (days)		
n	2	1
Mean	3.0	3.0
StD	0.00	
Median	3.0	3.0
Q1, Q3	3.0, 3.0	3.0, 3.0
Min, Max	3, 3	3, 3

Time From Onset to Resolution of First Grade >= 3 NT Immune Effector Cell-associated Event (days)		
n	4	2
Mean	18.0	12.5
StD	9.90	4.95
Median	19.0	12.5
Q1, Q3	11.5, 24.5	9.0, 16.0
Min, Max	5, 29	9, 16
Time from Onset of First Grade 1/2 NT to Progression to Grade >= 3 NT Immune Effector Cell-associated Event (days)		
n	4	1
Mean	2.3	2.0
StD	0.50	
Median	2.0	2.0
Q1, Q3	2.0, 2.5	2.0, 2.0
Min, Max	2, 3	2, 2

eCRF = electronic case report form; iiNT = Investigator-identified Neurologic Toxicity; Max = maximum; Min = minimum; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; Q1 = first quartile; Q3 = third quartile; SOC = standard of care; StD = standard deviation.
NT immune effector cell-associated events are defined as events recorded on the AE form of the eCRF for which the NT checkbox was selected. Multiple NT events occurring close to each other (e.g., if the start date of one event is within 7 days of the end date of an earlier event) are to be considered as an episode of events. Duration of NT events is calculated based on each NT episode. Time to resolution of NT event is defined when the last NT event of the episode ends.
Note: Neurologic Toxicity Immune Effector Cell-associated Events = Investigator-identified Neurologic Toxicity. Any iiNT events stop/start within 7 days (start date-stop date <= 7) will be considered in a single episode. Time to resolution of iiNT is defined when the last iiNT event of the first episode end. Subjects with an unresolved event in the episode are excluded from the summary.
Source: Table 14.3.2.11.20.1

Table 69. Investigator-identified Neurological Toxicity by Treatment, System Organ Class and Preferred Term

System Organ Class Preferred Term [a]	Liso-cel Arm (N = 92) n (%)	SOC Arm Post-crossover (N = 47) n (%)
Subjects With at Least One NT Immune Effector Cell-Associated Event	11 (12.0)	8 (17.0)
Nervous system disorders	11 (12.0)	8 (17.0)
Aphasia	4 (4.3)	3 (6.4)
Tremor	4 (4.3)	3 (6.4)
Encephalopathy	2 (2.2)	2 (4.3)
Cognitive disorder	0	2 (4.3)
Dizziness	2 (2.2)	0
Headache	2 (2.2)	0
Somnolence	1 (1.1)	1 (2.1)
Agraphia	1 (1.1)	0
Amnesia	1 (1.1)	0
Apraxia	1 (1.1)	0
Coordination abnormal	0	1 (2.1)
Disturbance in attention	1 (1.1)	0
Memory impairment	1 (1.1)	0
Resting tremor	1 (1.1)	0
Seizure	0	1 (2.1)
Psychiatric disorders	3 (3.3)	4 (8.5)
Confusional state	2 (2.2)	4 (8.5)
Mental status changes	1 (1.1)	0
General disorders and administration site conditions	1 (1.1)	0
Gait disturbance	1 (1.1)	0
Musculoskeletal and connective tissue disorders	1 (1.1)	0
Muscular weakness	1 (1.1)	0

AE = adverse event; eCRF = electronic case report form; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; NT = neurologic toxicity; SOC = standard of care.
NT immune effector cell-associated events are defined as events recorded on the AE form of the eCRF for which the NT checkbox was selected.
[a] Coded using MedDRA version 23.0. A subject is counted only once for multiple events within preferred term/system organ class
Source: Table 14.3.2.11.20.2

Cytopenia and Prolonged Cytopenia

Prolonged cytopenia was determined by laboratory-based assessment at 35 days after liso-cel infusion, for the liso-cel arm, or 35 days after the start of the last cycle of chemotherapy, including HDCT, for the SOC arm. In the liso-cel arm, 40 (43.5%) subjects had Grade ≥ 3 laboratory-based prolonged cytopenia (vs. 3, 3.3% subjects in the SOC arm), 34 (37.0%) subjects had Grade ≥ 3 decreased neutrophils (neutropenia) (vs. 2, 2.2% in the SOC arm), 34 (37.0%) subjects had Grade ≥ 3 decreased platelets (thrombocytopenia) (vs. 0 in the SOC arm), and 11 (12.0%) subjects had Grade ≥ 3 decreased hemoglobin (anemia) (vs. 1, 1.1% in the SOC arm).

Table 70, Summary of Cytopenia and Prolonged Cytopenia (Safety Analysis Set)

	SOC Arm			
	Non-crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) n (%)	Liso-cel Arm (N = 92) n (%)
Grade >=3 Cytopenia [a] from Randomization Through Prolonged Cytopenia Assessment	34 (82.9)	37 (74.0)	71 (78.0)	86 (93.5)
Grade >= 3 at Prolonged Cytopenia Assessment	0	3 (6.0)	3 (3.3)	40 (43.5)
Grade <= 2 at Prolonged Cytopenia Assessment	13 (31.7)	17 (34.0)	30 (33.0)	33 (35.9)
Unknown at Prolonged Cytopenia Assessment	21 (51.2)	17 (34.0)	38 (41.8)	13 (14.1)
Grade >=3 Anemia from Randomization Through Prolonged Cytopenia Assessment	10 (24.4)	20 (40.0)	30 (33.0)	29 (31.5)
Grade >= 3 at Prolonged Cytopenia Assessment	0	1 (2.0)	1 (1.1)	11 (12.0)
Grade <= 2 at Prolonged Cytopenia Assessment	3 (7.3)	9 (18.0)	12 (13.2)	14 (15.2)
Unknown at Prolonged Cytopenia Assessment	7 (17.1)	10 (20.0)	17 (18.7)	4 (4.3)
Grade >=3 Thrombocytopenia from Randomization Through Prolonged Cytopenia Assessment	29 (70.7)	32 (64.0)	61 (67.0)	49 (53.3)
Grade >= 3 at Prolonged Cytopenia Assessment	0	0	0	34 (37.0)
Grade <= 2 at Prolonged Cytopenia Assessment	11 (26.8)	16 (32.0)	27 (29.7)	6 (6.5)
Unknown at Prolonged Cytopenia Assessment	18 (43.9)	16 (32.0)	34 (37.4)	9 (9.8)
Grade >=3 Neutropenia from Randomization Through Prolonged Cytopenia Assessment	26 (63.4)	27 (54.0)	53 (58.2)	84 (91.3)
Grade >= 3 at Prolonged Cytopenia Assessment	0	2 (4.0)	2 (2.2)	34 (37.0)
Grade <= 2 at Prolonged Cytopenia Assessment	11 (26.8)	12 (24.0)	23 (25.3)	37 (40.2)
Unknown at Prolonged Cytopenia Assessment	15 (36.6)	13 (26.0)	28 (30.8)	13 (14.1)

HDCT = high-dose chemotherapy; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; SOC = standard of care.
Prolonged cytopenia is assessed at study day 64 visit for the liso-cel arm (35 days after liso-cel infusion) or 35 days after the start of the last cycle of chemotherapy, including HDCT, for the SOC arm. A window of ± 6 days around these target dates is considered; within this window, the closest central laboratory assessment to the target date is used and in case two assessments within the same window are equidistant to the target date, the worst result is taken. Laboratory assessments performed after starting a new antineoplastic therapy are not considered for analysis.
[a] Grade >= 3 cytopenia includes any grade >=3 anemia, thrombocytopenia or neutropenia.
Source: Table 14.3.2.11.22.1.1

A summary of recovery from prolonged cytopenia is reported in the Table below.

Table 71. Summary of Recovery from Prolonged Cytopenia (Safety Analysis Set)

	SOC Arm			
	Non-crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) n (%)	Liso-cel Arm (N = 92) n (%)
Grade >= 3 Anemia at Prolonged Cytopenia Assessment	0	1 (2.0)	1 (1.1)	11 (12.0)
Subjects with Hemoglobin Lab Results Post-prolonged Cytopenia Assessment	0	1 (2.0)	1 (1.1)	11 (12.0)
Recovered to Grade <= 2 by 35 Days Post-prolonged Cytopenia Assessment [a]	0	1 (100)	1 (100)	8 (72.7)
Recovered to Grade <= 2 by 62 Days Post-prolonged Cytopenia Assessment [a]	0	0	0	2 (18.2)
Recovered to Grade <= 2 by EOS [a]	0	0	0	0
Grade >= 3 Thrombocytopenia at Prolonged Cytopenia Assessment	0	0	0	34 (37.0)
Subjects with Platelets Lab Results Post-prolonged Cytopenia Assessment	0	0	0	33 (35.9)
Recovered to Grade <= 2 by 35 Days Post-prolonged Cytopenia Assessment [a]	0	0	0	24 (72.7)
Recovered to Grade <= 2 by 62 Days Post-prolonged Cytopenia Assessment [a]	0	0	0	2 (6.1)
Recovered to Grade <= 2 by EOS [a]	0	0	0	1 (3.0)
Grade >= 3 Neutropenia at Prolonged Cytopenia Assessment	0	2 (4.0)	2 (2.2)	34 (37.0)
Subjects with Neutrophils Lab Results Post-prolonged Cytopenia Assessment	0	1 (2.0)	1 (1.1)	34 (37.0)
Recovered to Grade <= 2 by 35 Days Post-prolonged Cytopenia Assessment [a]	0	1 (100)	1 (100)	25 (73.5)
Recovered to Grade <= 2 by 62 Days Post-prolonged Cytopenia Assessment [a]	0	0	0	3 (8.8)
Recovered to Grade <= 2 by EOS [a]	0	0	0	3 (8.8)

EOS = end of study; N = number of subjects in analysis set; HDCT = high-dose chemotherapy; n (%) = number (percentage) of subjects; SOC = standard of care.
Prolonged cytopenia is assessed at Study Day 64 visit for the liso-cel arm (35 days after liso-cel infusion) or 35 days after the start of the last cycle of chemotherapy, including HDCT, for the SOC arm. A window of ± 6 days around these target dates is considered; within this window, the closest central laboratory assessment to the target date is used and in case two assessments within the same window are equidistant to the target date, the worst result is taken. Laboratory assessments performed after starting a new antineoplastic therapy are not considered for analysis.
[a] Percentage is calculated based on the number of subjects with laboratory results available.
Source: Table 14.3.2.11.22.2.1

Other AESIs

Tumor Lysis Syndrome was reported in 2 (2.2%) subjects in the SOC arm. No events were reported in the liso-cel arm.

Macrophage activation syndrome was reported in 1 (1.1%) subject in the liso-cel arm who experienced a Grade 2 event of hemophagocytic lymphohistiocytosis with onset on Day 42 (data not shown). The event was reported as resolved on Day 47 without treatment, although the event was concurrent with CRS and the subject received treatment for CRS. No event of macrophage activation syndrome was reported in the SOC arm.

Grade ≥ 3 infections were reported in 14 (15.2%) subjects in the liso-cel arm and in 19 (20.9%) subjects in the SOC arm (data not shown).

Second primary malignancy only occurred in 1 subject in the SOC arm (Kaposi's sarcoma), which was reported as a post-treatment AE (data not shown).

Laboratory findings

Hematology Values Over Time

Graphs of mean hematology values over time (from day of JCAR017 administration through Day 29) in Study BCM-003 (Arm A-SOC arm and Arm B-liso-cel arm) are shown in Figures below.

Figure 34. Hematological Parameters – Arm A (total) – SOC Arm

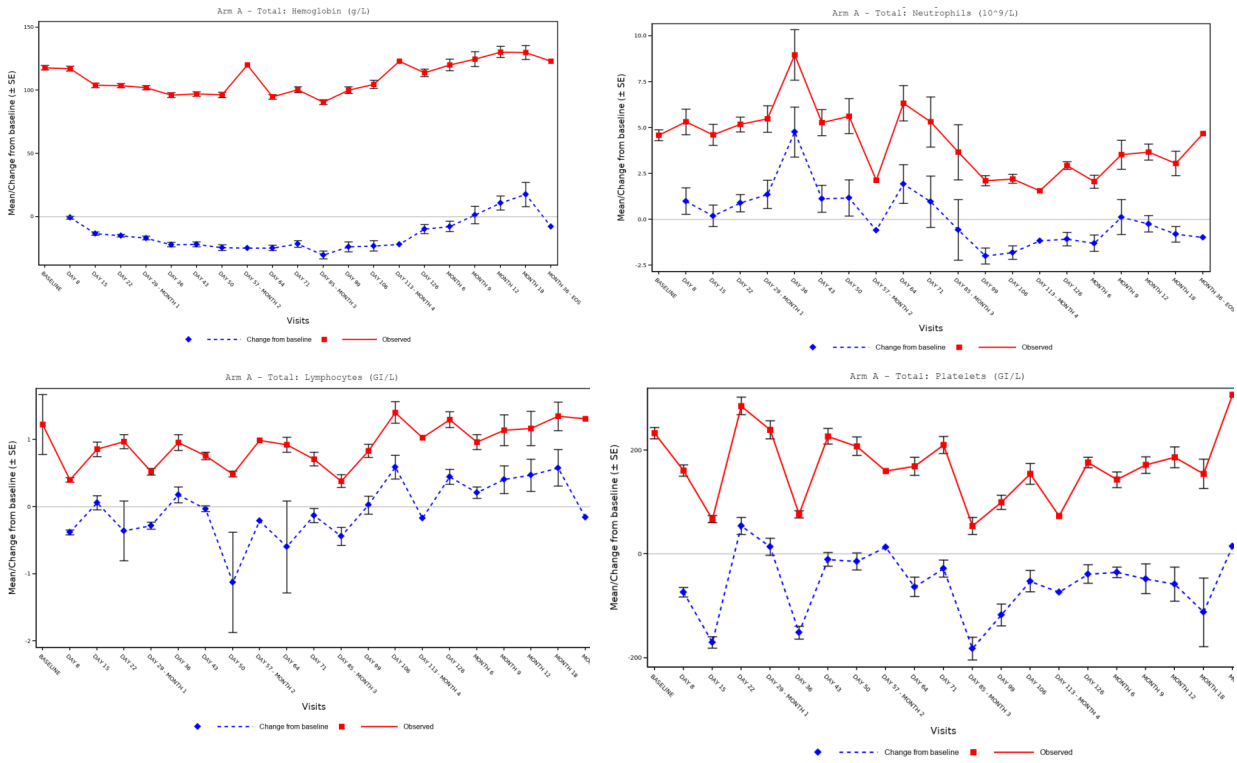
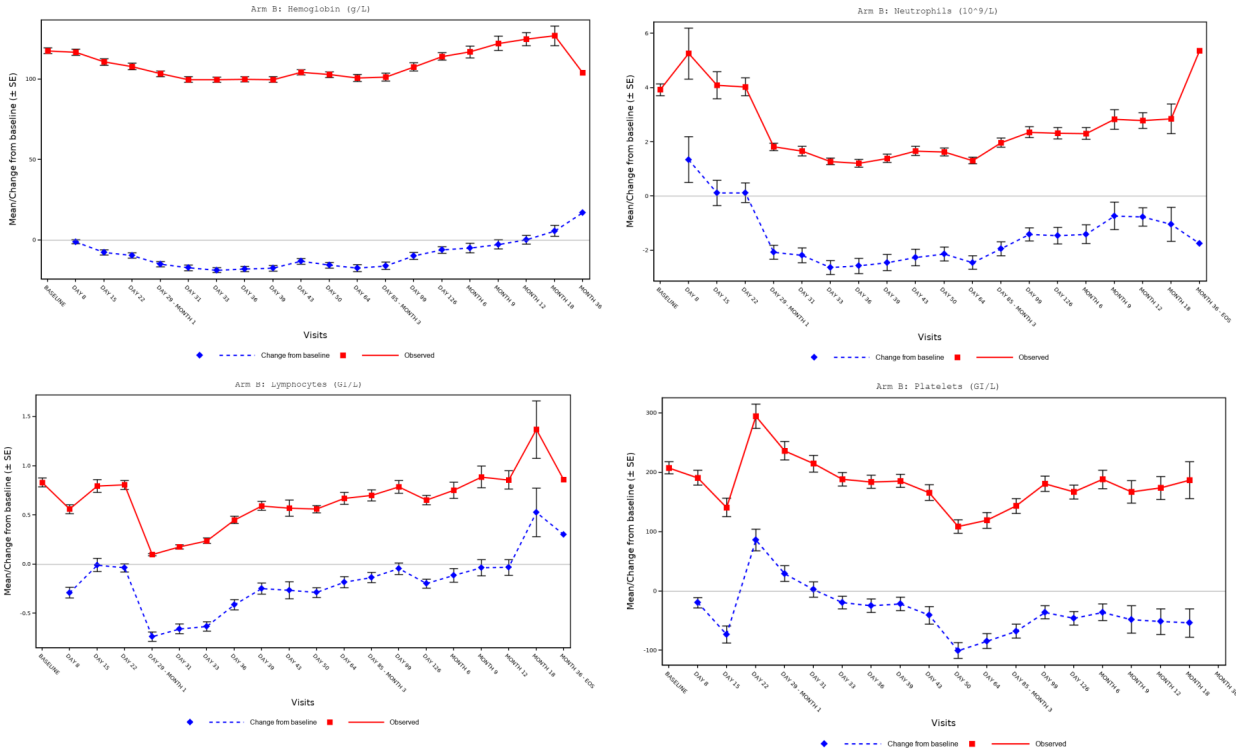


Figure 35. Hematological Parameters – Arm B – Liso-cel Arm



Clinical Chemistry Values Over Time

In the SOC arm, most serum chemistry parameters remained stable over time. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) fluctuated by visit, but there was no consistent trend over time. Lactate dehydrogenase appeared to gradually decline after the baseline visit (data not shown).

