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Application Type	Efficacy Supplement BLA - New Indication
STN	125714/225
CBER Received Date	November 22, 2023
PDUFA Goal Date	May 23, 2024
Division / Office	MHB/DCEH /OCE
Committee Chair	Kristen Britton
Clinical Reviewer(s)	Kristen Britton
Project Manager	Niloofar Kennedy
Priority Review	Yes
Reviewer Name(s)	Qianmiao (Ann) Gao, Ph.D.
Review Completion Date / Stamped Date	May 13, 2024
Supervisory Concurrence	Zhenzhen Xu, Ph.D. Team Leader, FDA/CBER/OBPV/DB/TEB1
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBPV/DB/TEB1
Applicant	Juno Therapeutics, Inc. a Bristol-Myers Squibb Company
Established Name	Lisocabtagene maraleucel (liso-cel, JCAR017)
(Proposed) Trade Name	Breyanzi
Pharmacologic Class	CD19-directed, genetically modified autologous T cell immunotherapy
Formulation(s), including Adjuvants, etc	The investigational product liso-cel is composed of autologous CD4+ and CD8+ T cells that express a CD19-specific CAR.
Dosage Form(s) and Route(s) of Administration	Cell Suspension for Infusion; Intravenous Infusion.
Dosing Regimen	Single dose of 100×10^6 CAR-positive viable T cells
Indication(s) and Intended Population(s)	For the third-line or later (3L+) treatment of adult patients with relapsed or refractory (R/R) Follicular Lymphoma (FL) who have received two or more lines of prior therapy

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GLOSSARY

Abbreviation	Definition
2L	Having received one line of prior therapy for the disease under study (second-line treatment)
2L+	Having received one or more line of therapy for the disease under study (second-line or later treatment)
3L	Having received two lines of prior therapy for the disease under study (third-line treatment)
3L+	Having received two or more lines of prior therapy for the disease under study (third-line or later treatment)
4L+	Having received three or more lines of prior therapy for the disease under study (fourth-line or later treatment)
AE	Adverse Event
AESI	Adverse event of special interest
BOR	Best Overall Response
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CR	Complete Response
CRi	Complete Response with Incomplete Marrow Recovery
CRS	Cytokine Release Syndrome
DLBCL	Diffuse Large B-cell Lymphoma
DNA	Deoxyribonucleic Acid
DOR	Duration Of Response
DSMB	Data Safety Monitoring Board
iiNT	Investigator-identified neurologic toxicity
IL	Interleukin
IRC	Independent Review Committee
IMP	Investigational Medicinal Product
ITT	Intent-to-treat
IV	Intravenous(ly)
JCAR017	lisocabtagene maraleucel, BMS-986387, liso-cel
Kg	Kilogram
Max	Maximum
Min	Minimum
NE	Not estimable, not evaluable
NHL	Non-Hodgkin lymphoma
nPR	Nodular partial response
NR	Not reached, not reported
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease

PEAS	Primary efficacy analysis set
PFS	Progression-Free Survival
PR	Partial Response
RD	Recommended Dose
R/R	Relapsed or Refractory
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SLL	Small Lymphocytic Lymphoma
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event

1. Executive Summary

Lisocabtagene maraleucel (JCAR017, liso-cel) is a CD19-directed genetically modified autologous cellular immunotherapy consisting of autologous T cells that have been transduced with a lentiviral vector encoding an anti-CD19, CD28/4-1BB chimeric antigen receptor (CAR). It was originally approved by the United States (US) Food and Drug Administration (FDA) on February 05, 2021, for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) after two or more lines of systemic therapy. This Efficacy Supplement Biologics Licensure Application (sBLA) seeks accelerated approval of liso-cel for the third-line or later (3L+) treatment of adult patients with relapsed or refractory (R/R) Follicular Lymphoma (FL) who have received two or more lines of prior therapy.

