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Application Type	Efficacy Supplement BLA - New Indication
STN	125714/227
CBER Received Date	11/30/2023
PDUFA Goal Date	05/31/2024
Division / Office	DCEH /OCE/MHB
Committee Chair	Baer Alan
Clinical Reviewer(s)	Cassandra Moran
Project Manager	Kennedy Niloofar
Priority Review	Yes
Reviewer Name(s)	Qianmiao Gao
Review Completion Date / Stamped Date	5/29/2024
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. BMS
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; Intravenous Infusion.
Dosing Regimen	Single dose containing 90 to 110 × 106 CAR-positive viable T cells
Indication(s) and Intended Population(s)	Treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of therapy, including a BTK inhibitor

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GLOSSARY

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse event of special interest
BOR	Best Overall Response
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CRR	Complete Response Rate
CRS	Cytokine Release Syndrome
DL1S	Dose level 1: 50×10^6 CAR+ T cells single-dose regimen
DL2S	Dose level 2: 100×10^6 CAR+ T cells single-dose regimen
DLBCL	Diffuse Large B-cell Lymphoma
DNA	Deoxyribonucleic Acid
DOR	Duration Of Response
DSMB	Data Safety Monitoring Board
iiNT	Investigator-identified neurologic toxicity
IL	Interleukin
IRC	Independent Review Committee
ITT	Intent-to-treat
IV	Intravenous(ly)
JCAR017	lisocabtagene maraleucel, BMS-986387, liso-cel
Kg	Kilogram
MCL	mantle cell lymphoma
Max	Maximum
Min	Minimum
NE	Not evaluable
NHL	Non-Hodgkin lymphoma
NR	Not reached
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PRR	Partial Response Rate
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 regular approval of liso-cel for the treatment of adult patients with relapsed or refractory Mantle Cell Lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor.

The primary source of evidence to support the efficacy and safety evaluation is from a Phase 1, open-label, non-randomized study (017001). Efficacy was established based on the primary efficacy endpoint overall response rate (ORR). Of the 68 subjects in the primary efficacy analysis set, there were 58 responders corresponding to an estimated ORR of 85.3% (95% CI: 74.6%, 92.7%). The efficacy was supported by duration of response (DOR) outcome. Among the responders in the primary efficacy analysis set, the median DOR was 13.3 (95% CI: 6.0, 23.3) months.

Among the 88 subjects who have received conforming liso-cel product, there were 44 (50.0%) deaths, and 47 (53.4%) subjects who experienced treatment-emergent serious adverse events.

I have verified all the efficacy results for Study 017001 on a descriptive basis. Because the threshold for hypothesis testing was not agreed upon for any endpoint, there is no inferential statistical procedure to apply to the efficacy data. Therefore, the sufficiency of these data to provide substantial evidence of effectiveness is deferred to the clinical review team.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Mantle cell lymphoma (MCL) is an aggressive form of non-Hodgkin lymphoma (NHL) that comprises between 6% and 8% of all NHL cases [1]. Initial response rates to treatment are high, but relapse is common. Outcomes for patients with relapsed or refractory (R/R) MCL are poor. Patients who progress after Bruton's tyrosine kinase inhibitor (BTKi) have a particularly poor outcome with median OS of 6-10 months [2]. There is no clearly established standard of care for treatment of R/R MCL.

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
08/11/2023	Pre-BLA meeting
11/03/2023	sBLA 125714/227 received
01/14/2024	sBLA Filing Meeting
02/28/2024	Internal Mid-cycle Meeting
05/31/2024	FDA Action Letter Goal Date

(Source: adapted from sBLA 125714/227; 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 017001. 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 125714/227.0.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study 017001

This was a Phase 1, open-label, multicohort, multigroup trial of liso-cel for adult subjects with R/R B-cell NHL. The study included two cohorts:

- DLBCL Cohort: enrolled subjects with diffuse large B cell lymphoma (DLBCL)
- MCL cohort: enrolled subjects with relapsed or refractory MCL

The clinical report submitted in this sBLA was focused on the subjects with R/R MCL. Therefore, this section focuses on the MCL cohort. The MCL cohort includes a dose-finding (DF), dose-expansion (DE), and dose-confirmation (DC) group.

6.1.1 Objectives

Objectives in the DF, DE, and DC groups are as follows:

DF: to evaluate the dose level and schedule of liso-cel needed for adequate safety and antitumor activity.