In the liso-cel arm most serum chemistry parameters remained stable over time (data not shown). ALT, AST, and bilirubin remained stable, with the exception of a spike at EOS visit. Only a single subject had these values reported at an EOS visit, and this subject's EOS visit occurred after disease progression (data not shown).

Coagulation Values Over Time

In the SOC arm, activated partial thromboplastin time (aPTT), fibrinogen, and international normalized ratio (INR) remained stable over time, while D-dimer increased initially but returned to normal range by Day 15 (data not shown).

Overall, in the liso-cel arm, aPTT, INR, and D-dimer remained stable over time while fibrinogen remained stable until Day 36, and then declined thereafter (data not shown).

Vital Signs

There were no notable abnormalities in vital signs aside from those findings associated with CRS and iiNT.

Safety in special populations

In Study BCM-003, there were no notable differences in the subgroup analyses by age, sex, race, and NHL subtype (data not shown).

Safety related to drug-drug interactions and other interactions

Liso-cel is a cellular product that is generally administered as a one-time infusion. Because it is a cellular product, it 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.

Use in pregnancy and lactation

As of the data cutoff date for Study BCM-003, no pregnancies have been reported.

Risk Summary

There is no information regarding liso-cel treatment of pregnant women. No animal reproductive and development toxicity studies have been conducted with liso-cel to evaluate whether it can cause fetal harm when administered to a pregnant female.

It is not known whether liso-cel has the potential to be transferred to the fetus. Based on the liso-cel mechanism of action, the transduced cells could theoretically cross the placenta and cause fetal B-cell lymphocytopenia and worsen the temporary hypogammaglobulinemia of infancy. Therefore, liso-cel is not recommended in women who are pregnant, and pregnancy after liso-cel infusion should be discussed with the treating physician.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Pregnant women who have received liso-cel may have hypogammaglobulinemia. Immunoglobulin levels and B-cells in newborns of mothers treated with liso-cel should be assessed.

Lactation

Risk Summary

There is no information regarding the presence of liso-cel in human milk, effects on the breastfed infant, or effects on milk production. The developmental and health benefits of breastfeeding should be weighed against the mother's clinical need for liso-cel and potential adverse effects for the infant from liso-cel, breastfeeding, and the underlying maternal condition.

Overdose

Overdose, as defined for Study BCM-003, can apply to the salvage immunochemotherapy regimen and HDCT, fludarabine (intravenous [IV]), cyclophosphamide (IV) or liso-cel (IV). On a per-dose basis, an overdose was defined as the following amount over the protocol-specified dose of these drug(s) assigned to a given subject, regardless of any associated AEs or sequelae:

- IV: ≥ 10% over the protocol-specified dose
- Per os (PO, oral): any amount over the protocol-specified dose

On a schedule or frequency basis, an overdose was defined as anything more frequent than the protocol required schedule or frequency. On an infusion rate basis, an overdose was defined as any rate faster than the protocol-specified infusion time reflected as infusion time (± 50%).

In Study BCM-003, overdoses (defined as at least 10% over the protocol-defined dose) of HDCT occurred in 4 subjects in the SOC arm and involved cytarabine in 4 subjects and etoposide in 2 subjects. No incident of HDCT overdose resulted in any adverse events.

Drug Abuse

No new information.

Withdrawal and Rebound

No cases of withdrawal symptoms related to liso-cel have been reported during human clinical trials.

Effects on ability to drive or operate machinery or impairment of mental ability

Breyanzi can have a major influence on the ability to drive and use machines. Due to the potential for neurologic events, including altered mental status or seizures, patients receiving Breyanzi should refrain from driving or operating heavy or potentially dangerous machines for at least 8 weeks after Breyanzi infusion.

Discontinuation due to adverse events

In Study BCM-003, in the liso-cel arm, no subjects had TEAEs that led to withdrawal of study drug (including bridging therapy and LDC; data not shown). As liso-cel was administered as a single dose for all subjects and follow-up continued for subjects regardless of AEs, this analysis does not permit a fair comparison with the SOC arm. In the SOC arm, 4 (4.4%) subjects had TEAEs that led to withdrawal of any study drug (see Table below). No events were reported in more than one subject. No subjects in the SOC arm post-crossover set had TEAEs leading to withdrawal of any study treatment.

Table 72. Treatment-emergent Adverse Events that Led to Withdrawal of Any Study Drug in the SOC Arm by System Organ Class and Preferred Term (Safety Analysis Set)

	SOC Arm		
System Organ Class Preferred Term [a]	Non-crossover (N = 41) n (%)	Crossover (N = 50) n (%)	Total (N = 91) n (%)
Subjects With at Least One TEAE Leading to Withdrawal of Any Study Drug	2 (4.9)	2 (4.0)	4 (4.4)
Psychiatric disorders	1 (2.4)	1 (2.0)	2 (2.2)
Confusional state	1 (2.4)	0	1 (1.1)
Substance-induced psychotic disorder	0	1 (2.0)	1 (1.1)
Blood and lymphatic system disorders	0	1 (2.0)	1 (1.1)
Thrombocytopenia	0	1 (2.0)	1 (1.1)
Ear and labyrinth disorders	0	1 (2.0)	1 (1.1)
Tinnitus	0	1 (2.0)	1 (1.1)
Renal and urinary disorders	1 (2.4)	0	1 (1.1)
Acute kidney injury	1 (2.4)	0	1 (1.1)

HDCT = high-dose chemotherapy; HSCT = hematopoietic stem cell transplant; LDC = lymphodepleting chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class..

Other Supportive Safety Information

Safety Analyses in the Pooled 2L and Pooled 3L+ Populations

Safety data from the time of liso-cel infusion for Study BCM-003 liso-cel arm (i.e., the liso-cel-treated analysis set from time of infusion, n= 89) were presented individually and within the context of the Pooled 2L LBCL Treated Set (n= 177), as well as side-by-side with safety data from the Pooled 3L+ LBCL Treated Set (n= 428) (Table 73). In the liso-cel-treated analysis set of Study BCM-003 (n= 89), 56 (62.9%) subjects received anticancer treatment for disease control. In the Pooled 2L LBCL Treated Set (n= 177) and the Pooled 3L+ LBCL Treated Set (n= 428), subjects receiving anticancer treatment for disease control were 111 (62.7%) and 256 (59.8%), respectively (Summary of clinical safety, data not

shown). Regarding lymphodepleting chemotherapy, in the liso-cel-treated analysis set of Study BCM-003 87.6% subjects received the full specified dose of fludarabine and cyclophosphamide with no missing doses, whereas in the Pooled 2L Treated Set and 3L+ LBCL Treated Set, most subjects (74.0% and 86.2%, respectively) received the full specified dose of fludarabine and cyclophosphamide with no missing doses (data not shown). In the liso-cel-treated analysis set of Study BCM-003, the median total liso-cel dose was 99.9 × 10^6 cells; the median CD8 and CD4 doses were 50.0 × 10^6 cells and 49.9 × 10^6 cells, respectively.

In the Pooled 2L Treated Set and Pooled 3L+ LBCL Treated Set, the median total liso-cel dose was 99.9 × 10^6 and 94.3 × 10^6 cells, respectively. In the Pooled 2L Treated Set, the median CD8 and CD4 doses were 49.9 × 10^6 cells and 49.9 × 10^6 cells, respectively, whereas in the Pooled 3L+ Treated Set, the median CD8 and CD4 doses were 47.5 × 10^6 cells and 47.7 × 10^6 cells, respectively.

In the liso-cel-treated analysis set of Study BCM-003, the median on-study follow up time was 5.32 months (range 1.0, 18.0 months). Among the 89 liso-cel-treated subjects of Study BCM-003, 38 (42.7%) subjects had ≥ 6 months of follow-up, 32 (36.0%) subjects had ≥ 9 months follow-up, 14 (15.7%) subjects had ≥ 12 months of follow up, and no subjects had ≥ 24 months of follow-up. Total on study follow up time was 54.2 patient years by the data cut-off. In the Pooled 2L Treated Set and Pooled 3L+ LBCL Treated Set, median on-study follow up time was 7.10 months (range 1.0, 26.5 months) and 11.55 months (range 0.2, 45.2 months), respectively.

Subject disposition in the liso-cel-treated analysis set of Study BCM-003, Pooled 2L and Pooled 3L+ LBCL Treated Sets, and the studies contributing to the Pooled 2L and Pooled 3L+ LBCL Treated Sets is summarized in the Table below.

Table 73. Summary of Safety Following the Initiation of Liso-cel Infusion - Pooled 2L and Pooled 3L+ LBCL Treated Sets

	2L LBCL				3L+ LBCL					2L and 3L + LBCL Total N=605 n (%)
	BCM-003 Arm B N=89 n (%)	017006 N=61 n (%)	BCM-001 Cohort 2 N=27 n (%)	2L Total N=177 n (%)	017001 DLBCL Cohort N=270 n (%)	BCM-001 Cohort 1, 3 and 7 N=52 n (%)	017007 N=80 n (%)	BCM-002 N=26 n (%)	3L+ Total N=428 n (%)	
Subjects with any TEAE	87 (97.8)	59 (96.7)	26 (96.3)	172 (97.2)	268 (99.3)	52 (100)	80 (100)	26 (100)	426 (99.5)	598 (98.8)
Subjects with any grade 3 or higher TEAE	79 (88.8)	48 (78.7)	25 (92.6)	152 (85.9)	213 (78.9)	49 (94.2)	59 (73.8)	19 (73.1)	340 (79.4)	492 (81.3)
Subjects with any grade 5 TEAE	1 (1.1)	2 (3.3)	1 (3.7)	4 (2.3)	7 (2.6)	2 (3.8)	0	2 (7.7)	11 (2.6)	15 (2.5)
Subjects with any serious TEAE	34 (38.2)	20 (32.8)	7 (25.9)	61 (34.5)	122 (45.2)	19 (36.5)	46 (57.5)	12 (46.2)	199 (46.5)	260 (43.0)
Death occurred after the first liso-cel infusion	11 (12.4)	20 (32.8)	9 (33.3)	40 (22.6)	133 (49.3)	29 (55.8)	30 (37.5)	8 (30.8)	200 (46.7)	240 (39.7)
Primary cause of death	6 (6.7)	16 (26.2)	7 (25.9)	29 (16.4)	110 (40.7)	23 (44.2)	24 (30.0)	5 (19.2)	162 (37.9)	191 (31.6)
Disease progression										
Adverse event	4 (4.5)	3 (4.9)	0	7 (4.0)	11 (4.1)	4 (7.7)	4 (5.0)	3 (11.5)	22 (5.1)	29 (4.8)
COVID-19	3 (3.4)	2 (3.3)	0	5 (2.8)	0	1 (1.9)	1 (1.3)	0	2 (0.5)	7 (1.2)
Unknown	1 (1.1)	0	0	1 (0.6)	5 (1.9)	1 (1.9)	0	0	6 (1.4)	7 (1.2)
Other [a]	0	1 (1.6)	2 (7.4)	3 (1.7)	7 (2.6)	1 (1.9)	2 (2.5)	0	10 (2.3)	13 (2.1)

a Refer to Listing 2.7.5 in Appendix 2 for details

Cytokine release syndrome is graded based on the Lee grading criteria. Other AEs are graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The most severe grade is used for AEs that occur more than once in an individual subject during the period.

Treatment-emergent adverse events (TEAEs) are defined as AEs occurring from the date of the initial liso-cel infusion (Day 1) through and including 90 days following the final cycle of liso-cel infusion (i.e., last dose for Study 017001; first dose for other studies). Any AE occurring after the initiation of subsequent anticancer therapy or liso-cel retreatment will not be considered as TEAE.

AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. A subject is counted only once for multiple events within preferred term/system organ class.

Source: Table 3.1.1.1 and Table 3.2.1.1 (TEAEs), Table 3.4.1.1 (Grade ≥3 TEAEs), Table 3.5.1.1 (Grade 5 TEAEs), Table 3.6.1.1 (serious TEAEs), and Table 3.9.1.2 (deaths) in Appendix 2

Table 74. Study Duration - Pooled 2L and Pooled 3L+ LBCL Treated Sets

	2L LBCL				3L + LBCL					
	BCM-003 Arm B N=89	017006 N=61	BCM-001 Cohort 2 N=27	2L Total N=177	017001 DLBCL Cohort N=270	BCM-001 Cohorts 1, 3 and 7 N=52	017007 N=80	BCM-002 N=26	3L+ Total N=428	2L and 3L + LBCL Total N=605
On-study follow-up time (months) [a]										
n	89	61	27	177	270	52	80	26	428	605
Mean (StD)	7.31 (4.712)	12.60 (7.208)	6.62 (5.349)	9.03 (6.313)	15.58 (9.655)	10.66 (9.090)	10.70 (7.446)	7.38 (5.138)	13.57 (9.374)	12.24 (8.833)
Median	5.32	12.25	5.32	7.10	19.89	6.18	8.56	6.21	11.55	10.15
Q1, Q3	3.48, 10.51	6.08, 18.00	2.50, 9.00	3.61, 12.94	5.88, 24.11	3.02, 20.34	4.71, 17.40	3.22, 10.64	4.90, 23.95	4.44, 23.36
Min, Max	1.0, 18.0	1.2, 26.5	1.0, 19.0	1.0, 26.5	0.2, 45.2	0.5, 24.7	0.4, 24.5	0.8, 18.0	0.2, 45.2	0.2, 45.2
Duration of on-study follow-up										
>= 1 Day, n (%)	89 (100)	61 (100)	27 (100)	177 (100)	270 (100)	52 (100)	80 (100)	26 (100)	428 (100)	605 (100)
>= 29 Days, n (%)	89 (100)	61 (100)	27 (100)	177 (100)	261 (96.7)	51 (98.1)	79 (98.8)	25 (96.2)	416 (97.2)	593 (98.0)
>= 2 Months, n (%)	85 (95.5)	56 (91.8)	22 (81.5)	163 (92.1)	247 (91.5)	44 (84.6)	74 (92.5)	23 (88.5)	388 (90.7)	551 (91.1)
>= 3 Months, n (%)	74 (83.1)	53 (86.9)	18 (66.7)	145 (81.9)	235 (87.0)	40 (76.9)	69 (86.3)	21 (80.8)	365 (85.3)	510 (84.3)
>= 6 Months, n (%)	38 (42.7)	46 (75.4)	12 (44.4)	96 (54.2)	201 (74.4)	27 (51.9)	53 (66.3)	13 (50.0)	294 (68.7)	390 (64.5)
>= 9 Months, n (%)	32 (36.0)	42 (68.9)	7 (25.9)	81 (45.8)	172 (63.7)	22 (42.3)	38 (47.5)	8 (30.8)	240 (56.1)	321 (53.1)
>= 12 Months, n (%)	14 (15.7)	32 (52.5)	5 (18.5)	51 (28.8)	155 (57.4)	20 (38.5)	30 (37.5)	4 (15.4)	209 (48.8)	260 (43.0)
>= 18 Months, n (%)	0	17 (27.9)	2 (7.4)	19 (10.7)	137 (50.7)	17 (32.7)	15 (18.8)	0	169 (39.5)	188 (31.1)
>= 24 Months, n (%)	0	4 (6.6)	0	4 (2.3)	85 (31.5)	8 (15.4)	7 (8.8)	0	100 (23.4)	104 (17.2)
Total on-study follow-up time (years)	54.2	64.1	14.9	133.2	350.6	46.2	71.3	16.0	484.2	617.3