The primary source of evidence to support efficacy and safety evaluation is from a Phase 2, open-label, non-randomized, multicohort study (JCAR017-FOL-001). Efficacy was established based on the primary efficacy endpoint overall response rate (ORR). Of the 94 subjects in the primary efficacy analysis set, there were 90 responders corresponding to an estimated ORR of 95.7% (95% CI: 89.5%, 98.8%). The efficacy was supported by duration of response (DOR) outcome. Among the responders in the primary efficacy analysis set, the median DOR was not reached (NR) with 95% CI of (18.04%, NR).

There were 14 (10.1%) deaths among the 139 subjects who underwent leukaphereses. Of the 107 subjects in the primary safety analysis set, 105 (98.1%) subjects experienced treatment-emergent adverse events (TEAE), and 71 (66.4%) subjects experienced adverse event of special interest (AESI).

I have verified the primary efficacy endpoint and the DOR endpoint analysis results for Study JCAR017-FOL-001. I recommend approval of liso-cel in the proposed indication in this sBLA, as the statistical analysis results provide evidence to support the effectiveness.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin lymphomas (NHL), accounting for about 10% to 20% of all lymphoma cases in Western countries [1, 2].

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1. Summary of major Pre- and Post-submission regulatory activities

Date	Milestone
08/07/2023	Type B Pre-sBLA meeting
11/22/2023	sBLA 125714/205 received
01/06/2024	sBLA Filing Meeting
02/20/2024	Internal Mid-cycle Meeting
05/23/2024	FDA Action Letter Goal Date

(Source: adapted from sBLA 125714/225; FDA reviewer's summary)

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the proposed product comes from Study JCAR017-FOL-001. This memo is focused on this study.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The basis of this statistical memo includes review of clinical study reports, datasets, protocols, and statistical analysis plans submitted under Module 5 of BLA 125714/225.0; and IR response submitted on Feb 22, 2024.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study JCAR017-FOL-001

This is a Phase 2 trial to assess the efficacy and safety of liso-cel in adult subjects with relapsed/refractory (R/R) follicular lymphoma (FL) and marginal zone lymphoma (MZL). The study included four cohorts:

- Cohort 1 (4L+ R/R FL): subjects who have received at least 3 prior lines of systemic therapy
- Cohort 2 (3L R/R FL): subjects who have received 2 prior lines of systemic therapy
- Cohort 3 (2L R/R FL): subjects who have received 1 prior line of combination systemic therapy
- Cohort 4 (3L+ R/R MZL): subjects who have received at least 2 prior systemic therapies

The clinical report submitted in this sBLA was focused on the R/R FL subjects. Therefore, this section focuses on the cohorts of R/R FL subjects, i.e., Cohort 1-3.

6.1.1 Objectives

Primary:

- To evaluate the efficacy of liso-cel in subjects with R/R FL.

Secondary

- To evaluate other measures of efficacy and the safety of liso-cel in subjects with R/R FL.

6.1.2 Design Overview

This is a Phase 2, open-label, non-randomized, multicohort study.

6.1.3 Population

Adult subjects with R/R FL were enrolled with cohort-specific history of treatments.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Leukapheresis:
Leukapheresis collection were to be performed on each eligible subject to obtain sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the production of liso-cel approximately 5 weeks prior to liso-cel administration on Day 1.

Lymphodepleting Chemotherapy (LDC):
Upon notification from the Sponsor that liso-cel would be available, LDC was to be initiated and be completed 2-7 days prior to liso-cel administration.

Liso-cel:
Liso-cel infusion was to be on Day 1.

6.1.6 Sites and Centers

FL subjects were enrolled at 30 sites in 10 countries (Austria, Canada, France, Germany, Italy, Japan, Spain, Sweden, United Kingdom, and United States).

6.1.7 Surveillance/Monitoring

An independent data safety monitoring board (DSMB), composed of a statistician and selected physicians with experience in hematology/oncology and/or T-cell therapy, were to review cumulative study data over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial.

6.1.8 Endpoints

Primary Endpoint:

- ORR, defined as the percentage of subjects with a BOR of CR or PR up to 60 months after liso-cel infusion as determined by IRC charter.

Secondary Endpoints:

- CRR: the percentage of subjects with a CR at any time up to 60 months after liso-cel infusion as determined by IRC charter.
- DOR: the time from first response (CR or PR) to disease progression or death from any cause, whichever occurred first up to 60 months after liso-cel infusion.