DE: to further assess the safety and efficacy of liso-cel.

DC: to further evaluate the safety and efficacy of liso-cel at the recommended dose level and schedule of administration.

6.1.2 Design Overview

MCL Cohort was a Phase 1, open-label study which included a DF, DE, and DC group.

6.1.3 Population

Adult subjects with R/R MCL who have received ≥ 2 prior lines of systemic MCL therapy and having been treated with an alkylating agent, Bruton's tyrosine kinase inhibitor, and rituximab (or other CD20-targeted agents).

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 4 weeks prior to liso-cel administration.

Anticancer Treatments between Screening and Lymphodepleting Chemotherapy (Bridging Therapy)
If deemed necessary by the treating physician, anticancer treatment was allowed for disease control during liso-cel manufacture.

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

Liso-cel:
Liso-cel infusion was to be on Day 1. Liso-cel was administered as separate IV infusions that consisted of CD8+ CAR+ T cells and CD4+ CAR+ T cells.

6.1.6 Sites and Centers

The study was conducted at 14 sites in the United States.

6.1.7 Surveillance/Monitoring

An independent data safety monitoring board (DSMB) were to review cumulative study data approximately quarterly over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint:
Overall Response Rate (ORR), defined as the proportion of subjects with a best overall response (BOR) of either CR or PR based by IRC assessment.

Secondary Endpoints:
Complete Response Rate (CRR), defined as the proportion of subjects with a BOR of CR by IRC assessment.

Duration of Response (DOR), defined as the time from the first documentation of CR or PR to the earlier date of disease progression or death.

Reviewer's note:
Success criteria were not defined for the study.

The primary efficacy analysis results reported in this memo is based upon the response data determined by FDA clinical review team using FDA adjudicated response as per IRC by 2014 Lugano criteria, rather than the applicant's assessment (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 were to be performed in the order of ORR → CRR:

ORR:
H_{01}: ORR ≤ 40% vs. H_{a1} ORR > 40%

CRR:
H_{02}: CRR ≤ 18% vs. H_{a2} ORR > 18%

Reviewer's note:
The proposed historical ORR of 40% and CRR of 18% in the null hypotheses were not agreed upon with FDA.

Based on clinical team's assessment, the results from MCL cohort provide substantial evidence of effectiveness in support of traditional approval. The basis of the conclusion of substantial evidence of effectiveness is the magnitude of benefit primarily driven by high and durable ORR. The ORR and DOR represent a clinical benefit for this patient population because there are no other effective therapies in the heavily pretreated R/R MCL setting.

Multiplicity Adjustment:
The Type I error rate was controlled at one-sided 0.025 by fixed-sequence testing procedure in the order of ORR → CRR, i.e., the null hypothesis on CRR was to be tested only if the null hypothesis on ORR was rejected.

Analysis populations:
Leukapheresed (Intent to Treat) Set included all subjects who have signed informed consent, met 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.

Primary Analysis Set (PAS) included subjects with MCL that have PET-positive disease at baseline and have failed at least 2 prior lines of systemic therapy including an alkylating agent, a BTKi, and rituximab (or other CD20-targeted agent), treated at the recommended regimen with conforming product, and from the DF, DE, and DC groups.

Reviewer's note:
Primary Analysis Set (PAS)
The Primary Analysis Set for Efficacy defined by FDA clinical review team was PAS, proposed by the applicant but limited to those subjects who received the proposed marketing dose of 90 to 110 × 10^6 CAR+ T cells.

Leukapheresed (Intent to Treat) Set
During the review of sBLA, the applicant proposed to further limit the Leukapheresed Set to include only subjects who have received 2 prior lines of therapy. The clinical team considered the revision acceptable as it aligns with the population in PAS.

Statistical methods:
ORR
The hypothesis on ORR was to be tested by Exact binomial test.

CRR
The hypotheses on CRR was to be tested by Exact binomial test.

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

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

Sample size and power calculation:
The planned sample size for DC group was at least 30 subjects, for a planned total of at least 50 in the PAS from DF, DE, and DC groups combined. The sample size of 50 subjects was determined based on one-sided 0.025 Type I error rate and 93% power to detect an ORR of 65% versus 40%, using exact binomial one sample test.

The planned sample size of 50 subjects would provide 97% power to detect a CRR of 40% versus 18% based on one-sided 0.025 Type I error rate.