[a] The on-study follow-up time is defined as time from the liso-cel infusion to the earliest of (date of death, date of last known alive, or cutoff date) divided by 30.4375.
Source: Table 2.3.1.1 in Appendix 2

Table 75. Subject Disposition - Pooled 2L and Pooled 3L+ LBCL Treated Sets

	2L LBCL				3L + LBCL					
	BCM-003 Arm B N=89 n (%)	017006 N=61 n (%)	BCM-001 Cohort 2 N=27 n (%)	2L Total N=177 n (%)	017001 DLBCL Cohort N=270 n (%)	BCM-001 Cohorts 1, 3 and 7 N=52 n (%)	017007 N=80 n (%)	BCM-002 N=26 n (%)	3L+ Total N=428 n (%)	2L and 3L + LBCL Total N=605 n (%)
Study Status										
Ongoing	77 (86.5)	26 (42.6)	16 (59.3)	119 (67.2)	3 (1.1)	9 (17.3)	28 (35.0)	16 (61.5)	56 (13.1)	175 (28.9)
Completed study	0	7 (11.5)	0	7 (4.0)	120 (44.4)	8 (15.4)	11 (13.8)	0	139 (32.5)	146 (24.1)
Discontinued from study	12 (13.5)	28 (45.9)	11 (40.7)	51 (28.8)	147 (54.4)	35 (67.3)	41 (51.3)	10 (38.5)	233 (54.4)	284 (46.9)
Adverse event	0	0	0	0	0	0	0	0	0	0
Death	10 (11.2)	20 (32.8)	8 (29.6)	38 (21.5)	132 (48.9)	19 (36.5)	28 (35.0)	8 (30.8)	187 (43.7)	225 (37.2)
COVID-19 related	0	0	0	0	0	0	1 (1.3)	0	1 (0.2)	1 (0.2)
Lost to follow-up	0	0	0	0	4 (1.5)	0	0	0	4 (0.9)	4 (0.7)
Other [a]	1 (1.1)	2 (3.3)	1 (3.7)	4 (2.3)	1 (0.4)	9 (17.3)	6 (7.5)	1 (3.8)	17 (4.0)	21 (3.5)
Study termination by sponsor	0	0	0	0	0	0	0	0	0	0
Subject withdrew consent	1 (1.1)	6 (9.8)	2 (7.4)	9 (5.1)	10 (3.7)	7 (13.5)	6 (7.5)	1 (3.8)	24 (5.6)	33 (5.5)
Enrolled in the long term follow-up study	1 (1.1)	4 (6.6)	1 (3.7)	6 (3.4)	81 (30.0)	12 (23.1)	9 (11.3)	0	102 (23.8)	108 (17.9)
Subjects received retreatment	0	2 (3.3)	0	2 (1.1)	17 (6.3)	0	0	0	17 (4.0)	19 (3.1)

Summary of Results from Pooled Safety Analyses

Treatment-emergent AEs

The overall frequency of any grade TEAEs reported in the liso-cel-treated analysis set of Study BCM-003 (87 [97.8%] subjects) was comparable to that reported in the Pooled 2L LBCL Treated Set (172 [97.2%] subjects) and the Pooled 3L+ LBCL Treated Set (426 [99.5%] subjects). The most common adverse

reactions of any grade were neutropenia (76%), anemia (57%), thrombocytopenia (53%), CRS (49%), and headache (32%).

Grade 3 or Higher TEAEs

The overall frequency of Grade 3 or higher TEAEs reported in the liso-cel-treated analysis set of Study BCM-003 (79 [88.8%] subjects) was comparable to that reported in the Pooled 2L LBCL Treated Set (152 [85.9%] subjects) and the Pooled 3L+ LBCL Treated Set (340 [79.4%] subjects). The most common Grade 3 or higher adverse reactions included neutropenia (74%), anemia (45%), thrombocytopenia (45%), lymphopenia (20%), leukopenia (12%), febrile neutropenia (7%), infection with an unspecified pathogen (6%), and bacterial infections (6%).

Treatment-emergent AEs Related to Liso-cel

The overall frequency of liso-cel related TEAEs reported in the liso-cel-treated analysis set of Study BCM-003 (77 [86.5%] subjects) was comparable with that reported in the Pooled 2L LBCL Treated Set (149 [84.2%] subjects), but it was slightly higher than that reported in the Pooled 3L+ LBCL Treated Set (334 [78.0%] subjects) (see Table below).

Table 76. Liso-cel-related TEAEs by System Organ Class and Preferred Term Occurring in ≥ 10% of Subjects in either Pooled 2L LBCL or Pooled 3L+ LBCL Treated Set

	2L LBCL				3L + LBCL					
System Organ Class Preferred Term	BCM-003 Arm B N=89 n (%)	017006 N=61 n (%)	BCM-001 Cohort 2 N=27 n (%)	2L Total N=177 n (%)	017001 DLBCL Cohort N=270 n (%)	BCM-001 Cohorts 1, 3 and 7 N=52 n (%)	017007 N=80 n (%)	BCM-002 N=26 n (%)	3L+ Total N=428 n (%)	2L and 3L + LBCL Total N=605 n (%)
Subjects with any liso-cel-related TEAE	77 (86.5)	48 (78.7)	24 (88.9)	149 (84.2)	201 (74.4)	46 (88.5)	70 (87.5)	17 (65.4)	334 (78.0)	483 (79.8)
Immune system disorders	45 (50.6)	26 (42.6)	14 (51.9)	85 (48.0)	123 (45.6)	20 (38.5)	36 (45.0)	10 (38.5)	189 (44.2)	274 (45.3)
Cytokine release syndrome	44 (49.4)	23 (37.7)	13 (48.1)	80 (45.2)	113 (41.9)	19 (36.5)	32 (40.0)	10 (38.5)	174 (40.7)	254 (42.0)
Blood and lymphatic system disorders	56 (62.9)	25 (41.0)	16 (59.3)	97 (54.8)	74 (27.4)	32 (61.5)	53 (66.3)	2 (7.7)	161 (37.6)	258 (42.6)
Neutropenia	47 (52.8)	19 (31.1)	15 (55.6)	81 (45.8)	44 (16.3)	27 (51.9)	35 (43.8)	0	106 (24.8)	187 (30.9)
Anaemia	32 (36.0)	10 (16.4)	4 (14.8)	46 (26.0)	37 (13.7)	19 (36.5)	18 (22.5)	1 (3.8)	75 (17.5)	121 (20.0)
Thrombocytopenia	36 (40.4)	7 (11.5)	6 (22.2)	49 (27.7)	31 (11.5)	19 (36.5)	20 (25.0)	0	70 (16.4)	119 (19.7)
Leukopenia	6 (6.7)	8 (13.1)	3 (11.1)	17 (9.6)	9 (3.3)	10 (19.2)	27 (33.8)	1 (3.8)	47 (11.0)	64 (10.6)
Lymphopenia	9 (10.1)	7 (11.5)	2 (7.4)	18 (10.2)	9 (3.3)	3 (5.8)	10 (12.5)	0	22 (5.1)	40 (6.6)
Nervous system disorders	21 (23.6)	22 (36.1)	4 (14.8)	47 (26.6)	102 (37.8)	11 (21.2)	30 (37.5)	7 (26.9)	150 (35.0)	197 (32.6)
Headache	11 (12.4)	2 (3.3)	0	13 (7.3)	36 (13.3)	2 (3.8)	10 (12.5)	3 (11.5)	51 (11.9)	64 (10.6)
Tremor	4 (4.5)	10 (16.4)	2 (7.4)	16 (9.0)	30 (11.1)	4 (7.7)	7 (8.8)	3 (11.5)	44 (10.3)	60 (9.9)
General disorders and administration site conditions	29 (32.6)	22 (36.1)	9 (33.3)	60 (33.9)	81 (30.0)	25 (48.1)	25 (31.3)	4 (15.4)	135 (31.5)	195 (32.2)
Fatigue	10 (11.2)	17 (27.9)	0	27 (15.3)	48 (17.8)	6 (11.5)	11 (13.8)	3 (11.5)	68 (15.9)	95 (15.7)
Pyrexia	16 (18.0)	4 (6.6)	7 (25.9)	27 (15.3)	19 (7.0)	18 (34.6)	8 (10.0)	1 (3.8)	46 (10.7)	73 (12.1)

Death

In the liso-cel-treated analysis set of Study BCM-003, 11 (12.4%) subjects died any time after first liso-cel infusion. In comparison, 40 (22.6%) subjects in the Pooled 2L LBCL Treated Set and 200 (46.7%) subjects in the Pooled 3L+ LBCL Treated Set died any time after first liso-cel infusion.

One (1.1%) subject in the liso-cel-treated analysis set of Study BCM-003 died due to a TEAE. In comparison, 4 (2.3%) subjects in the Pooled 2L LBCL Treated Set and 11 (2.6%) subjects in the Pooled 3L+ LBCL Treated Set died due to a TEAE.

Table 77. Summary of Death - Pooled 2L and Pooled 3L+ LBCL Treated Sets

	2L LBCL				3L + LBCL					
	BCM-003 Arm B N=89 n (%)	017006 N=61 n (%)	BCM-001 Cohort 2 N=27 n (%)	2L Total N=177 n (%)	017001 DLBCL Cohort N=270 n (%)	BCM-001 Cohorts 1, 3 and 7 N=52 n (%)	017007 N=80 n (%)	BCM-002 N=26 n (%)	3L+ Total N=428 n (%)	2L and 3L + LBCL Total N=605 n (%)
Death occurred after the first liso-cel infusion	11 (12.4)	20 (32.8)	9 (33.3)	40 (22.6)	133 (49.3)	29 (55.8)	30 (37.5)	8 (30.8)	200 (46.7)	240 (39.7)
Primary cause of death										
Disease progression	6 (6.7)	16 (26.2)	7 (25.9)	29 (16.4)	110 (40.7)	23 (44.2)	24 (30.0)	5 (19.2)	162 (37.9)	191 (31.6)
Adverse event	4 (4.5)	3 (4.9)	0	7 (4.0)	11 (4.1)	4 (7.7)	4 (5.0)	3 (11.5)	22 (5.1)	29 (4.8)
COVID-19	3 (3.4)	2 (3.3)	0	5 (2.8)	0	1 (1.9)	1 (1.3)	0	2 (0.5)	7 (1.2)
Unknown	1 (1.1)	0	0	1 (0.6)	5 (1.9)	1 (1.9)	0	0	6 (1.4)	7 (1.2)
Other [a]	0	1 (1.6)	2 (7.4)	3 (1.7)	7 (2.6)	1 (1.9)	2 (2.5)	0	10 (2.3)	13 (2.1)
Death occurred after first liso-cel infusion and within 30 days post liso-cel infusion	1 (1.1)	0	0	1 (0.6)	9 (3.3)	1 (1.9)	0	1 (3.8)	11 (2.6)	12 (2.0)
Primary cause of death										
Disease progression	1 (1.1)	0	0	1 (0.6)	6 (2.2)	0	0	0	6 (1.4)	7 (1.2)
Adverse event	0	0	0	0	3 (1.1)	1 (1.9)	0	1 (3.8)	5 (1.2)	5 (0.8)
COVID-19	0	0	0	0	0	0	0	0	0	0

[a] Listing L.2.7.5 in Appendix 2 for by-subject details.

Source: Table 3.9.1.2 in Appendix 2

Table 78. Grade 5 TEAE by System Organ Class and Preferred Term - Pooled 2L and Pooled 3L+ LBCL Treated Sets

	2L LBCL				3L + LBCL					
System Organ Class Preferred Term	BCM-003 Arm B N=89 n (%)	017006 N=61 n (%)	BCM-001 Cohort 2 N=27 n (%)	2L Total N=177 n (%)	017001 DLBCL Cohort N=270 n (%)	BCM-001 Cohorts 1, 3 and 7 N=52 n (%)	017007 N=80 n (%)	BCM-002 N=26 n (%)	3L+ Total N=428 n (%)	2L and 3L + LBCL Total N=605 n (%)
Subjects with any grade 5 TEAE	1 (1.1)	2 (3.3)	1 (3.7)	4 (2.3)	7 (2.6)	2 (3.8)	0	2 (7.7)	11 (2.6)	15 (2.5)
Infections and infestations	0	2 (3.3)	0	2 (1.1)	2 (0.7)	1 (1.9)	0	2 (7.7)	5 (1.2)	7 (1.2)
COVID-19	0	1 (1.6)	0	1 (0.6)	0	0	0	0	0	1 (0.2)
COVID-19 pneumonia	0	1 (1.6)	0	1 (0.6)	0	0	0	0	0	1 (0.2)
Candida sepsis	0	0	0	0	0	1 (1.9)	0	0	1 (0.2)	1 (0.2)
Pneumonia	0	0	0	0	0	0	0	1 (3.8)	1 (0.2)	1 (0.2)
Progressive multifocal leukoencephalopathy	0	0	0	0	1 (0.4)	0	0	0	1 (0.2)	1 (0.2)
Septic shock	0	0	0	0	1 (0.4)	0	0	0	1 (0.2)	1 (0.2)
Staphylococcal sepsis	0	0	0	0	0	0	0	1 (3.8)	1 (0.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	2 (0.7)	1 (1.9)	0	0	3 (0.7)	3 (0.5)
Diffuse alveolar damage	0	0	0	0	1 (0.4)	0	0	0	1 (0.2)	1 (0.2)
Pulmonary haemorrhage	0	0	0	0	1 (0.4)	0	0	0	1 (0.2)	1 (0.2)
Respiratory failure	0	0	0	0	0	1 (1.9)	0	0	1 (0.2)	1 (0.2)
Cardiac disorders	0	0	0	0	1 (0.4)	0	0	0	1 (0.2)	1 (0.2)
Cardiomyopathy	0	0	0	0	1 (0.4)	0	0	0	1 (0.2)	1 (0.2)

General disorders and administration site conditions	0	0	0	0	1 (0.4)	0	0	0	1 (0.2)	1 (0.2)
Multiple organ dysfunction syndrome	0	0	0	0	1 (0.4)	0	0	0	1 (0.2)	1 (0.2)
Immune system disorders	0	0	1 (3.7)	1 (0.6)	0	0	0	0	0	1 (0.2)
Haemophagocytic lymphohistiocytosis	0	0	1 (3.7)	1 (0.6)	0	0	0	0	0	1 (0.2)
Metabolism and nutrition disorders	1 (1.1)	0	0	1 (0.6)	0	0	0	0	0	1 (0.2)
Failure to thrive	1 (1.1)	0	0	1 (0.6)	0	0	0	0	0	1 (0.2)
Nervous system disorders	0	0	0	0	1 (0.4)	0	0	0	1 (0.2)	1 (0.2)
Leukoencephalopathy	0	0	0	0	1 (0.4)	0	0	0	1 (0.2)	1 (0.2)

Serious Adverse Events

Overall, 34 (38.2%) subjects in the liso-cel-treated analysis set of Study BCM-003 reported serious TEAEs. In comparison, serious TEAEs were reported by 61 (34.5%) subjects in the Pooled 2L LBCL Treated Set and 199 (46.5%) subjects in the Pooled 3L+ LBCL Treated Set. The most frequently reported serious TEAE in both pooled groups was CRS (13.5% in BCM-003 Arm B vs. 12.4% in Pooled 2L vs. 18.5% in Pooled 3L+ LBCL). Other most common serious adverse reactions in BCM-003 were neutropenia (7%), pyrexia (5%), bacterial infectious disorders (5%), infection with an unspecified pathogen (5%), thrombocytopenia (3%), febrile neutropenia (3%), aphasia (2%), anemia (2%), headache (2%), pulmonary embolism (2%), encephalopathy (1%), and tremor (1%).