Reviewer's note:
For the primary efficacy analysis, the clinical reviewer assessed the response not based on IRC charter as proposed by the applicant, but on FDA algorithm (details in clinical reviewer's memo).

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol and statistical analysis plan are described in the following:

Statistical hypothesis:
Hypothesis testing on ORR and CRR were to be performed in each of the two prespecified testing sequences:

Testing Sequence 1:
Hypotheses were to be tested in the following order:
1. 3L+ r/r FL (Pooled Cohort 1 and 2): H_{01} ORR $\leq$ 60% vs. H_{a1} ORR > 60%
2. 4L+ r/r FL (Cohort 1): H_{02} ORR $\leq$ 50% vs. H_{a2} ORR > 50%
3. 3L+ r/r FL (Pooled Cohort 1 and 2): H_{03} CRR $\leq$ 30% vs. H_{a3} CRR > 30%
4. 4L+ r/r FL (Cohort 1): H_{04} CRR $\leq$ 20% vs. H_{a4} CRR > 20%

Testing Sequence 2:
Hypotheses were to be tested in the following order:
1. 2L r/r FL (Cohort 3): H_{05} ORR ≤ 50% vs. H_{a5} ORR > 50%
2. 2L r/r FL (Cohort 3): H_{06} CRR ≤ 19% vs. H_{a6} CRR > 19%

Reviewer's note:
Per the clinical reviewer's assessment, the data for (b) (4) *was not adequate for approval in this patient population due to small sample size and the population heterogeneity. The evaluation of efficacy in this sBLA focused on 3L+ treatment of R/R FL (i.e., for subjects in Pooled Cohort 1 and 2). Therefore, only the testing results in Testing Sequence 1 were assessed.*

Multiplicity Adjustment:
The Type I error rate within Testing Sequence 1 was controlled at one-sided 0.025 by fixed-sequence testing procedure on H_{01} - H_{04}, i.e., the null hypothesis H_{02} was to be tested only if the null hypothesis H_{01} was rejected, and so on.

The Type I error rate was not controlled across Testing Sequence 1 and 2 because Testing Sequence 1 and 2 were to assess different indications.

Analysis populations:
Leukapheresed (Intent to Treat) Set included all subjects who have signed informed consent, meet all inclusion/exclusion criteria, and underwent leukapheresis.

Liso-cel-treated Analysis Set included all subjects who have received a dose of conforming liso-cel product.

Liso-cel-treated Efficacy Analysis Set included all subjects in the Liso-cel-treated Analysis Set who have positive disease present before liso-cel administration based on IRC assessment. Subjects who do not have baseline assessment repeated after anticancer therapy for disease control and before liso-cel administration were to be excluded from the Liso-cel-treated Efficacy Analysis Set.

Reviewer's note:
Primary Efficacy Analysis Set
The applicant proposed Liso-cel-treated Efficacy Analysis Set as Primary Efficacy Analysis Set. The Primary Efficacy Analysis Set defined by FDA clinical review team was liso-cel-treated Efficacy Analysis Set in the Pooled Cohort 1 and 2 excluding subjects with the duration of follow-up less than 9 months.

Statistical methods:
ORR
Hypotheses on ORR were to be tested by Exact binomial test.

CRR
Hypotheses on ORR were to be tested by Exact binomial test.

DOR
Kaplan-Meier (KM) method was to be used to analyze DOR for responders and DOR for subjects whose BOR was CR or PR.

Two censoring rules were prespecified in SAP for the intercurrent event of start of new anti-lymphoma therapy before PD/death:

"FDA Censoring Rule":
Subject is censored at last adequate assessment date with no evidence of PD before starting new subsequent anti-lymphoma therapy.

"EMA Censoring Rule":
Subject is followed and outcome is considered in the primary efficacy analysis regardless the start of new subsequent anti-lymphoma therapy, until documented PD or death date, whichever is earlier.

The applicant adopted EMA censoring rule for DOR analysis in the primary analysis.