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

	Total
Parameter	N=88
Age, years	
n	88
Median	68.5
Min, Max	36, 86
Age Group, n (%)	
≥ 65 years	64 (72.7)
≥ 75 years	18 (20.5)
Sex, n (%)	
Male	67 (76.1)
Female	21 (23.9)
Race Group, n (%)	
White	77 (87.5)
Others: Include Other Races	8 (9.1)
Unknown or Missing	3 (3.4)
Race, n (%)	
Asian	5 (5.7)
Black or African American	2 (2.3)
Native Hawaiian or Other Pacific Islander	1 (1.1)
White	77 (87.5)
Not Reported	3 (3.4)
Ethnicity, n (%)	
Hispanic Or Latino	4 (4.5)

(Source: Adapted from BLA 125714/227.0 Module 5.3.5; FDA reviewer's summary)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

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

	Total
	N=88
Prior Treatment, n (%) [a]	
Hematopoietic stem cell transplant	29 (33.0)
Allogeneic	6 (6.8)
Autologous	26 (29.5)
Radiotherapy	24 (27.3)
Systemic treatment	88 (100)
Number of prior systemic treatments [b]	
N	88
Mean (StD)	3.7 (1.94)
Median	3.0
Min, Max	1, 11
Number of prior systemic treatments [b] n(%)	
1 prior regimen	3 (3.4)
2 prior regimens	28 (31.8)
3 prior regimens	19 (21.6)
4 prior regimens	12 (13.6)
≥5 prior regimens	26 (29.5)

[a] Only regimens post diagnosis of MCL are included. Bridging anticancer therapy for disease control was not counted as a prior systemic regimen unless the outcome was complete response.
[b] HSCT was not included as systemic therapy.
(Source: Adapted from BLA 125714/227.0 Module 5.3.5; FDA reviewer's summary)

6.1.10.1.3 Subject Disposition

Table 4: Subject Disposition in Liso-cel-treated Analysis Set

Disposition Parameter	Liso-cel-treated Analysis Set N=88 n (%)	Primary Analysis Set N=68 n (%)
Completed study	30 (34)	20 (23)
Still on study	10 (11)	9 (10)
Discontinued study	48 (54)	39 (57)
Death	44 (50)	35 (40)
Withdrew Consent	4 (5)	4 (5)

(Source: Adapted from BLA 125714/227.0 Module 5.3.5; FDA reviewer's summary)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Efficacy was established based on ORR in the primary efficacy analysis set. Of the 68 subjects, there were 58 responders corresponding to an estimated ORR of 85.3% (95% CI: 74.6, 92.7). The null hypothesis H_{01}: ORR ≤ 40% was rejected with a one-sided p-value < .0001.