Adverse Events of Special Interest

Overall, similar frequencies of AESIs were reported in the liso-cel-treated analysis set of Study BCM-003, the Pooled 2L LBCL Treated Set, and the Pooled 3L+ LBCL Treated Set. The majority of reported AESIs were mild to moderate in severity. The most frequently occurring AESIs were cytokine release syndrome and iiNT.

Table 79. Treatment-emergent AESIs by Grade - Pooled 2L and Pooled 3L+ LBCL Treated Sets

	2L LBCL				3L + LBCL					
	BCM-003 Arm B N=89 n (%)	017006 N=61 n (%)	BCM-001 Cohort 2 N=27 n (%)	2L Total N=177 n (%)	017001 DLBCL Cohort N=270 n (%)	BCM-001 Cohorts 1, 3 and 7 N=52 n (%)	017007 N=80 n (%)	BCM-002 N=26 n (%)	3L+ Total N=428 n (%)	2L and 3L + LBCL Total N=605 n (%)
CRS or NT	45 (50.6)	30 (49.2)	13 (48.1)	88 (49.7)	127 (47.0)	21 (40.4)	39 (48.8)	11 (42.3)	198 (46.3)	286 (47.3)
Grade 1-2	40 (44.9)	26 (42.6)	12 (44.4)	78 (44.1)	98 (36.3)	16 (30.8)	31 (38.8)	8 (30.8)	153 (35.7)	231 (38.2)
Grade 3-4	5 (5.6)	4 (6.6)	1 (3.7)	10 (5.6)	29 (10.7)	5 (9.6)	8 (10.0)	3 (11.5)	45 (10.5)	55 (9.1)
Grade 5	0	0	0	0	0	0	0	0	0	0
SAE	14 (15.7)	10 (16.4)	3 (11.1)	27 (15.3)	71 (26.3)	10 (19.2)	30 (37.5)	7 (26.9)	118 (27.6)	145 (24.0)
CRS	44 (49.4)	23 (37.7)	13 (48.1)	80 (45.2)	113 (41.9)	19 (36.5)	32 (40.0)	10 (38.5)	174 (40.7)	254 (42.0)
Grade 1-2	43 (48.3)	22 (36.1)	13 (48.1)	78 (44.1)	107 (39.6)	17 (32.7)	32 (40.0)	10 (38.5)	166 (38.8)	244 (40.3)
Grade 3-4	1 (1.1)	1 (1.6)	0	2 (1.1)	6 (2.2)	2 (3.8)	0	0	8 (1.9)	10 (1.7)
Grade 5	0	0	0	0	0	0	0	0	0	0
SAE	12 (13.5)	8 (13.1)	1 (3.7)	21 (11.9)	44 (16.3)	7 (13.5)	23 (28.8)	5 (19.2)	79 (18.5)	100 (16.5)
NT	9 (10.1)	19 (31.1)	4 (14.8)	32 (18.1)	80 (29.6)	9 (17.3)	24 (30.0)	6 (23.1)	119 (27.8)	151 (25.0)
Grade 1-2	5 (5.6)	16 (26.2)	3 (11.1)	24 (13.6)	53 (19.6)	4 (7.7)	16 (20.0)	3 (11.5)	76 (17.8)	100 (16.5)
Grade 3-4	4 (4.5)	3 (4.9)	1 (3.7)	8 (4.5)	27 (10.0)	5 (9.6)	8 (10.0)	3 (11.5)	43 (10.0)	51 (8.4)
Grade 5	0	0	0	0	0	0	0	0	0	0
SAE	3 (3.4)	3 (4.9)	2 (7.4)	8 (4.5)	39 (14.4)	7 (13.5)	19 (23.8)	3 (11.5)	68 (15.9)	76 (12.6)

Infusion Related Reaction	0	0	1 (3.7)	1 (0.6)	3 (1.1)	0	0	1 (3.8)	4 (0.9)	5 (0.8)
Grade 1-2	0	0	1 (3.7)	1 (0.6)	3 (1.1)	0	0	1 (3.8)	4 (0.9)	5 (0.8)
Grade 3-4	0	0	0	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0	0	0	0
SAE	0	0	0	0	0	0	0	0	0	0
Macrophage Activation Syndrome	1 (1.1)	0	1 (3.7)	2 (1.1)	0	2 (3.8)	0	0	2 (0.5)	4 (0.7)
Grade 1-2	1 (1.1)	0	0	1 (0.6)	0	0	0	0	0	1 (0.2)
Grade 3-4	0	0	0	0	0	2 (3.8)	0	0	2 (0.5)	2 (0.3)
Grade 5	0	0	1 (3.7)	1 (0.6)	0	0	0	0	0	1 (0.2)
SAE	0	0	1 (3.7)	1 (0.6)	0	2 (3.8)	0	0	2 (0.5)	3 (0.5)
Tumor Lysis Syndrome	0	0	0	0	2 (0.7)	0	0	0	2 (0.5)	2 (0.3)
Grade 1-2	0	0	0	0	0	0	0	0	0	0
Grade 3-4	0	0	0	0	2 (0.7)	0	0	0	2 (0.5)	2 (0.3)
Grade 5	0	0	0	0	0	0	0	0	0	0
SAE	0	0	0	0	0	0	0	0	0	0
Grade >= 3 Infections	12 (13.5)	4 (6.6)	2 (7.4)	18 (10.2)	33 (12.2)	7 (13.5)	8 (10.0)	5 (19.2)	53 (12.4)	71 (11.7)
Grade 3-4	12 (13.5)	2 (3.3)	2 (7.4)	16 (9.0)	31 (11.5)	6 (11.5)	8 (10.0)	3 (11.5)	48 (11.2)	64 (10.6)
Grade 5	0	2 (3.3)	0	2 (1.1)	2 (0.7)	1 (1.9)	0	2 (7.7)	5 (1.2)	7 (1.2)
Grade >= 3 Bacterial Infections	5 (5.6)	2 (3.3)	2 (7.4)	9 (5.1)	11 (4.1)	2 (3.8)	2 (2.5)	1 (3.8)	16 (3.7)	25 (4.1)
Grade 3-4	5 (5.6)	2 (3.3)	2 (7.4)	9 (5.1)	11 (4.1)	2 (3.8)	2 (2.5)	0	15 (3.5)	24 (4.0)
Grade 5	0	0	0	0	0	0	0	1 (3.8)	1 (0.2)	1 (0.2)
Grade >= 3 Fungal Infections	0	0	0	0	2 (0.7)	2 (3.8)	1 (1.3)	0	5 (1.2)	5 (0.8)
Grade 3-4	0	0	0	0	2 (0.7)	1 (1.9)	1 (1.3)	0	4 (0.9)	4 (0.7)
Grade 5	0	0	0	0	0	1 (1.9)	0	0	1 (0.2)	1 (0.2)
Grade >= 3 Viral Infections	2 (2.2)	2 (3.3)	0	4 (2.3)	4 (1.5)	0	1 (1.3)	0	5 (1.2)	9 (1.5)
Grade 3-4	2 (2.2)	0	0	2 (1.1)	3 (1.1)	0	1 (1.3)	0	4 (0.9)	6 (1.0)
Grade 5	0	2 (3.3)	0	2 (1.1)	1 (0.4)	0	0	0	1 (0.2)	3 (0.5)
Grade >= 3 Infections - Pathogen unspecified	5 (5.6)	1 (1.6)	0	6 (3.4)	22 (8.1)	4 (7.7)	5 (6.3)	5 (19.2)	36 (8.4)	42 (6.9)
Grade 3-4	5 (5.6)	1 (1.6)	0	6 (3.4)	21 (7.8)	4 (7.7)	5 (6.3)	4 (15.4)	34 (7.9)	40 (6.6)
Grade 5	0	0	0	0	1 (0.4)	0	0	1 (3.8)	2 (0.5)	2 (0.3)

Subgroups

Due to the limitation of the small sample size for certain subgroups in the liso-cel-treated analysis set of Study BCM-003, the MAH showed data focused on subgroup analyses in the Pooled 2L Treated Set, with comparisons with that of the Pooled 3L+ LBCL Treated Set under each subgroup category.

Age

In the Pooled 2L LBCL Treated Set, safety was generally similar among subjects < 65 years (n= 62), ≥ 65 to < 70 years (n= 23), ≥ 70 to < 75 years (n= 51), and ≥ 75 to < 85 years (n= 41). There were no subjects ≥ 85 years in the Pooled 2L LBCL Treated Set. A higher frequency of iiNT was reported in subjects ≥ 75 to < 85 years (31.7%) compared with subjects < 65 years (9.7%).

Sex, Ethnicity, and Race

No clinically relevant differences were noted between sex, race, or ethnicity subgroups for subjects treated with liso-cel in the Pooled 2L LBCL Treated Set, which was consistent with what was observed in the Pooled 3L+ LBCL Treated Set.

Region

In the Pooled 2L LBCL Treated Set, TEAEs and AESIs were generally similar in subjects from the US (n= 117) and the EU (n= 53), which was consistent with what was observed in the Pooled 3L+ LBCL Treated Set. The number of subjects from Japan included in the Pooled 2L Treated Set (n= 7) was too small to conclude on the differences in the occurrence of AEs.

LDH Prior to LDC

In the Pooled 2L LBCL Treated Set, TEAEs and AESIs were generally similar in subjects with LDH ≥ 500 U/L (n= 24) and those with LDH < 500 U/L (n= 153). The results in the Pooled 2L LBCL Treated Set were similar to what was observed in the Pooled 3L+ LBCL Treated Set.

SPD Prior to LDC

In the Pooled 2L LBCL Treated Set, TEAEs and AESIs were generally similar in subjects with SPD < 50 cm^2 (n= 151) and those with SPD ≥ 50 cm^2 (n= 20). In the Pooled 2L LBCL Treated Set, the frequency of CRS was higher in subjects with SPD ≥ 50 cm^2 (75.0%) compared with those with SPD < 50 cm^2 (41.1%), which was consistent with what was observed in the Pooled 3L+ LBCL Treated Set.

Histology

In the Pooled 2L LBCL Treated Set, safety was generally similar across subjects with disease histology DLBCL NOS de novo (n= 103), DLBCL tiNHL (including tFL) (n= 15), HGL (HGBCL) (n= 47), and PMBCL (n= 8). The number of subjects with disease histology FL3B (n= 3) and T cell/histiocyte-rich large B-cell lymphoma (HRBCL) (n= 1) was too small to draw meaningful conclusions. In the Pooled 2L LBCL Treated Set, a lower frequency of CRS was noted in subjects with disease histology DLBCL tiNHL (26.7%) compared with HGL (HGBCL) (48.9%) and PMBCL (62.5%).

While the results across the disease histology subgroups in the Pooled 2L LBCL Treated Set were generally consistent with what was observed in the Pooled 3L+ LBCL Treated Set, the following differences in AESIs were observed:

- A lower frequency of CRS in subjects with disease histology DLBCL tiNHL in the Pooled 2L LBCL Treated Set (26.7%) compared with the Pooled 3L+ LBCL Treated Set (42.5%).
- A lower frequency of iiNT in subjects with disease histology HGL (HGBCL) in the Pooled 2L LBCL Treated Set (14.9%) compared with the Pooled 3L+ LBCL Treated Set (28.8%).
- A lower frequency of iiNT (12.5%) and a higher frequency of CRS (62.5%) in subjects with disease histology PMBCL in the Pooled 2L LBCL Treated Set, compared with that of the Pooled 3L+ LBCL Treated Set (33.3% for iiNT and 46.7% for CRS). However, interpretation is limited by the relatively small number of subjects with disease histology PMBCL in the Pooled 2L LBCL Treated Set (n= 8).

Baseline CRP

In the Pooled 2L LBCL Treated Set, no differences in TEAEs and AESIs were observed in subjects with CRP < 20 mg/L (n= 100) and those with CRP ≥ 20 mg/L (n= 39), which was consistent with what was observed in the Pooled 3L+ LBCL Treated Set.

When comparing safety between the Pooled 2L and Pooled 3L+ LBCL Treated Sets, a higher frequency of CRS was reported in the Pooled 2L LBCL Treated Set (47.0%) compared with the Pooled 3L+ LBCL

Treated Set (31.5%) in subjects with CRP < 20 mg/L, while a lower frequency of iiNT was reported in the Pooled 2L LBCL Treated Set (15.4%) compared with the Pooled 3L+ LBCL Treated Set (34.8%) in subjects with CRP ≥ 20 mg/L.

Systemic Bridging Therapy

In the Pooled 2L LBCL Treated Set, the frequency of TEAEs and AESIs was similar in subjects who received systemic bridging therapy (n= 111) and in those who did not receive bridging therapy (n= 66).

Screening ECOG

In the Pooled 2L LBCL Treated Set, the frequency of TEAEs and AESIs was similar in subjects with Screening ECOG PS of 0 (n= 74), 1 (n= 78), and 2 (n= 25).

Creatinine Clearance

In the Pooled 2L LBCL Treated Set, the frequencies of TEAEs and AESIs were similar in subjects with CrCl < 60 mL/min (n= 24) compared to subjects with CrCl ≥ 60 mL/min (n= 149), which was consistent with what was observed in the Pooled 3L+ LBCL Treated Set.

Screening LVEF

In the Pooled 2L LBCL Treated Set, the number of subjects with LVEF < 50% was too small to draw meaningful conclusions (n= 5). In subjects with LVEF ≥ 50%, rates of TEAEs and AESIs were similar in the Pooled 2L LBCL Treated Set compared to the Pooled 3L+ LBCL Treated Set.

Refractory Status and CNS Lymphoma Involvement

In the Pooled 2L LBCL Treated Set, the frequency of TEAEs and AESIs were similar in subjects with refractory status (n= 115) compared with subjects with relapsed status (n= 62) and the results were similar to those observed in the Pooled 3L+ LBCL Treated Set.

In the Pooled 2L LBCL Treated Set, the number of subjects with CNS lymphoma involvement was too small to draw meaningful conclusions (n= 2).

Pre-Leukapheresis ALC

In the Pooled 2L LBCL Treated Set, the numbers of subjects with pre-leukapheresis ALC < 0.3×10^9 cells/L (n= 7) and with pre-leukapheresis ALC unknown (n= 1) were too small to draw any clinically meaningful conclusion. In subjects with pre-leukapheresis ALC ≥ 0.3×10^9 cells/L, rates of TEAEs and AESIs were similar in the Pooled 2L LBCL Treated Set compared to the Pooled 3L+ LBCL Treated Set.

Screening HCT-CI

In the Pooled 2L LBCL Treated Set, no clear differences in TEAEs and AESIs were identified in subjects with HCT-CI < 3 (n= 117) and those with HCT-CI ≥ 3 (n= 60).

Clinical Laboratory Evaluations

Hematology and chemistry laboratory abnormalities were similar in the liso-cel-treated analysis set of Study BCM-003, the Pooled 2L and Pooled 3L+ LBCL Treated Sets.

Safety Analyses in the Modified Pooled 2L and Pooled 3L+ Populations

Additional pooled safety analyses from time of liso-cel infusion were conducted for the subset of subjects who received a dose of liso-cel within the dose range of 44 to 120×10^6 CAR+ viable T cells in the Pooled 2L and Pooled 3L+ LBCL Treated Sets (i.e., the Modified Pooled 2L LBCL Treated Set [n= 177] and Modified Pooled 3L+ LBCL Treated Set [n= 381], respectively). As all subjects in the Pooled 2L LBCL

Treated Set (n= 177) received a dose of liso-cel within the above dose range, these 177 subjects also composed the Modified Pooled 2L LBCL Treated Set.