Reviewer's note:
The review team decided to handle the intercurrent event of start of new anti-lymphoma therapy before PD/Death with FDA censoring rule in the primary analysis on DOR, which is determined based on the clinical team's recommendation and discussion between clinical and statistics team.

Interim Analyses:
No interim analysis for efficacy was planned or performed.

Sample size and power calculation:
Cohort 1 (4L+ r/r FL):
A sample size of 50 subjects was planned to be treated, based on one-sided 0.025 Type I error rate and 90% power to detect an ORR of 74% versus 50%, and a CRR of 42% versus 20%, using exact binomial one sample test. The actual number of subjects who received conforming liso-cel was 59.

Cohort 2 (3L r/r FL):
A sample size of 40 subjects was planned to be treated in Cohort 2, leading to a total of 90 subjects for 3L+ FL in Pooled Cohort 1 and 2, based on a Type I error rate of one-sided 0.025 Type I error rate and 90% power to detect an ORR of 77% versus 60%, and a CRR of 48% versus 30%, using exact binomial one sample test. The actual number of subjects who received conforming liso-cel was 48.

Cohort 3 (2L r/r FL):
A sample size of 20 subjects was planned to be treated, based on a Type I error rate of one-sided 0.025 Type I error rate and 80% power to detect an ORR of 80% versus 50%,

and a CRR of 50% versus 19%, using exact binomial one sample test. The actual number of subjects who received conforming liso-cel was 23.

Missing data and Imputation:
No missing data handling or imputation strategy was prespecified or performed for the primary analysis.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Table 2. Key Demographic - Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Age Group (Years) - N (%)					
< 65	34 (57.6)	31 (64.6)	65 (60.7)	18 (78.3)	83 (63.8)
≥ 65 - < 75	18 (30.5)	14 (29.2)	32 (29.9)	5 (21.7)	37 (28.5)
≥ 75	7 (11.9)	3 (6.3)	10 (9.3)	0	10 (7.7)
Sex - N (%)					
Female	24 (40.7)	17 (35.4)	41 (38.3)	6 (26.1)	47 (36.2)
Male	35 (59.3)	31 (64.6)	66 (61.7)	17 (73.9)	83 (63.8)
Ethnicity - N (%)[a]					
Hispanic or Latino	4 (6.8)	1 (2.1)	5 (4.7)	1 (4.3)	6 (4.6)
Not Hispanic or Latino	39 (66.1)	35 (72.9)	74 (69.2)	15 (65.2)	89 (68.5)
Not Reported	16 (27.1)	12 (25.0)	28 (26.2)	7 (30.4)	35 (26.9)
Primary Race - N (%)[b]					
Asian	7 (11.9)	3 (6.3)	10 (9.3)	2 (8.7)	12 (9.2)
Black or African American	3 (5.1)	0	3 (2.8)	1 (4.3)	4 (3.1)
White	31 (52.5)	29 (60.4)	60 (56.1)	9 (39.1)	69 (53.1)
Not Collected or Unknown	18 (30.5)	16 (33.3)	34 (31.8)	11 (47.8)	45 (34.6)

(Source: Adapted from BLA 125714/225.0 Module 5.3.5)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 3. Summary of Prior Anticancer Therapies - Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Number of Lines of Prior Therapies - N (%)					
1	0	0	0	22 (95.7)	22 (16.9)
2	0	47 (97.9)	47 (43.9)	0	47 (36.2)
3	24 (40.7)	1 (2.1)	25 (23.4)	1 (4.3)	26 (20.0)
4	18 (30.5)	0	18 (16.8)	0	18 (13.8)
≥ 5	17 (28.8)	0	17 (15.9)	0	17 (13.1)
Number of Lines of Prior Radiation Therapies[a] - N (%)					
0	54 (91.5)	47 (97.9)	101 (94.4)	22 (95.7)	123 (94.6)
1	2 (3.4)	1 (2.1)	3 (2.8)	0	3 (2.3)
2	2 (3.4)	0	2 (1.9)	1 (4.3)	3 (2.3)
≥ 5	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Number of Lines of Prior Systemic Therapies - N (%)					
1	0	0	0	23 (100.0)	23 (17.7)
2	0	48 (100.0)	48 (44.9)	0	48 (36.9)
3	26 (44.1)	0	26 (24.3)	0	26 (20.0)
4	19 (32.2)	0	19 (17.8)	0	19 (14.6)
≥ 5	14 (23.7)	0	14 (13.1)	0	14 (10.8)