6.1.11.2 Analyses of Secondary Endpoints

DOR

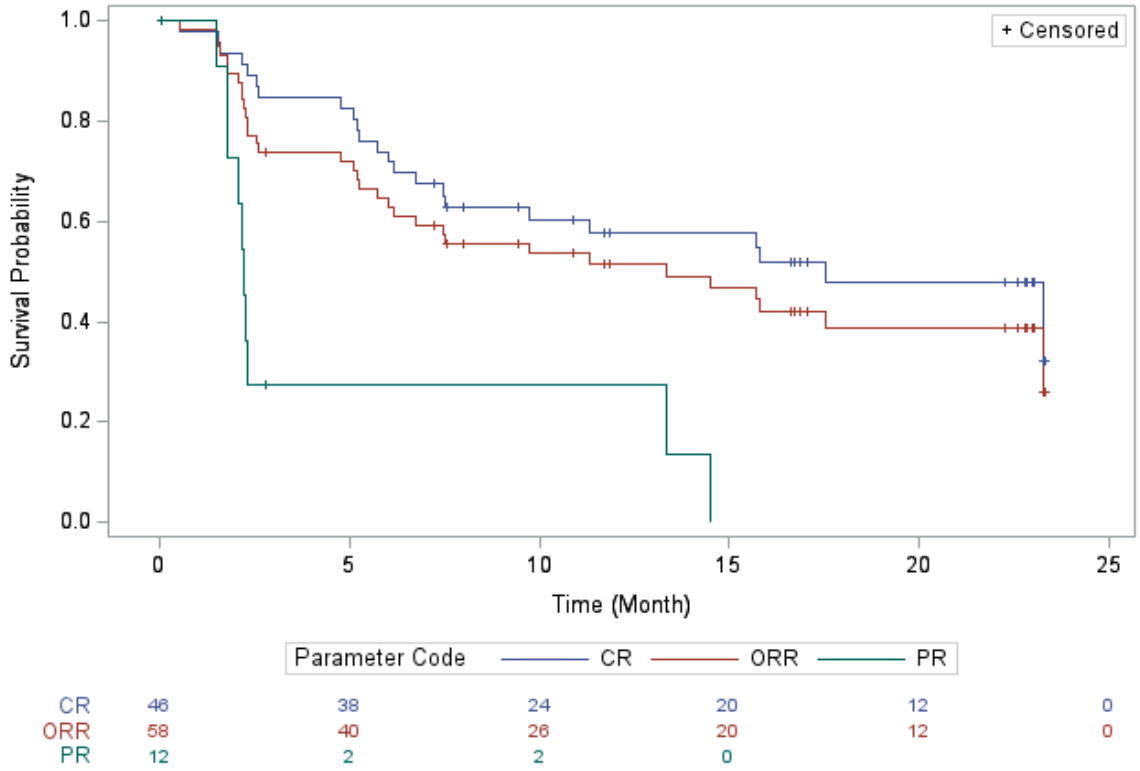
Efficacy assessment was supported by the DOR analyses. Among the 58 responders in the primary efficacy analysis set, the median DOR was 13.3 (95% CI: 6.0, 23.3) months. Table 5 shows the results of DOR assessment. Figure 1 shows the KM curve for DOR, DOR for subjects whose BOR was CR, DOR for subjects whose BOR was PR, among the 58 responders.

Table 5: Duration of Response in the Primary Efficacy Analysis Set

Number of Responders	58
DOR (months)	
Median [95% CI][a]	13.3 [6.0, 23.3]
Range	0.0^{+}, 23.3^{+}
Rate at 12 months (%) [95% CI][b]	51.4 [37.5, 63.7]
Rate at 18 months (%) [95% CI][b]	38.8 [25.0, 52.4]
DOR if Best Response is CR (months)	N=46
Median [95% CI][a]	17.5 [7.5, NR[c]]
Range	0.6, 23.3^{+}
Rate at 12 months (%) [95% CI][b]	57.8 [41.9, 70.7]
Rate at 18 months (%) [95% CI][b]	48.0 [31.6, 62.6]
DOR if Best Response is PR (months)	N=12
Median [95% CI][a]	2.2 [1.8, 13.3]
Range	0.0^{+}, 14.5
Rate at 12 months (%) [95% CI][b]	27.3 [6.5, 53.9]
Rate at 18 months (%) [95% CI][b]	0.0 [NE, NE[d]]
Duration of Follow-up	N = 58
Median [95% CI][a]	22.2 [16.7, 22.8]

CI=confidence interval; NR=not reached.
[a] Kaplan-Meier method was used to obtain 2-sided 95% CIs.
[b] KM estimate of probability of continued response at the specified month.
[c] Not reached
[d] Not evaluable
+ Indicates a censored value.
(Source: FDA reviewer's summary)

Figure 1. KM curve for DOR, CR, and PR - 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 (i.e., H_{02}: CRR ≤ 18%) was rejected with a one-sided p-value < .0001. Table 6 shows the outcomes of CR and PR in the primary efficacy analysis set.

Table 6: Response Outcomes in the Primary Efficacy Analysis Set

Outcome	Primary Efficacy Analysis Set N=68
Overall Response Rate, n (%) [95% CI] [a]	58 (85.3) (74.6, 92.7)
Complete Response, n (%) [95% CI] [a]	46 (67.6) (55.2, 78.5)
Partial Response, n (%) [95% CI] [a]	12 (17.6) (9.5, 28.8)

[a] 2-sided 95% exact Clopper-Pearson Confidence Interval.
(Source: FDA reviewer's summary)

6.1.11.3 Subpopulation Analyses

DC Group

The analysis on response was performed for subjects in the DC group of primary analysis set. The outcomes as shown in Table 7 were consistent with the findings in the primary analysis set.