Safety in the Outpatient Setting

Subjects were considered to have received outpatient treatment if their first liso-cel infusion day did not overlap with any hospitalization stays during the study.

In the liso-cel arm in Study BCM-003 and in the Pooled 3L+ LBCL Studies (017001 DLBCL Cohort, BCM-001 Cohort 7, and 017007), 19 and 85 subjects respectively, were treated with liso-cel in the outpatient setting.

Summary of Results from Outpatient Set

Out of 19 subjects treated in an outpatient setting in the liso-cel arm of Study BCM-003, all had TEAEs, and 18 (94.7%) subjects had Grade ≥ 3 events. There were no Grade 5 TEAEs. The most frequent Grade ≥ 3 events were neutropenia (68.4%), anemia (57.9%), thrombocytopenia (42.1%), and lymphopenia (42.1%) . A total of 10 (52.6%) subjects experienced at least one event of CRS and 1 subject experienced iiNT.

Out of 85 subjects treated in an outpatient setting in the Pooled 3L+ LBCL Studies, all had TEAEs, and 63 (74.1%) subjects had Grade ≥ 3 events. There were no Grade 5 TEAEs. The most frequent Grade ≥ 3 events were neutropenia (52.9%), anemia (27.1%), leukopenia (23.5%), and thrombocytopenia (21.2%). A total of 32 (37.6%) subjects experienced at least one event of CRS and 27 (31.8%) subjects experienced iiNT.

Table 80. Treatment-emergent Adverse Events and Adverse Events of Special Interest in the Liso-cel-treated Population (Study BCM-003 and Pooled 3L+ LBCL Studies) - Outpatient Set

	2L LBCL	3L + LBCL				
	BCM-003 Arm B N=19 n (%)	17001 DLBCL Cohort N=25 n (%)	BCM-001 Cohort 7 N=6 n (%)	17007 N=54 n (%)	3L + Total N=85 n (%)	2L and 3L + LBCL Overall Total N=104 n (%)
Subjects with any TEAE	19 (100)	25 (100)	6 (100)	54 (100)	85 (100)	104 (100)
Subjects with any Grade 3 or higher TEAE	18 (94.7)	17 (68.0)	6 (100)	40 (74.1)	63 (74.1)	81 (77.9)
Subjects with any Grade 5 TEAE	0	0	0	0	0	0
Subjects with any serious TEAE	13 (68.4)	18 (72.0)	1 (16.7)	32 (59.3)	51 (60.0)	64 (61.5)
CRS or NT	10 (52.6)	15 (60.0)	0	25 (46.3)	40 (47.1)	50 (48.1)
Grade 1-2	10 (52.6)	13 (52.0)	0	18 (33.3)	31 (36.5)	41 (39.4)
Grade 3-4	0	2 (8.0)	0	7 (13.0)	9 (10.6)	9 (8.7)
Grade 5	0	0	0	0	0	0
SAE	9 (47.4)	12 (48.0)	0	24 (44.4)	36 (42.4)	45 (43.3)
CRS	10 (52.6)	12 (48.0)	0	20 (37.0)	32 (37.6)	42 (40.4)
Grade 1-2	10 (52.6)	11 (44.0)	0	20 (37.0)	31 (36.5)	41 (39.4)
Grade 3-4	0	1 (4.0)	0	0	1 (1.2)	1 (1.0)
Grade 5	0	0	0	0	0	0
SAE	8 (42.1)	10 (40.0)	0	19 (35.2)	29 (34.1)	37 (35.6)
NT	1 (5.3)	11 (44.0)	0	16 (29.6)	27 (31.8)	28 (26.9)
Grade 1-2	1 (5.3)	9 (36.0)	0	9 (16.7)	18 (21.2)	19 (18.3)
Grade 3-4	0	2 (8.0)	0	7 (13.0)	9 (10.6)	9 (8.7)
Grade 5	0	0	0	0	0	0
SAE	1 (5.3)	2 (8.0)	0	14 (25.9)	16 (18.8)	17 (16.3)

Safety to Support Product Label

Updated Safety data to Support Product Label. Additional pooled safety analyses from time of liso-cel infusion for the subset of subjects who received a dose of liso-cel within the dose range of 44 to 120

x 10^6 CAR+ viable T cells in the Modified Pooled 2L LBCL Treated Set (n=177) and Modified Pooled 3L+ LBCL Treated Set (n= 384) showed overall consistent results, and support the integration of safety data across 2L and 3L+ LBCL subjects to inform the product label following liso-cel infusion in LBCL

Sections 4.4 and 4.8 of the SmPC now reflect the updated data and the modified pooled 2L LBCL treated set (n=177) which now includes BCM-003, 017006, and BCM-001 cohort 2.

Consequently, the description of selected adverse reactions in the SmPC has been changed.

Table 81. Treatment-emergent AESI by Grade Modified Pooled 2L and 3L+ LBCL Treated Set

	2L LBCL				3L + LBCL					
	BCM-003 Arm B N=89 n (%)	017006 N=61 n (%)	BCM-001 Cohort 2 N=27 n (%)	2L Total N=177 n (%)	017001 DLBCL Cohort N=229 n (%)	BCM-001 Cohorts 1, 3 and 7 N=55 n (%)	017007 N=78 n (%)	BCM-002 N=22 n (%)	3L+ Total N=384 n (%)	2L and 3L + LBCL Total N=561 n (%)
CRS or NT	45 (50.6)	30 (49.2)	13 (48.1)	88 (49.7)	101 (44.1)	21 (38.2)	37 (47.4)	10 (45.5)	169 (44.0)	257 (45.8)
Grade 1-2	40 (44.9)	26 (42.6)	12 (44.4)	78 (44.1)	75 (32.8)	16 (29.1)	29 (37.2)	7 (31.8)	127 (33.1)	205 (36.5)
Grade 3-4	5 (5.6)	4 (6.6)	1 (3.7)	10 (5.6)	26 (11.4)	5 (9.1)	8 (10.3)	3 (13.6)	42 (10.9)	52 (9.3)
Grade 5	0	0	0	0	0	0	0	0	0	0
SAE	14 (15.7)	10 (16.4)	3 (11.1)	27 (15.3)	58 (25.3)	10 (18.2)	29 (37.2)	6 (27.3)	103 (26.8)	130 (23.2)
CRS	44 (49.4)	23 (37.7)	13 (48.1)	80 (45.2)	87 (38.0)	19 (34.5)	31 (39.7)	10 (45.5)	147 (38.3)	227 (40.5)
Grade 1-2	43 (48.3)	22 (36.1)	13 (48.1)	78 (44.1)	81 (35.4)	17 (30.9)	31 (39.7)	10 (45.5)	139 (36.2)	217 (38.7)
Grade 3-4	1 (1.1)	1 (1.6)	0	2 (1.1)	6 (2.6)	2 (3.6)	0	0	8 (2.1)	10 (1.8)
Grade 5	0	0	0	0	0	0	0	0	0	0
SAE	12 (13.5)	8 (13.1)	1 (3.7)	21 (11.9)	34 (14.8)	7 (12.7)	23 (29.5)	5 (22.7)	69 (18.0)	90 (16.0)
NT	9 (10.1)	19 (31.1)	4 (14.8)	32 (18.1)	64 (27.9)	9 (16.4)	23 (29.5)	5 (22.7)	101 (26.3)	133 (23.7)
Grade 1-2	5 (5.6)	16 (26.2)	3 (11.1)	24 (13.6)	40 (17.5)	4 (7.3)	15 (19.2)	2 (9.1)	61 (15.9)	85 (15.2)
Grade 3-4	4 (4.5)	3 (4.9)	1 (3.7)	8 (4.5)	24 (10.5)	5 (9.1)	8 (10.3)	3 (13.6)	40 (10.4)	48 (8.6)
Grade 5	0	0	0	0	0	0	0	0	0	0
SAE	3 (3.4)	3 (4.9)	2 (7.4)	8 (4.5)	35 (15.3)	7 (12.7)	18 (23.1)	2 (9.1)	62 (16.1)	70 (12.5)

Modified Pooled 2L and 3L+ LBCL Treated Set includes Pooled 2L and 3L+ LBCL Treated Set subjects within dose range of 44 - 120 x 10^6 cells.
CRS=Cytokine release syndrome, NT=Neurological toxicity.
AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. A subject is counted only once for multiple events within preferred term/system organ class.
Infection includes grade 3 or higher TEAEs from Infections and infestations SOC, by AE high level group term (HLGT).
Cytokine release syndrome is graded based on the Lee grading criteria (Lee 2014). Other AEs are graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The most severe grade is used for AEs that occur more than once in an individual subject during the period.
Treatment-emergent adverse events (TEAEs) are defined as AEs occurring from the date of the initial JCAR017 infusion (Day 1) through and including 90 days following the final cycle of JCAR017 infusion (i.e., last dose for Study 017001; first dose for other studies). Any AE occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment will not be considered as TEAE.
Source: nhl_ir\..\maa_iss_2l\..\maa\..\t_teaesi_m.sas; Snapshot: 2022-07-14 for BCM-003, 2022-07-22 for LTFU BCM-003, 2022-04-20 for BCM-001, 2022-04-14 for LTFU BCM-001, 2021-11-19 for 017006 and 017007, 2021-11-16 for LTFU 017006 and 017007, 2021-02-26 for 017001, 2021-02-25 for LTFU 017001, 2019-09-25 for BCM-002; Data cutoff: 2022-05-13 for BCM-003 and LTFU BCM-003, 2022-03-02 for BCM-001 and LTFU BCM-001, 2021-09-24 for 017006, 017007, and for LTFU 017006, 017007, 2021-01-04 for 017001 and LTFU 017001, 2019-08-01 for BCM-002; Output: Version1; Run: 2022-09-30T07:22:09

<u>For patients who received one prior line of therapy</u>:

CRS occurred in 45% of patients, 1% of whom experienced Grade 3 CRS (no fatal events). The median time to onset was 4 days (range: 1 to 63 days, with the upper limit due to CRS onset, without fever, reported in one patient), and the median duration of CRS was 4 days (range: 1 to 16 days). The most common manifestations of CRS included pyrexia (44%), hypotension (12%), chills (5%), hypoxia (5%), tachycardia (4%), headache (3%), and fatigue (2%). In clinical studies, 42 out of 177 (24%) patients received tocilizumab and/or a corticosteroid for CRS after liso-cel infusion. Eighteen (10%) patients received tocilizumab only, 24 (14%) patients received tocilizumab and a corticosteroid, and no patients received corticosteroids only.

NT occurred in 18% of patients receiving liso-cel, including Grade 3 in 5% of patients (no fatal events). The median time to onset of the first event was 8 days (range: 1 to 63 days); 97% of all neurologic toxicities occurred within the first 8 weeks following liso-cel infusion. The median duration of neurologic toxicities was 6 days (range: 1 to 89 days). The most common neurologic toxicities included encephalopathy (10%), tremor (8%), aphasia (5%), dizziness (2%), and headache (1%).

Febrile neutropenia has been observed in 7% of patients.

Infections (all grades) occurred in 25% of patients. **Grade 3 or higher infections** occurred in 10% of patients. **Grade 3 or higher infections with an unspecified pathogen** occurred in 3% of patients, **bacterial infections** occurred in 5%, and **viral and fungal infections** occurred in 2% and none of the patients, respectively.

Grade 3 or higher cytopenias present at Day 35 following liso-cel administration, occurred in 35% of patients, and included thrombocytopenia (28%), neutropenia (26%), and anaemia (9%).

Hypogammaglobulinemia occurred in 7% of patients.

For patients who received two or more prior lines of therapy for LBCL (n= 384 patients infused with liso-cel from 4 pooled studies (TRANSCEND [017001], TRANSCEND WORLD [JCAR017-BCM-001, cohort 1, 3 and 7], PLATFORM [JCAR017-BCM-002] and OUTREACH [017007]):

CRS occurred in 38% of patients, 2% of whom experienced Grade 3 or 4 (severe or life-threatening) CRS. There were no fatal events. Among patients who died after receiving liso-cel, 4 had ongoing CRS events at the time of death. The median time to onset was 4 days (range: 1 to 14 days) and the median duration was 5 days (range: 1 to 17 days). The most common manifestations of CRS included pyrexia (38%), hypotension (18%), tachycardia (13%), chills (9%), and hypoxia (8%). In clinical studies, 74 out of 384 (19%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of liso-cel. Thirty-seven (10%) patients received tocilizumab only, 29 (8%) received tocilizumab and a corticosteroid and 8 (2%) received corticosteroids only.

NT occurred in 26% of patients receiving liso-cel, including Grade 3 or 4 in 10% of patients (no fatal events). The median time to onset of the first event was 9 days (range: 1 to 66 days); 99% of all neurologic toxicities occurred within the first 8 weeks following liso-cel infusion. The median duration of neurologic toxicities was 10 days (range: 1 to 84 days). The most common neurologic toxicities included encephalopathy (18%), tremor (9%), aphasia (8%), delirium (7%), headache (4%), ataxia (3%) and dizziness (3%). Seizures (2%) and cerebral oedema (0.3%) also occurred in patients treated with liso-cel.

Febrile neutropenia has been observed in 9% of patients.

Infections (all grades) occurred in 38% of patients. **Grade 3 or higher infections** occurred in 12% of patients. **Grade 3 or higher infections with an unspecified pathogen** occurred in 8% of patients, **bacterial infections** occurred in 4% of patients, **viral and fungal infections** occurred in 1% of patients.

Grade 3 or higher cytopenias present at Day 29 following liso-cel administration, occurred in 38% of patients, and included thrombocytopenia (31%), neutropenia (21%) and anaemia (7%).

Hypogammaglobulinemia occurred in 11% of patients.

Post marketing experience

Liso-cel was first approved in the US on 05-Feb-2021 for the treatment of adult patients with R/R LBCL after 2 or more lines of systemic therapy. It was subsequently approved in Japan and Switzerland for patients with R/R LBCL who have received 2 or more therapies, and it was most recently approved in the EU on 04-Apr-2022 for the treatment of adult patients with R/R DLBCL, PMBCL, and FL3B, after 2 or more lines of systemic therapy.

Currently, post-marketing data are available from the US as presented in the Periodic Adverse Drug Experience Reports (PADERs; reporting periods: 05-Feb-2021 through 04-May-2021, 05-May-2021 through 04-Aug-2021, 05-Aug-2021 through 04-Nov-2021, and 05-Nov-2021 through 04-Feb-2022). Review of these post-marketing data did not reveal any new safety concerns for liso-cel. The post-marketing data were consistent with the safety profile of liso-cel as previously reported and described in the product label.

2.6.1. Discussion on clinical safety

The safety evaluation was primarily based on ongoing Study BCM-003, which was conducted in subjects with R/R LBCL after 1 prior therapy who were eligible for high-dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplant (HSCT). Safety data included 183 subjects (n=92 liso-cel; n=91 SOC). Additionally, safety data from time of liso-cel infusion of liso-cel-treated 2L LBCL subjects from Study BCM 003 liso-cel arm as well as other 2L studies (Study 017006, and Study BCM-001 [Cohort 2]) and the marketed indication of 3L+ LBCL (Study 017001 [DLBCL Cohort], Study BCM 001 [Cohorts 1, 3, and 7], Study 017007, and Study BCM-002) were pooled to allow for a side-by-side comparison. Notably, the most relevant difference between patients included in the Arm B (liso-cel arm) of Study BCM-003 and the Pooled 2L LBCL was the "transplant-not intended" in the second treated set. The MAH clarified that "transplant not-intended" (TNI) patients were those deemed ineligible for high-dose chemotherapy and HSCT due to age, performance status or comorbidity, while also having adequate organ function for CAR T-cell treatment based on the Investigator judgement. Therefore, taking into account a broader indication for Breyanzi, including the transplant-not intended subjects, the MAH supported the integration of the safety data across 2L and 3L+ LBCL subjects to inform the product label following liso-cell infusion in LBCL.