[a] Includes only stand-alone radiotherapies.
(Source: Adapted from BLA 125714/225.0 Module 5.3.5)

6.1.10.1.3 Subject Disposition

Table 4. Subjects Disposition

	4L+ FL Cohort 1	3L FL Cohort 2	2L FL Cohort 3
Leukapheresed (ITT) Set	65	49	25
Leukapheresed but did not Receive Liso-cel	6	1	2
Reason for Not Receiving Liso-cel			
Received Nonconforming Product	3	1	1
Adverse Event	1	0	0
Failure to Meet Inclusion/Exclusion Criteria	1	0	1
Not Reported	1	0	0
Liso-cel-treated Set	59	48	23
Liso-cel-treated Efficacy Set	53	48	23
Subjects Completed Treatment Period	59	47	22
Subjects Discontinued Treatment Period	0	1	1
Primary Reason for Treatment Period Discontinuation			
Adverse Event	0	0	1
Withdrawal by Subject	0	1	0

(Source: Adapted from BLA 125714/225.0 Module 5.3.5; FDA reviewer's summary)

The primary analysis was based on the data cutoff date of 27 January, 2023.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

The primary efficacy evaluation of liso-cel was focused on the indication of 3L+ R/R FL. Efficacy was established based on ORR in the primary efficacy analysis set in the pooled Cohort 1 and 2. Of the 94 subjects, there were 90 responders corresponding to an estimated ORR of 95.7% (95% CI: 89.5%, 98.8%). The null hypothesis H_{01}: ORR ≤ 60% for 3L+ r/r FL was rejected with a one-sided p-value < .0001.

6.1.11.2 Analyses of Secondary Endpoints

DOR

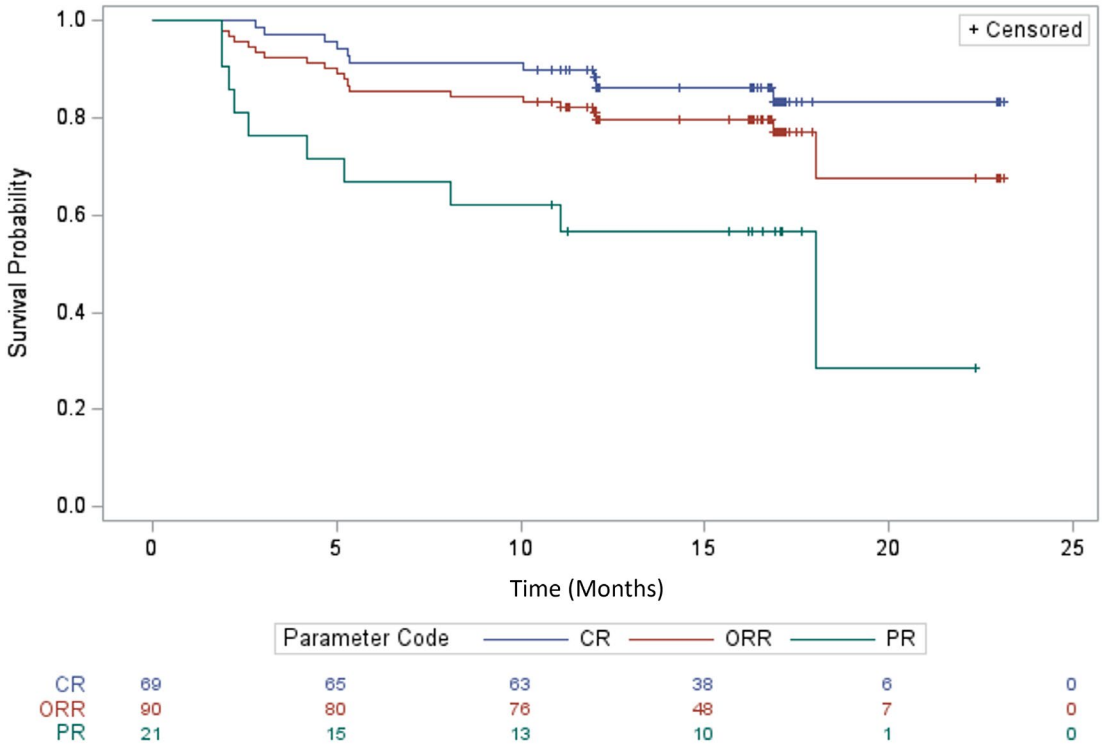
Efficacy assessment was supported by the DOR analyses. Among the 90 responders in the primary efficacy analysis set, the median DOR was not reached (NR) with 95% CI of (18.04%, NR). Table 5 shows the results of DOR assessment. Figure 1 shows the KM curve for DOR, DOR for subjects whose BOR was CR, DOR for subjects whose BOR was PR, among the 90 responders.

Table 5. DOR in the Primary Efficacy Analysis Set

	Primary efficacy analysis set N = 94
Responders	N = 90
Responders with Event, N (%)	20 (22.2)
Death, N (%)	3 (3.3)
Progressive Disease, N (%)	17 (18.9)
Responders Censored, N (%)	70 (77.8)
DOR (months)	
Median [95% CI] [a]	NR (18.0, NR)
Range [b]	1.9, 23.1+
Rate at 12 months, % (95% CI) [c]	80.9 (71.0, 87.7)
Rate at 18 months, % (95% CI) [c]	77.1 (65.9, 85.0)
DOR if best response is CR (months)	N = 69
Median [95% CI] [a]	NR [NR, NR]
Range [b]	2.8, 23.1+
Rate at 12 months, % (95% CI) [c]	88.2 (77.7, 93.9)
Rate at 18 months, % (95% CI) [c]	83.1 (70.0, 90.9)
DOR if best response is PR (months)	N = 21
Median [95% CI] [a]	18.0 [4.2, NR]
Range [b]	1.9, 22.4+
Rate at 12 months, % (95% CI) [c]	56.7 (33.3, 74.7)
Rate at 18 months, % (95% CI) [c]	56.7 (33.3, 74.7)
Follow-Up (Months)	
Median (95% CI) [a]	16.8 (16.3, 17.0)
Min, Max [b]	1.9, 23.1+

[a] Based on Kaplan-Meier estimates.
[b] + indicates a censored value.
[c] KM estimate of probability of continued response at the specified month.
(Source: FDA reviewer's summary)

Figure 1. DOR with BOR being CR/PR in the Primary Efficacy Analysis Set



(Source: FDA reviewer's summary)

CR and PR

Efficacy assessment was further supported by results of CR and PR. The null hypothesis for CRR in the Pooled Cohort 1 and 2 (i.e., CRR ≤ 30% for 3L+ R/R/ FL) was rejected with a one-sided p-value < .0001. Table 6 shows the outcomes of BOR evaluation, including results of ORR, CR, and PR in the primary efficacy analysis set.

Table 6 Response Rate in the Primary Efficacy Analysis Set

	3L+ R/R FL N = 94
Best Overall Response	
Complete Response (CR) N (%)	69 (73.4)
Partial Response (PR) N (%)	21 (22.3)
Stable Disease (SD) N (%)	1 (1.1)
Progressive Disease (PD) N (%)	2 (2.1)
No Evidence of Disease (NED) N (%)	0
Not Evaluable (NE) N (%)	1 (1.1)
Overall Response Rate (ORR)	
N (%)	90 (95.7)
95% CI [a]	(89.5, 98.8)
Complete Response Rate (CRR)	
N (%)	69 (73.4)
95% CI [a]	(63.3, 82.0)
Partial Response Rate (PRR)	
N (%)	21 (22.3)
95% CI [a]	(14.4, 32.1)

[a] Two-sided 95% confidence interval based on exact Clopper-Pearson method.
(Source: FDA reviewer's summary)

6.1.11.3 Subpopulation Analyses

The null hypothesis for ORR and CRR in Cohort 1 (i.e., ORR ≤ 50%, and CRR ≤ 20%, respectively) were both rejected with a one-sided p-value < .0001. Table 7 shows the response outcomes for subject included in the primary efficacy analysis set in Cohort 1 and Cohort 2.