In Study BCM-003, baseline demographic and characteristics for the ITT analysis set were balanced between the liso-cel and the SOC arm and were representative of a 2L LBCL population. However, the female population was less represented in the SOC arm as were the elderly patients in the age group ≥ 75 years. The impact of these differences on the safety profile has been discussed pooling Study BCM-003 subjects with other 2L LBCL studies (Studies 017006 and BCM-001 Cohort 2), that enrolled elderly patients. Safety was generally similar among subjects < 65 years (n= 62), ≥ 65 to < 70 years (n= 23), ≥ 70 to < 75 years (n= 51), and ≥ 75 to < 85 years (n= 41) in the Pooled 2L LBCL Treated Set, with the exception of higher frequency of iiNT reported in subjects ≥ 75 to < 85 years (31.7%) compared to subjects < 65 years (9.7%) or lower frequency of iiNT in subjects < 65 years and < 75 years in the Pooled 2L LBCL Treated Set (9.7% and 14%, respectively) compared to the Pooled 3L+ LBCL Treated Set (29.4% and 27%, respectively). Furthermore, no significant differences were noted in the subgroups by sex.

The overall incidences of TEAEs and SAEs were similar for subjects in the liso-cel and SOC arms. However, the AE profiles were different but in line with the respective mechanism of action for liso-cel and SOC. A similar pattern of TEAEs to the Liso-cel was observed in subjects who crossed over to liso-cel from the SOC arm.

Hematological AEs were the most frequently reported Grade 3-4 TEAE in both arms, but the incidence of Grade 3-4 TEAEs of neutropenia and lymphopenia appeared higher in the liso-cel arm as compared with the SOC arm. There was no parallel increase in infection or febrile neutropenia that appeared to be higher in the SOC arm.

Overall, the pattern of treatment-related TEAEs reported in the liso-cel arm was similar to that reported in the SOC arm with the exception of some system organ class categories: more subjects in the liso-cel arm experienced treatment-related TEAEs in the system organ classes of Immune System Disorder and Investigations than in the SOC arm, including cytokine release syndrome (CRS) which is a characteristic AE of CAR T-cell therapies. Conversely, more subjects in the SOC arm experienced treatment-related TEAEs in the Metabolism and Nutrition Disorder system organ class.

CRS was also the most frequently reported SAE in the liso-cel arm (12 subjects [13.0%]), together to febrile neutropenia (7 subjects [7.6%]), neutropenia (7 subjects [7.6%]), and pyrexia (6 subjects [6.5%]), whereas in the SOC arm the most frequently reported SAEs were febrile neutropenia (9 subjects [9.9%]), pyrexia (7 subjects [7.7%]), acute kidney injury (5 subjects [5.5%]), and neutropenia (4 subjects [4.4%]).

The overall number of deaths was n= 8 (8.8%) in the SOC arm, n= 13 (14.1%) in the liso-cel arm and n= 16 (34%) in the SOC arm post-crossover. The majority of deaths, including those in the SOC arm after crossover, were due to disease progression. Two subjects in the SOC arm died to a Grade 5 TEAE: a sepsis and an acute respiratory distress syndrome, both considered not related to any study drug. Two subjects in the SOC arm died due to AEs not-considered treatment-emergent: one subject for multiorgan failure and one for cardiac arrest, both in the context of disease progression. In the liso-cel arm, two subjects died due to an AE: one subject for PT of failure to thrive considered not related to study drug, and one subject died of COVID-19 during the treatment period. More details have been provided by the MAH on the deaths occurred in the liso-cel arm (n=3, 3.3%) and in the SOC arm post-crossover (n=3, 6.4%) in which the cause of death category was "other". These deaths were due either to sepsis or COVID-19. It should be noted that COVID-19 was the cause of death in 4 out of 6 patients in Study BCM-003 and no COVID-19 vaccination was reported for these patients. It should be noted that all these deaths occurred before the COVID-19 vaccination was initiated in the respective countries, with the exception of one subject. The MAH specified that a "Dear Investigator Letter" was sent to sites on 10-May-2021 advising that Investigators should apply their clinical judgment in weighing the benefits and risks of COVID-19 vaccination for cancer patients who were participating in BMS Cellular Therapy clinical trials. Consequently, at the time of the Primary Analysis in the Addendum CSR (data cut-off 13-May-2022), 85 out of 184 randomized subjects were reported to have been vaccinated for SARS-CoV-2 (53 in the liso-cel Arm and 32 in the SOC Arm). Patients receiving CD19 CAR T-cell therapy for relapsed/refractory lymphoma experienced prolonged and profound B-cell aplasia and hypogammaglobulinemia, placing them at higher risk of severe COVID-19. Independently, it has been recently reported that, despite attenuated humoral response to mRNA-based vaccines, patients demonstrate normal or heightened functional T-cell responses, including antiviral T-cell activity against SARS-CoV-2 variants including Omicron (*Oh et al. Blood 2022, Atanackovic et al. Blood 2022*). Collectively, these data reinforce the importance of COVID-19 vaccination following CD19 CAR T-cell therapy (as strongly recommended by ASTCT, Center for International Blood and Marrow Transplant Research-CIBMTR and the National Marrow Donor Program-NMDP in alignment with CDC/ACIP recommendations), despite long-term B-cell aplasia and the patients should be counselled on the importance of prevention measures. The statement on COVID-19 has been updated accordingly in Section 4.4 of the SmPC.

AESIs included the following categories: CRS, neurologic toxicity immune effector cell associated events (i.e., iiNT), cytopenia and prolonged cytopenia, TLS, MAS, Grade ≥ 3 infection, and second primary malignancies. As expected, the frequency of AESIs was greater in the liso-cel arm than in the SOC arm.

In the liso-cel arm, 45 (48.9%) subjects experienced at least one event of CRS with a median time to onset of 5.0 days (range 1 to 63 days). Out of 45 subjects who showed CRS signs or symptoms, 21 subjects received tocilizumab. Of these, 12 also received additional treatment with corticosteroids. The 3 most frequently reported symptoms of CRS were pyrexia (44 [47.8%] subjects), hypotension (9 [9.8%] subjects), and chills and headache (both reported in 4 [4.3%] subjects). The median time to resolution as of the data cut-off date of 4.0 days (range 1 to 16 days). Similar results were observed for subjects in the SOC arm post-crossover. No subject had ongoing CRS at time of death. Only 1 subject in the liso-cel arm reported Grade ≥ 3 CRS, graded according to the Lee criteria (Lee, 2014), with a reported symptom of hypertransaminasaemia (Grade 3), with onset 9.0 days after the start of liso-cel infusion and resolution within 2.0 days. The event was detailed, noting that not all criteria for CRS were met for this subject (lack of recorded fever). However, the Investigator deemed the overall presentation consistent with CRS due to lack of an alternative explanation, and the Sponsor accepted this determination.

Out of 92 subjects in the liso-cel arm, 11 (12%) subjects experienced iiNT. The median time to onset of iiNT was 11.0 days (range 7 to 25 days), whereas the median time to resolution was 6.0 days (range 1 to 30 days). Of the 11 subjects who experienced iiNT, aphasia and tremor were reported in 4 (4.3%) subjects each and encephalopathy, dizziness, headache, and confusional state were reported in 2 (2.2%) subjects each. Seven received either tocilizumab (n= 1) or corticosteroids (n= 6) for treatment of their event. No subjects received vasopressors for iiNT and all subjects recovered with no neurologic sequela.

Cytopenia and prolonged cytopenia were reported less frequently in the SOC arm compared with the liso-cel arm (prolonged cytopenia n=3, 3.3% in SOC arm vs n=40, 43.5% in liso-cel arm). However, most subjects recovered from prolonged cytopenia by the pre-selected timepoints of 35 or 62 days post-prolonged cytopenia diagnosis.

Between other AESIs, tumor lysis syndrome was reported only in 2 (2.2%) subjects in the SOC arm; macrophage activation syndrome was reported in 1 (1.1%) subject in the liso-cel arm who experienced a Grade 2 event of hemophagocytic lymphohistiocytosis with onset on Day 42 and resolved on Day 47 without treatment (although the event was concurrent with CRS and the subject received treatment for CRS). Grade ≥ 3 infections were reported in 14 (15.2%) subjects in the liso-cel arm and in 19 (20.9%) subjects in the SOC arm; second primary malignancy only occurred in 1 subject in the SOC arm (Kaposi sarcoma), which was reported as a post-treatment AE.

Changes in hematology laboratory results in the SOC arm were difficult to discern, possibly because subjects received differing numbers of cycles of salvage immunochemotherapy. However, some trends were apparent: hemoglobin declined gradually through Day 85, after which it began to rise gradually; neutrophils appeared relatively stable until Day 64, after which they declined. Leukocytes were depressed from Day 64 through to the end of the study and Platelets decreased from baseline to Day 15. They increased markedly on Day 22 and declined thereafter, only to gradually increase again starting from Day 85. In liso-cel arm, neutrophils showed a decline through Day 29, followed by a period of relative stability, followed by a gradual increase from Day 64 onward. Lymphocyte counts were low at Day 29, followed by an increase over the remainder of the study, concurrent with liso-cel expansion. Platelet counts appeared decreased from baseline to Day 15. They increased markedly on Day 22 and declined thereafter, to then gradually increase again starting from Day 50. Hemoglobin levels remained generally stable throughout the study. Regarding laboratory findings, in the liso-cel arm most serum chemistry parameters remained stable over time. In particular, ALT, AST, and bilirubin remained stable, with the exception of a spike at the EOS visit. Only a single subject had these values reported at an EOS

visit, and this subject's EOS visit occurred after disease progression. More details have been provided on this case. Moreover, no other transaminase aberrances to signal a safety concern were observed in the liso-cel arm.

Regarding decreased fibrinogen, 2 subjects randomized to the liso-cel arm experienced the AE of hypofibrinogenemia requiring standard interventions. Hypofibrinogenemia appeared to be associated with recent onset CRS. Safety narratives for these 2 subjects were also provided. However, no clinical events such as disseminated intravascular coagulation or haemorrhage/bleeding were related to this AE.

Finally, there were no notable differences in the analyses within the subgroup analyses by age, sex, race and NHL subtype.

Overall, the safety data reported in liso-cel-treated subjects from the time of liso-cel infusion in the Study BCM 003 liso-cel arm seems to be consistent with that observed in the 2L and 3L+ LBCL populations and no new safety concerns have been identified. However, some differences could be observed.

It should be noted that there was a higher frequency of liso-cel TEAEs within Blood and lymphatic system disorders, in particular for neutropenia (52.8% in BCM-003 Arm B vs 45.8% in Pooled 2L vs 37.6% in Pooled 3L+) and thrombocytopenia (40.4% in BCM-003 Arm B vs 27.7% vs 16.4% in Pooled 3L+). However, when analysing treatment-emergent laboratory abnormalities, this difference was not observed. Moreover, no increased risk of severe infections or type of infections were reported. No association between thrombocytopenia and haemorrhagic events was also observed.

Neurological toxicities, defined as events within the ND/PD system organ class, occurred in 49 (55.1%) subjects in the liso-cel-treated analysis set of Study BCM-003, compared with 98 (55.4%) subjects in the Pooled 2L LBCL Treated Set, and 300 (70.1%) subjects in the Pooled 3L+ Treated Set. As requested, the MAH evaluated neurological toxicities, defined as events within the ND/PD system organ class, using the data cut-off date from the Primary Analysis in the BCM-003 Addendum CSR (data cut-off date of 13-May-2022). TEAEs in the ND/PD system organ class occurred in 59 (64.1%) subjects in the liso-cel arm and 57 (62.6%) subjects in the SOC arm. These included treatment-related events in 32 (34.8%) subjects in the liso-cel arm and 28 (30.8%) subjects in the SOC arm, Grade 3/4 events in 12 (13.0%) subjects in the liso-cel arm and 8 (8.8%) subjects in the SOC arm, and serious events in 5 (5.4%) subjects in the liso-cel arm and 5 (5.5%) subjects in the SOC arm. The most commonly (≥ 10% of subjects) occurring neurological toxicity TEAEs included headache (43.5%), dizziness (23.9%), insomnia (20.7%), and tremor (12.0%) in the liso-cel arm and headache (23.1%), dizziness (14.3%), dysgeusia (12.1%), and insomnia and peripheral sensory neuropathy (11.0% each) in the SOC arm. The median time to onset from randomization was 29.0 days (range 1 to 106 days), whereas the median duration of the episodes was 77.0 days (range 1 to 1148 days). Only 2 subjects did not recover at the time of the cut-off data, 56 subjects recovered with no sequelae and 1 subject was recovering. In the liso-cel arm, out of the 59 subjects who reported NT, 44 subjects (47.8%) received at least one concomitant medication for treatment-emergent NT, and paracetamol was the most frequent medication used in both arms (13.2% in SOC arm and 19.6% in liso-cel arm). Among subjects who experienced a treatment-emergent NT event, those randomized into the liso-cel arm had a higher frequency of any ND/PD system organ class condition in their medical history compared to those randomized into the SOC arm. However, a specific association between prior clinical conditions/comorbidities and the development of a particular NT event cannot be inferred.

In addition, the MAH specified that a total of 16 subjects have been identified with primary or secondary CNS lymphoma across liso-cel studies: 5 subjects with primary CNS lymphoma (all in Study BCM-001 Cohort 5) and 11 subjects with secondary CNS lymphoma (7 subjects in Study 017001 DLBCL Cohort, 2 subjects in Study 017007, and 1 subject each in Study BCM-003 and BCM-001 Cohort 2). Efficacy has

been observed in liso-cel treated subjects with primary and secondary CNS involvement. The safety profile was similar in both subjects with CNS lymphoma and those without CNS lymphoma. No increased risks have been observed for adverse events of special interest (AESI) including cytokine release syndrome (CRS) and neurological toxicity (NT) in those subjects with CNS involvement. However, for the small number of patients any definitive conclusion can be drawn.

The MAH also clarified that the frequencies of any-grade hypogammaglobulinemia AESIs in Study BCM-003 were comparable to the Pooled 2l LBCL treated Set and lower than the Pooled 3L+ LBCL Treated Set (6.7% vs. 6.2% vs. 12.4%, respectively), as well as for any-grade secondary malignancy AESI (0% vs. 0.6% and 1.6%, respectively), probably reflecting less severely pre-treated patients in Study BCM-003.

Therapy-related myeloid neoplasms (t-MN) are aggressive leukemia, associated with high-risk features and low survival. Recently, exposure to CAR-T, including liso-cel, has been linked to t-MN development in a series of NHL patients (*Alkhateeb et al Blood Cancer Journal 2022*). Given the strikingly short interval between CAR-T and the development of t-MN, especially in those NHL patients who had dysplasia or clonal abnormalities before CAR-T, the MAH has been asked to comment this potentially fatal complications, including the need for specific vigilance measures. A cumulative search of the BMS corporate safety database was conducted to identify any potential therapy-related myeloid neoplasm (t-MN) cases. The overall cumulative patient exposure to liso-cel from all sources (clinical trials, commercial, and named-patient programs) is approximately 1767 patients, and a total of 27 cases were identified. Of these, 21 cases reported MDS, 4 cases reported acute myeloid leukaemia (AML), and 1 case each reported acute erythroid leukaemia and leukaemia. The median interval from CAR T infusion to onset of t-MN was 359 days (11.77 months), whereas the average interval from initial chemotherapy to onset of t-MN was 7.6 years, which might suggest that these events could be explained by prior chemotherapy. The only known case with the diagnosis of myelodysplastic syndrome (MDS), made 3 months after liso-cel infusion, showed cytogenetic abnormalities in bone marrow biopsy 13 days before liso-cel infusion. Furthermore, secondary malignancies (which include MDS and AML) are listed as an important potential risk in the Risk Management Plan.

Finally, due to the limitation of the small sample size for certain subgroups in the liso-cel-treated analysis set of Study BCM-003, the subgroup analyses focus on the Pooled 2L Treated Set, with comparisons with the Pooled 3L+ LBCL Treated Set under each subgroup category.