Table 7 Response Rate in Cohort 1 and Cohort 2

	Cohort 1 4L+ R/R FL N = 50	Cohort 2 3L R/R FL N = 44
Best Overall Response		
Complete Response (CR) N (%)	36 (72.0)	33 (75.0)
Partial Response (PR) N (%)	11 (22.0)	10 (22.7)
Stable Disease (SD) N (%)	1 (2.0)	0
Progressive Disease (PD) N (%)	2 (4.0)	0
No Evidence of Disease (NED) N (%)	0	0
Not Evaluable (NE) N (%)	0	1 (2.3)
Overall Response Rate (ORR)		
N (%)	47 (94.0)	43 (97.7)
95% CI [a]	(83.5, 98.7)	(88.0, 99.9)
Complete Response Rate (CRR)		
N (%)	36 (72.0)	33 (75.0)
95% CI [a]	(57.5, 83.8)	(59.7, 86.8)
Partial Response Rate (PRR)		
N (%)	11 (22.0)	10 (22.7)
95% CI [a]	(11.5, 36.0)	(11.5, 37.8)

[a] Two-sided 95% confidence interval based on exact Clopper-Pearson method.
(Source: Adapted from applicant's response submitted on Feb 22, 2024; FDA reviewer's summary)

Table 8 shows the results of DOR assessment for subject included in the primary efficacy analysis set in Cohort 1 and Cohort 2.

Table 8. DOR in Cohort 1 and Cohort 2

	Cohort 1 4L+ R/R FL	Cohort 2 3L R/R FL
Responders	N = 47	N = 43
Responders with Event, N (%)	11 (23.4)	9 (20.9)
Death, N (%)	2 (4.3)	1 (2.3)
Progressive Disease, N (%)	9 (19.1)	8 (18.6)
Responders Censored, N (%)	36 (76.6)	34 (79.1)
DOR (Months)		
Median (95% CI) [a]	NR (18.0, NR)	NR (NR, NR)
Min, Max [b]	1.9, 23.0+	1.9, 23.1+
Continued Response Rate [c]		
At 12 Months % (95% CI)	80.8 (66.3, 89.5)	80.9 (65.4, 90.0)
At 18 Months % (95% CI)	77.1 (61.0, 87.2)	77.4 (60.6, 87.7)
Follow-Up (Months)		
Median (95% CI) [a]	16.9 (16.4, 17.1)	16.2 (12.0, 16.9)
Min, Max [b]	1.9, 23.0+	1.9, 23.1+

[a] Based on Kaplan-Meier estimates.
[b] + indicates a censored value.
[c] KM estimate of probability of continued response at the specified month.
(Source: Adapted from applicant's response submitted on Feb 22, 2024; FDA reviewer's summary)

6.1.11.4 Dropouts and/or Discontinuations

Refer to Table 5 Subjects Disposition in Section 6.1.10.1.3.

6.1.12 Safety Analyses

6.1.12.1 Methods

Descriptive statistics was used to summarize safety outcomes. Deaths were summarized in the leukapheresed set. Treatment-emergent adverse events (TEAE) and adverse event of special interest (AESI) were summarized in the primary safety analysis set defined by the clinical reviewer, which includes the 107 FL patients with two or more prior lines of systemic therapy and treated with conforming liso-cel.

6.1.12.3 Deaths

Among the 139 subjects who underwent leukaphereses, there were 14 (10.1%) deaths. Table 9 describes the primary cause of deaths.