Overall, in the Pooled 2L and Pooled 3L+ LBCL Treated Sets, CRS and iiNT were more frequent in subjects with higher disease burden (SPD ≥ 50 cm2), or with more aggressive disease (HGBCL or subjects who required bridging). A lower frequency of iiNT was noted in certain subgroups in the Pooled 2L LBCL Treated Set compared with the Pooled 3L+ LBCL Treated Set. However, the number of subjects in certain subgroups was too small to draw any clinically meaningful conclusion. Regarding specifically Study BCM-003, the MAH underlines that there were no notable differences in the analyses within these subgroups in the liso-cel-treated analysis set of Study BCM-003, and the results across the subgroups in the liso-cel-treated analysis set of Study BCM-003 were generally consistent with what was observed in the Pooled 2L and Pooled 3L+ LBCL Treated Sets.

In the liso-cel arm in Study BCM-003 and in the Pooled 3L+ LBCL Studies (017001 DLBCL Cohort, BCM-001 Cohort 7, and 017007), 19 and 85 subjects respectively, were treated with liso cel in the outpatient setting. No new safety concerns were identified.

Additional pooled safety analyses from time of liso-cel infusion for the subset of subjects who received a dose of liso-cel within the dose range of 44 to 120 x 10^6 CAR+ viable T cells in the Modified Pooled 2L LBCL Treated Set (n=177) and Modified Pooled 3L+ LBCL Treated Set (n= 384) showed overall consistent results, and support the integration of safety data across 2L and 3L+ LBCL subjects to inform the product

label following liso-cel infusion in LBCL. Therefore, the proposed product label has been updated to include the transplant-not intended subjects from Studies 017006 (19-Nov-2021 data cut-off date) and BCM-001 Cohort 2 (02-Mar-2022 data cut-off date). Additionally, the ADR table includes updated data for Study BCM-003 (13-May-2022 data cut-off date) and Study BCM-001 Cohorts 1, 3, and 7 (02-Mar-2022 data cut-off date).

Regarding the surface expression of EGFRt that could serve as a target for selective depletion of Breyanzi using anti-EGFR antibodies such as cetuximab as a strategy to mitigate severe adverse events associated with CAR T cells, the MAH specified that, in the liso-cel clinical development program, only two subjects with chronic lymphocytic leukaemia (CLL) (Study 017004) received an anti-EGFR antibody (cetuximab), with an unknown posology. In both cases cetuximab was administered for the treatment of suspected neurotoxicity. To date, there has been no use of cetuximab for Breyanzi depletion in large B-cell lymphoma (LBCL) liso-cel studies. In light of the information above, the MAH updated the statement on clinical use of anti-EGFR antibodies in Section 4.5 of the SmPC.

2.6.2. Conclusions on clinical safety

No new safety concerns were identified in this 2L patient population studied in BCM-003. The overall safety profile for subjects treated with liso-cel was similar to that of subjects treated with SOC, with notable differences as expected with regard to AESIs that are known side effects specific to CAR T cell therapy. Overall, the safety events reported in this study were consistent with those previously observed in the marketed indication of 3L+ LBCL and were manageable. In particular, similar rates of CAR T-cell-associated toxicities were observed in this 2L LBCL population when compared to the 3L+ LBCL population. Overall, liso-cel demonstrates a manageable and consistent safety profile in patients with 2L LBCL, which is consistent with the 3L+ population. The data presented in the Summary of Product Characteristics (SmPC) reflect the entire clinical experience at the recommended dose range.

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 with this application.

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

Overall, the updates introduced in the RMP version 2.4 are in line with the application for an extension of indication to include treatment of adult patients with Second-line (2L) Transplant Intended (TI) Large B-Cell Lymphoma (LBCL). The MAH did not propose any change of safety specification, pharmacovigilance activities or risk minimization measures. There are no changes to the conditions and obligations of MA.

The PRAC considered that the risk management plan version 2.4 is acceptable.

The CAT endorsed this advice without changes.

The CAT endorsed the Risk Management Plan version 2.4 with the following content:

Safety concerns

Table 82 Summary of Safety Concerns

Important identified risks	Cytokine release syndrome
	Neurologic toxicity
	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
	Cerebral oedema
	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

Table 83: 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	Primary Objective: To characterise the incidence and severity of selected ADRs, as outlined in the SmPC, in patients treated with liso-cel in the postmarketing setting, and to monitor for potential clinically important AEs that have not yet been identified as part of the liso-cel safety profile.	CRS/MAS[a]/HLH[a] NT Infections Hypogammaglobulinaemia TLS	Protocol Submission to EMA Date of protocol approval by PRAC Start of data collection[c]	14-Apr-2022 01-Dec-2022 Q1 2023

Table 83: ***Ongoing and Planned Additional Pharmacovigilance Activities***

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
	Secondary Objectives: To assess long-term effectiveness in patients treated with liso-cel in the postmarketing setting. To assess the liso-cel safety and effectiveness profile in certain subgroups including but not limited to: • 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 lymphocyte count (< 0.3 × 10^9/L). • Subjects treated with out-of-specification product.	Cytopenia, including bone marrow failure Secondary malignancies /insertional oncogenesis Impact on pregnancy and lactation (for pregnancy events) Long-term safety Aggravation of GvHD[a] Cerebral oedema[b] Safety in patients ≥ 75 years	Safety reports[d] Interim reports[e] Date of Study Completion[f]	Safety reports every 6 months (eg, aligned with the reporting period of the PSURs); additional reports every 3 months if a new safety concern is identified At Year 5, 10, and 15 or when last patient is out of the registry-based study Q4 2042
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
LTFU study (GC-LTFU-001)/ Ongoing	Long-term follow-up of safety and efficacy for all paediatric and adult subjects exposed do a GM T cell therapy in Bristol-Myers Squibb sponsored, or Bristol-Myers Squibb alliance partner sponsored, clinical trials in accordance with	Infections Cytopenia, including bone marrow failure Autoimmune disorders	Subjects to be followed up for 15 years. Interim reports (5 and 10 years from FSFV [Jul 2018]).	 Q3 2023 and Q3 2028

Table 83: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
	Health Authorities' guidance for long-term (up to 15 years) follow-up of subjects treated with gene therapy products.	Secondary malignancies/insertional oncogenesis Impact on pregnancy and lactation Long-term safety Safety in patients < 18 years old Generation of replication competent lentivirus	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.	Estimated Q3 2038 Q3 2038 Q3 2039 Submitted in accordance with the EURD list
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. European Commission decision + 5 years European Commission decision + 10 years European Commission decision + 15 years	Submitted in accordance with the EURD list. Q2 2026 Q2 2031 Q2 2036

Risk minimisation measures

Table 84: 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire

Table 84: ***Summary of Risk Minimisation Measures***

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: • Educational programme for HCPs and patients • Controlled Distribution Programme	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)
Neurologic toxicity	**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)
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) LTFU study (GC-LTFU-001)
Hypogammaglobulinaemia	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)
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), 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	**Routine pharmacovigilance activities beyond adverse**

Table 84: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		reactions reporting and signal detection: None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)
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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) 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
	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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Included under the category of Other AEs considered related to liso-cel treatment in PASS (JCAR017-BCM-005).
Secondary malignancies/insertional oncogenesis	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire

Table 84: ***Summary of Risk Minimisation Measures***

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable
Cerebral oedema	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire (as part of NT) **Additional pharmacovigilance activities:** Included under the category of NT considered related to liso-cel treatment in PASS (JCAR017-BCM005).
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 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Transmission of infectious agents	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 (Risk of transmission of infectious agents exists. Guidance on monitoring patients for signs and symptoms of infections), and 6.6, PL Section 2 and Labelling Section 10 - handling instructions	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.

Table 84: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Reduced viability of liso-cel due to inappropriate product handling	**Routine risk minimisation measures:** SmPC Sections 4.2, 6.3, 6.4, 6.5 and 6.6, PL Section 5 and Labelling Section 9 - handling instructions	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: • Educational programme for HCPs • Controlled Distribution Programme	**Additional pharmacovigilance activities:** None.
Missing Information		
Impact on pregnancy and lactation	**Routine risk minimisation measures:** SmPC Section 4.6, PL Section 2- warnings and advice	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) for pregnancy events LTFU study (GC-LTFU-001).
Long-term safety	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001).
Safety in patients < 18 years old	**Routine risk minimisation measures:** SmPC Section 4.2, PL Section 2 - warnings and advice	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001).
	Routine risk minimisation measures:	**Routine pharmacovigilance activities beyond adverse**

Table 84: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Safety in patients ≥ 75 years	None	**reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Annex II condition for PASS JCAR017-BCM-005 has also been adapted including the newly approved Indication in 2Line treatment. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- a full user test has already been assessed in the IMA

- the route of administration is the same of the already approved indication

- the safety profile is similar as the previously approved indication

- lisocabtagene maraleucel is administered by a health care professional and the instructions for preparation, administration, storage and disposal are that already reflected in the approved PL

- the general design and layout of the proposed PL have not changed compared to the tested one

- no major changes are foreseen for the new indication.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Breyanzi Lisocabtagene maraleucel) is included in the additional monitoring list as

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It has a PASS imposed either at the time of authorisation or afterwards;

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH requested an extension of the approved indication of Breyanzi to include 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.

Non-Hodgkin lymphomas (NHLs) with a large B cell histology (i.e., large B cell lymphomas, LBCLs) are a broad group of lymphoproliferative neoplasms characterised by biological heterogeneity and aggressive clinical behaviour. DLBCL is the single most common form of NHL, accounting for 30% to 40% of all NHL cases.

HGBCL is a very aggressive form of large B-cell lymphoma that has been initially recognised as a distinct condition in the 2016 revision of the WHO classification of lymphoid neoplasms. HGBCL cases harbour the dual rearrangement of MYC and BCL2 and/or BCL6 genes, accounting for 5% to 7% of all DLBCLs.

PMBCL is a rare form of large B-cell lymphoma (2.4% of all NHLs) characterised by female predominance, younger age at diagnosis, and primary mediastinal involvement.

FL3B is a rarer subtype of follicular lymphoma (FL) that shares biological similarities to DLBCL and, compared to low-grade FL, is characterised by an aggressive clinical behaviour.

3.1.2. Available therapies and unmet medical need

All LBCLs share the same treatment paradigm, which is largely based on evidence from DLBCL trials. Treatment outcomes and prognosis are known to vary, however, across subtypes, and are influenced by several patient- and disease-related factors. Frontline treatment of advanced stage LBCL is usually based on the combination of anthracycline-including polychemotherapy regimens and anti-CD20 monoclonal antibodies, such as the standard R-CHOP regimen (i.e., rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). In a higher risk population, R-CHP plus polatuzumab has been recently shown to yield higher PFS and EFS rates compared to R-CHOP, although no survival benefit could be demonstrated (see e.g., Tilly H et al, NEJM 2022). Approximately 60-80% of patients with DLBCL, PMBCL and FL3B (depending on age and other baseline risk factors) are expected to achieve long-term remission-cure with frontline immunochemotherapy. The outcome of HGBCL with standard immunochemotherapy is less favourable.

Approximately 10-40% of DLBCL patients are refractory to frontline immunochemotherapy or experience disease relapse. Most relapses occur in the first two years after completing treatment, but up to one-fifth occur more than five years after treatment. Lower ORRs and shorter OS have been reported in the PARMA and CORAL studies in subjects with refractory DLBCL or with early relapse after frontline chemotherapy (e.g., <12 months)

Salvage treatment with non-cross resistant chemotherapy followed by high dose chemotherapy and autologous hematopoietic stem cell transplant (ASCT) has long been considered the standard of care in this setting and has been associated with long-term survival/cure in approximately half of patients with first relapsed DLBCL. Subjects with DLBCL were largely prevalent in all studies investigating the efficacy of 2nd line salvage strategies, thus the extent of the efficacy of salvage regimens in LGBL histologies

other than DLBCL is uncertain. The role of salvage chemotherapy, usually administered for 2-3 cycles, is to reduce the burden of disease and determine residual chemosensitivity. Only subjects who achieve CR/Deauville 4 PR according to PET/CT are eligible for ASCT, since patients with inadequate response have been shown not to benefit from transplant consolidation. Several salvage immunochemotherapy regimens are currently available (e.g. R-DHAP, R-ESHAP, R-GEMOX, R-ICE, R-GDP) and none was demonstrated to be clearly superior to the others, although differences in the toxicity profile might guide treatment choices.

In addition to standard immunochemotherapy (e.g. R-GemOx, bendamustine + rituximab etc.), novel options have been recently approved for non-transplant eligible (NTE) subjects with R/R DLBCL, including the combination of the anti-CD19 monoclonal antibody tafasitamab (Minjuvi) with lenalidomide (Tafa-R) and the pola-BR regimen (including the anti-CD79b conjugated monoclonal antibody polatuzumab vedotin [Polivy] in combination with bendamustine and rituximab, see the NCCN guidelines v. 5.2022). Although ORR as high as 45-58% (CRR ~40%) could be observed with these new regimens (mDoR in the range 12.6-34.6 months), limited data are currently available for the higher risk subset of patients identified by the Breyanzi claimed indication (i.e. subjects who are refractory or have relapsed within 12 months of initial therapy). Only a minority of subjects in the Minjuvi registrational trial had primary refractory (18.5%) or early (<12 months) relapsed disease (23.5%), and only 13 patients (28.3%) received the Pola-BR combination as their 2nd line treatment in pivotal study GO29365.

Overall, a medical need for new effective alternatives to the currently available treatments can be recognized in the targeted high risk 2nd line setting, with the aim to improve remission rates and increase long-term disease control/cure.

3.1.3. Main clinical studies

Pivotal study BCM-003 is a randomised, open-label Phase III trial designed to compare the efficacy of liso-cel vs. standard of care (SOC) in a subset of patients with large B-cell lymphomas at higher risk of salvage failure because of primary refractoriness or early relapse following frontline immunochemotherapy. This is the first evidence from a randomised control trial for Breyanzi.

Supportive data in NTE subjects were provided by single-arm studies 017006 and BCM-001 Cohort 2.

3.2. Favourable effects

From October 2018 to December 2020, 184 patients with high-risk 2nd line LBCLs underwent leukapheresis and were randomised in study BCM-003. Results from the inferential interim analysis at 80% information fraction demonstrated the superiority of Breyanzi vs. SOC in the target population.

The **median EFS by IRC** was **2.3** months (95%CI 2.2, 4.3) with SOC and **10.1** months (95%CI 6.1, NE) with liso-cel, resulting in a statistically significant and clinically relevant **HR** of **0.349** (95%CI 0.229, 0.530; p<0.0001). The 6-month EFS rates were 33.4% and 63.3% in the SOC and liso-cel arms, respectively. The results from all the pre-specified sensitivity analyses for EFS were consistent with the primary analysis, including EFS by Investigator's assessment (HR 0.343, 95%CI 0.225, 0.522) and EFS by IRC not including subjects who were PET/TC negative after bridging chemotherapy (HR 0.353, 95%CI 0.209, 0.595).

The **median PFS by IRC** was **5.7** months (95%CI 3.9, 9.4) in the SOC arm and **14.8** months (95%CI 6.6, NE) in the liso-cel arm, respectively. The **HR** for PFS was **0.406** (95%CI 0.250, 0.659, p=0.0001), consistent with the primary EFS analysis. Although immature, **PFS2** data were consistent with PFS data (**HR 0.494**, 95%CI 0.321, 0.760).

Although not sufficiently mature, the survival analysis showed a positive trend favouring liso-cel: **median OS** was 16.4 months (95%CI 11.0, NE) and NE (15.8, NE) in the SOC and liso-cel arm, respectively, equivalent to a **HR** of **0.509** (95%CI 0.258, 1.004; p=0.0257).

CRR by IRC was also higher with liso-cel (**66.3%**; 95%CI 55.7, 75.8) compared to SOC (**39.1%**; 95%CI 29.1, 49.9; p<0.0001). A similar effect was also observed in the CRR analysis by Investigator and in the ORR analysis (**ORR by IRC 47.8%** vs. **85.9%** in the SOC and liso-cel arms, respectively).