Table 9. Overall Summary of Deaths

Safety Parameter	Number (%) Subjects				
	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2	2L FL Cohort 3	Total 2L+ FL Cohorts 1, 2, 3
Leukapheresed Set	N = 65	N = 49	N = 114	N = 25	N = 139
Deaths	8 (12.3)	5 (10.2)	13 (11.4)	1 (4.0)	14 (10.1)
Primary Cause of Death					
PD	3 (4.6)	2 (4.1)	5 (4.4)	0	5 (3.6)
AE [a]	3 (4.6)	0	3 (2.6)	1 (4.0)	4 (2.9)
Cardiac Event	1 (1.5)	0	1 (0.9)	0	1 (0.7)
Other [b]	0	3 (6.1)	3 (2.6)	0	3 (2.2)
New Malignancy, or Complications from New Malignancy	1 (1.5)	0	1 (0.9)	0	1 (0.7)

[a] Death from AE (NOS) included: Cohort 1: acute respiratory failure hypoxic (LDC-infusion), acute myeloid leukemia (from Day 91 after infusion), progressive multifocal leukoencephalopathy (from Day 91 after infusion), and Cohort 3: HLH (Day 1-30).
[b] Death from other cause included: Cohort 2: 2 cases of COVID-19 and erythema multiform.
(Source: Adapted from BLA 125714/225.0 Module 5.3.5; FDA reviewer's summary)

6.1.12.4 Nonfatal Serious Adverse Events

Table 10 summarizes the TEAEs for the primary safety analysis set. TEAE was defined as an AE that started any time from initiation of liso-cel administration through and including 90 days following liso-cel administration.

Table 10 Overall Summary of TEAEs

	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2
Liso-cel-treated Analysis Set	N = 59	N = 48	N = 107
Subjects with any TEAE	58 (98.3)	47 (97.9)	105 (98.1)
Grade ≥ 3	47 (79.7)	36 (75.0)	83 (77.6)
Grade 5	0	0	0
Serious	15 (25.4)	13 (27.1)	28 (26.2)
Liso-cel-related	54 (91.5)	41 (85.4)	95 (88.8)
Liso-cel-related serious TEAE	13 (22.0)	9 (18.8)	22 (20.6)
Liso-cel-related Grade ≥ 3	33 (55.9)	31 (64.6)	64 (59.8)
Liso-cel-related Grade 5	0	0	0
LDC-related	48 (81.4)	30 (62.5)	78 (72.9)

(Source: Adapted from BLA 125714/225.0 Module 5.3.5; FDA reviewer's summary)

6.1.12.5 Adverse Events of Special Interest (AESI)

Table 11 summarizes the AESI for the primary safety analysis set, including cytokine release syndrome (CRS) and investigator-identified neurologic toxicity (iiNT).

Table 11 Overall Summary of AESI

	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2
Liso-cel-treated Analysis Set	N = 59	N = 48	N = 107
Subjects with any AESI	39 (66.1)	32 (66.7)	71 (66.4)
CRS	35 (59.3)	28 (58.3)	63 (58.9)
iiNT [a]	8 (13.6)	8 (16.7)	16 (15.0)

[a] iiNT was captured using the preferred term Neurotoxicity and graded using NCI CTCAE v.5.0 on the basis of the highest individual symptom grade.
(Source: Adapted from BLA 125714/225.0 Module 5.3.5; FDA reviewer's summary)

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This sBLA seeks accelerated approval of the CAR-T product liso-cel for the third-line or later (3L+) treatment of adult patients with relapsed or refractory (R/R) Follicular Lymphoma (FL) who have received two or more lines of prior therapy.

The primary source of evidence to support efficacy and safety evaluation is from a Phase 2, open-label, non-randomized, multicohort study. Efficacy was established based on the primary endpoint ORR. Of the 94 subjects in the primary efficacy analysis set, there were 90 responders corresponding to an estimated ORR of 95.7% (95% CI: 89.5%, 98.8%). The efficacy was supported by DOR outcomes. Among the responders in the primary efficacy analysis set, the median DOR was not reached (NR) with 95% CI of (18.0%, NR).

There were 14 (10.1%) deaths among the 139 subjects who underwent leukaphereses. Of the 107 subjects in the primary safety analysis set, 105 (98.1%) subjects experienced TEAE, and 71 (66.4%) subjects experienced AESI.

10.2 Conclusions and Recommendations

I have verified the primary efficacy endpoint and the DOR endpoint analysis results for Study JCAR017-FOL-001. The statistical analysis results provide evidence to support the effectiveness of liso-cel in the proposed indication in this sBLA.

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