Updated efficacy data from the non-inferential **primary analysis of study BCM-003** with a longer follow-up (mFU ~17.5 months) confirmed the results observed in the 80% interim analysis: the **updated HR for EFS by IRC** was **0.356** (95%CI 0.243, 0.522), the **mEFS** was **NR** in the experimental arm (NE, 95%CI 9.5, NE) vs. **2.4** months (95%CI 2.2, 4.9) in the control arm.

The **updated PFS by IRC** also showed a consistent benefit with Breyanzi: the updated **HR** was **0.400** (95%CI 0.261, 0.615) and the KM plots trend was consistent with what observed for EFS.

The **updated CRR by IRC** was improved in both the SOC (CRR **43.5%**) and liso-cel arm (**73.9%**). The **updated mDoCR** was **9.3** months (95%CI 5.1, NE) in the control arm vs. **NE** (95%CI NE, NE) in the liso-cel arm.

No statistically significant effect could be observed in the **updated OS analysis**: the **HR** was **0.724** (95%CI 0.443, 1.183).

A consistently high anti-tumour activity could be observed across supportive studies 017006 and BCM-001 Cohort 2 in NTE subjects with R/R LBCL who received liso-cel as their 2nd line treatment: the **ORR** in study **017006** was **67.6%** (95%CI 55.7, 78) in the leukapheresed analysis set and **80.3%** (95%CI 68.2, 89.4) in the liso-cel treated set. The **ORR** in study **BCM-001 Cohort 2** was **53.1%** (95%CI 34.7, 70.9) and **63%** (95%CI 42.4, 80.6) in the leukapheresed and in the liso-cel treated analysis set, respectively.

Deep and durable responses could be observed in both studies: in study **017006**, the **CRR** was **45.9%** (95%CI 34.2, 57.9) in the leukapheresed analysis set and **54.1%** (95%CI 40.8, 66.9) in the liso-cel treated analysis sets, respectively. With a median follow-up of 15.5 months, the **mDoR** was **12.1** months (95%CI 6.24, NR) and the **mDoCR** was **21.65** months (95%CI 12.09, NR). In study **BCM-002 Cohort 2,** the **CRR** was **37.5%** (95%CI 21.1, 56.3) and **48.1%** (28.7, 68.1) in the leukapheresed and in the liso-cel treated analysis set, respectively. The **mDoR** (as per EMA censoring rules) was **12.1** months (95%CI 2.23, NE) and the **mDoCR** was **12.1** months (95%CI 1.64, NE).

3.3. Uncertainties and limitations about favourable effects

Study population

- Rarer LGBL subtypes were poorly represented (e.g., FL3B 0.5%, THRBCL 2.7%), hampering the possibility for dedicated B/R evaluations. The protocol of PASS JCAR017-BCM-005 has to be adapted to include subjects treated with Breyanzi as 2nd line therapy, expanding the collection of efficacy and safety data in these rare subgroups in the post-marketing setting (**REC**).
- No prospective analysis of CD19 expression was planned in study BCM-003, and central confirmation of disease did not require systematic CD19 expression testing. Overall, no/very limited information with Breyanzi in subjects with CD19-negative disease are currently available from the Breyanzi development programme, as reflected in Section 4.4 of the SmPC. Further characterisation of the correlation between liso-cel efficacy and CD19 expression (as assessed by either flow cytometry or IHC at the time of relapse) is needed and data will be provided post opinion.

- Subjects with secondary CNS involvement could be enrolled in study BCM-003, yet only 4 subjects with CNS involvement were actually treated in the pivotal study. Specific B/R evaluations are hampered by the reduced sample size. A warning on the limited clinical experience of use of Breyanzi for secondary CNS lymphoma is already included in section 4.4 of the SmPC.

Results generalisability

- Subgroup analyses for EFS and PFS must be interpreted with caution, due to sample size limitations, yet the treatment effect was, overall, consistent across the most relevant subsets, including subgroups defined by sAAIPI, refractoriness to frontline treatment and prior chemotherapy response status, age, sex and region. Where sufficient data were available, no significant differences in EFS could be observed in subgroups defined by histologic subtypes.
- Male subjects were more frequent in the SOC (66.3%) compared to the liso-cel arm (47.8%): male gender has been associated with a poor prognosis in DLBCL patients treated with rituximab-containing regimens, thus a possible impact of such imbalance on study results cannot be excluded.

Long-term clinical benefit

- Cross-over from SOC to liso-cel was allowed for subjects who failed to achieve CR/PR at week 9 (i.e., after 3 cycles of SOC), experienced disease progression (PD) or were in need to receive a new antineoplastic therapy due to efficacy concerns after week 18 post-randomisation. In principle, the introduction of a one-way cross-over to liso-cel might result in OS evaluations being confounded. On the other hand, it is recognised that anti-CD19 CAR T-cell products are the current 3rd line efficacy standard and introducing the possibility for "in study" cross-over could provide some insight in terms of better treatment sequence (i.e., liso-cel in 2nd line vs. SOC followed by liso-cel in non-responders).

Prognostic/predictive factors

- Univariate and multivariate analyses showed a relationship between a T cell attribute in one of the two cell components of liso-cel and clinical efficacy outcomes. The biological/clinical rationale of this correlation is unclear, and further validation is needed to conclude on its possible predictive value. A consistent trend towards clinical benefit with liso-cel vs. SOC could still be observed acrossthe full range observed for this attribute .

3.4. Unfavourable effects

Unfavorable effects of liso-cel are the generally known identified risks, i.e., CRS, neurotoxicity and hematotoxicity. Comparing both treatment arms of BCM-003 Study, the following observations were made:

- overall, the frequency of TEAEs reported in both treatment arms was similar. Almost all subjects in each arm experienced at least 1 TEAE; hematologic toxicities were the most frequently reported TEAEs in both arms. A majority of subjects in both arms reported Grade 3-4 TEAEs and TEAEs considered related to a study drug;

- the safety profile in subjects in the SOC arm who did not crossover to liso-cel treatment, 80.5% of whom received HDCT, was similar to that expected for subjects who receive HDCT;
- the incidence of the Grade 3-4 TEAEs of neutropenia and lymphopenia appeared higher in the liso-cel arm as compared to the SOC arm. However, this did not result in increased risk of febrile neutropenia and severe infections as the incidence of Grade 3-4 TEAEs of febrile neutropenia and severe infections appeared to be numerically higher in the SOC arm (20.9% each) compared with the liso-cel arm (12.0% and 15.2%, respectively);
- as expected, the frequency of AESIs was greater in the liso-cel arm than in the SOC arm. The majority of AESIs reported in both arms were mild to moderate in severity and manageable with protocol-specified guidelines and/or local standards of care. The most frequently reported AESI category reported in both arms was neurological toxicity (63.7%, liso-cel; 64.1%, SOC), which was defined as all TEAEs within the Nervous system disorders or Psychiatric disorders system organ class;

Specifically, in the liso-cel arm of BCM-003 (n= 92; data cut-off date of 8-March-2021):

- 45 (48.9%) subjects experienced at least one event of CRS. Only 1 subject reported Grade ≥3 CRS, graded according to the Lee criteria, and no Grade 4 or Grade 5 CRS events were reported;
- 11 (12.0%) subjects in the liso-cel arm experienced any grade iiNT. The majority of events were mild to moderate in severity. Four (4.3%) subjects experienced Grade ≥3 iiNT (none were Grade 4 or 5);
- 40 (43.5%) subjects in the liso-cel arm experienced prolonged cytopenia (defined as a Grade ≥3 or higher central laboratory results of decreased hemoglobin, neutrophils, or platelets observed at the Study Day 64 visit for the liso-cel arm, 35 days after liso-cel infusion);
- 14 (15.2%) subjects in the liso-cel arm experienced Grade ≥3 infections;
- Safety profile from the additional follow-up of BCM-003 (data cut-off date of 13-May-2022) was consistent with that previously submitted in the initial SCS.

Safety Analyses in the Pooled 2L and Pooled 3L+ Populations

Overall, the safety profile of liso-cel in the liso-cel-treated analysis set of Study BCM-003 was similar to that observed in the Pooled 2L LBCL Treated Set, and consistent with that observed in the Pooled 3L+ LBCL Treated Set. No new safety concerns were identified. The type and frequency of AESIs were as expected since they are known side effects specific to CAR T-cell therapy. Similar rates of CAR T cell-associated toxicities were observed in the liso-cel-treated analysis set of Study BCM-003, as in the Pooled 2L and Pooled 3L+ LBCL treated populations.

Safety Analyses in the Modified Pooled 2L and Pooled 3L+ Populations

At the dose range of 44 to 120 × 10^6 CAR+ viable T cells, the safety profile of liso-cel was consistent among the liso-cel-treated analysis set of Study BCM-003, the Modified Pooled 2L LBCL Treated Set, and the Modified Pooled 3L+ LBCL Treated Set.

3.5. Uncertainties and limitations about unfavourable effects

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. The disadvantage and limitation is that the MAH applies for an extension of indication with a rather limited follow-up time in the safety data package provided (DCO of 8 March 2021: median follow-up of 5.32 months [range 1.0, 18.0 months] for subjects

treated with liso-cel), which revealed some uncertainties, in particular on long-term safety. However, using the updated data cut-off date (13-May-2022), the follow-up time for Study BCM-003 increased from a median of 5.32 months to a median of 16.43 months and the median follow-up for 2L total and 3L+ total was 15.64 and 11.40 months respectively.

The safety profile of liso-cel as second-line treatment in the intended target population appears acceptable, since no new safety concerns have been identified.

3.6. Effects Table

Table 85. Effects Table for Breyanzi for the treatment of adult patients with DLBCL, HGBCL, PMBCL and FL3B

Effect	Short description	Unit	Treatment (liso-cel)	Control (SOC)	Uncertainties / Strength of evidence	References
Favourable Effects						
BCM-003 Inferential interim analysis at 80% information fraction (DCO 08 Mar 2021)						
Median EFS	IRC assessment	months (95%CI)	10.1 (6.1, NE)	2.3 (2.2, 4.3)	Strong effect but limited follow-up to evaluate the potential for long-term disease control/cure	Study JCAR017-BCM-003 CSR
Median PFS	IRC assessment	months (95%CI)	14.8 (6.6, NE)	5.7 (3.9, 9.4)		
Median OS	IRC assessment	Months (95%CI)	NE (15.8, NE)	16.4 (11.0, NE)	Positive trend, but data were immature	
CRR	IRC assessment	% 95%CI	66.3 (55.7, 75.8)	39.1 (29.1, 49.9)		
BCM-003 Primary analysis (DCO 13 May 2022)						
Median EFS	IRC assessment	months (95%CI)	NE (9.5, NE)	2.4 (2.2, 4.3)	Longer term follow-up data confirmed the clinical effect observed in the 80% IA	Study JCAR017-BCM-003 CSR
Median PFS	IRC assessment	months (95%CI)	NE (12.6, NE)	6.2 (4.3, 8.6)		
Median OS	IRC assessment	Months (95%CI)	NE (29.5, NE)	29.9 (17.9, NE)	Confirmed positive trend, but data still immature	
CRR	IRC assessment	% 95%CI	73.9 (63.7, 82.5)	43.5 (33.2, 54.2)		
Unfavourable Effects (DCO 08 Mar 2021)						
iiNT		N (%)	11/92 (12%)	N/A	Safety profile consistent across treatment lines	Study JCAR017-BCM-003 CSR
Neurological		N (%)	59/92	58/91		

Effect	Short description	Unit	Treatment (liso-cel)	Control (SOC)	Uncertainties / Strength of evidence	References
Toxicity			(64.1%)	(63.7%)		
CRS		N (%)	45/92 (48.9%)	0		
Prolonged cytopenia	≥ Grade 3	N (%)	40/92 (43.5%)	3/91 (3.3%)		
Infections	≥ Grade 3	N (%)	14/92 (15.2%)	19/91 (20.9%)		
Deaths	Overall deaths	N (%)	13/92 (14.1%)	8/91 (8.8%)		
	Due to PD	N (%)	7 (7.6%)	4 (4.4%)		
	Due to TEAES	N (%)	2 (2.2%)	4 (4.4%)		

Abbreviations: CI = confidence interval; CRR = complete response rate; EFS = event-free survival; HR = hazard ratio; IRC=independent review committee; ITT = intent-to-treat; N/A: not applicable; NE = not evaluable; OS = overall survival; PFS = progression-free survival; SOC = standard of care.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The current salvage strategy in 2nd line LBCLs is aimed at achieving high remission rates to maximize clinical benefit from HDCT and ASCT and obtain long-term disease control. For subjects not eligible to ASCT (NTE), limited options are available, and their impact on long-term disease control is unsatisfactory. An unmet medical need for more effective alternatives can be recognised, especially in the high-risk subgroup of patients who are refractory to frontline immunochemotherapy or experience early relapse.

Efficacy data from pivotal study BCM-003 showed how, in the targeted high-risk population, liso-cel was able to induce higher CRR/ORR compared to SOC, which resulted in a clinically relevant and statistically significant prolongation of EFS and PFS. Despite the high rate of subjects who crossed over to liso-cel in the SOC arm and the immaturity of the updated survival analysis, a positive trend could also be observed in terms of OS. Further OS follow up data will be collected post opinion.

A consistent high anti-tumour activity could also be observed also across supportive studies, indicating the possibility to achieve deep and durable responses also in a frailer (NTE), high risk patient population that received Breyanzi as second line treatment, and further supporting the broad claimed indication.

No significant differences in terms of treatment effect were observed across relevant subgroups defined by response status to first-line treatment (primary refractory/relapsed), definition of early relapse and LBCL histology. Although low numbers did not allow for specific B/R evaluations in the rarest subgroups (e.g., PMBCL, FL3B), homogeneity in treatment response and consistency in CD19 expression across all

the considered histologies support the extrapolation of a similar clinical benefit with Breyanzi in the broad claimed indication. Further data in rare LBCL variants will be collected in the post-approval setting.

No new safety concerns were identified in the targeted 2nd line population: the overall safety profile for subjects treated with liso-cel was similar to that of subjects treated with SOC, with notable differences as expected with regard to AESIs that are known side effects specific to CAR T cell therapy. Overall, the reported safety AEs were consistent with those previously observed in the marketed indication (i.e., 3rd+ line LBCL) and were, in most cases, manageable. In particular, similar rates of CAR T-cell-associated toxicities were observed across treatment lines.

3.7.2. Balance of benefits and risks

Based on the available evidence, the clinical benefit of liso-cel as salvage treatment for 2nd line high-risk patients with LBCLs is considered to outweigh the known unfavourable effects with anti-CD19 CAR T cell therapy.

3.7.3. Additional considerations on the benefit-risk balance

The MAH committed to further investigate the efficacy and safety of Breyanzi in subjects with rarer LBCL histologies in PASS study JCAR017-BCM-005, to provide updated long-term data in NTE subjects with R/R LBCL from the final CSRs of studies 017006 and BCM-001 Cohort 2, to further investigate the correlation between CD19 expression of neoplastic cells and Breyanzi activity and to provide final study results including OS follow up data post opinion for study JCAR017-BCM-003.

3.8. Conclusions

The B/R of Breyanzi in the targeted high-risk 2nd line indication is considered positive.

4. Recommendations

Outcome

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

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

Extension of indication to include treatment of adult patients with Second-line (2L) Transplant Intended (TI) Large B-Cell Lymphoma (LBCL) for BREYANZI, based on interim analyses from pivotal study JCAR017-BCM-003; this is a global randomized multicentre Phase III Trial to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell Non-Hodgkin Lymphomas (TRANSFORM); As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The annex II and the Package Leaflet is updated in accordance. The MAH also took the opportunity to implement editorial changes in line to the core SmPC.

Version 2.4 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics, annex II and Package Leaflet and to the Risk Management Plan (RMP) (final version 2.4).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II 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 Yescarta, Kymriah, Minjuvi Polivy, Gazyvaro and Lunsumio within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Breyanzi-H-C-4731-II-0005'