Table 7: Response Outcomes in the DC Group of PAS

Outcome	DC Group in PAS N=54
Overall Response Rate, n (%) [95% CI] [a]	46 (85.2) (72.9, 93.4)
Complete Response, n (%) [95% CI] [a]	38 (70.4) (56.4, 82.0)
Partial Response, n (%) [95% CI] [a]	8 (14.8) (6.6, 27.1)

[a] 2-sided 95% exact Clopper-Pearson Confidence Interval.
(Source: FDA reviewer's summary)

Leukapheresed (Intent to Treat) Set

The analysis on response was repeated in the Leukapheresed Set. The outcomes as shown in Table 8 were consistent with the findings in the primary analysis set.

Table 8: Response Outcomes in the Leukapheresed Set

Outcome	Leukapheresed Set N=89
Overall Response Rate, n (%) [95% CI] [a]	65 (73.0) (62.6, 81.9)
Complete Response, n (%) [95% CI] [a]	51 (57.3) (46.4, 67.7)
Partial Response, n (%) [95% CI] [a]	14 (15.7) (8.9, 25.0)

[a] 2-sided 95% exact Clopper-Pearson Confidence Interval.
(Source: FDA reviewer's summary)

6.1.11.4 Dropouts and/or Discontinuations

Refer to Table 4 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, Serious Treatment-emergent adverse events (TEAE), and adverse event of special interest (AESI) were summarized in the Liso-cel-treated Analysis Set (n=88) which is considered as primary safety analysis set by the clinical team.

6.1.12.3 Deaths

Among the 88 subjects who received conforming liso-cel product, there were 44 (50.0%) deaths.

6.1.12.4 Nonfatal Serious Adverse Events

Table 9 summarizes the Treatment-emergent Serious Adverse Events in the primary safety analysis set.

Table 9: Treatment-emergent Serious Adverse Events Reported in ≥ 2 Subjects by System Organ Class and Preferred Term - Liso-cel-treated Analysis Set

	Number (%) of Subjects
System Organ Class and Preferred Term	N=88
Subjects with any Serious TEAE	47 (53.4)
Immune system disorders	21 (23.9)
Cytokine release syndrome	21 (23.9)
Infections and infestations	9 (10.2)
Upper respiratory tract infection	2 (2.3)
Nervous system disorders	8 (9.1)
Encephalopathy	2 (2.3)
Psychiatric disorders	7 (8.0)
Confusional state	5 (5.7)
Mental status changes	2 (2.3)
General disorders and administration site conditions	4 (4.5)
Pyrexia	3 (3.4)
Metabolism and nutrition disorders	4 (4.5)
Decreased appetite	2 (2.3)
Respiratory, thoracic and mediastinal disorders	2 (2.3)
Pleural effusion	2 (2.3)

(Source: Adapted from BLA 125714/227.0 Module 5.3.5; FDA reviewer's summary)

6.1.12.5 Adverse Events of Special Interest (AESI)

Table 10 summarizes the AESI for the primary safety analysis set.

Table 10: Overall Summary of AESI

Liso-cel-treated Analysis Set	N = 88
Subjects with any treatment-emergent AESI	
CRS	54 (61.4)
iiNT [a]	27 (30.7)
Prolonged Cytopenia	35 (39.8)
Grade ≥ 3 Infection	13 (14.8)
MAS	0
Hypogammaglobulinemia	6 (6.8)
IRR	2 (2.3)
SPM	3 (3.4)
TLS	2 (2.3)
Autoimmune Disorders	0

[a] iiNT was defined as events from the nervous system disorders or psychiatric disorders (ND/PD) system organ classes reported in subjects who received liso-cel and for whom the investigator identified the event(s) as a CAR+ T-cell-related neurological toxicity by selecting the CNS AE checkbox and related to liso-cel on the AE eCRF.
(Source: Adapted from BLA 125714/227.0 Module 5.3.5; FDA reviewer's summary)

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This sBLA seeks regular approval of liso-cel for the treatment of adult patients with relapsed or refractory Mantle Cell Lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor.

The primary source of evidence to support efficacy and safety evaluation is from a Phase 1, open-label, non-randomized study (017001). Efficacy was established based on the primary efficacy endpoint overall response rate (ORR). Of the 68 subjects in the primary efficacy analysis set, there were 58 responders corresponding to an estimated ORR of 85.3% (95% CI: 74.6%, 92.7%). The efficacy was supported by duration of response (DOR) outcome. Among the responders in the primary efficacy analysis set, the median DOR was 13.3 (95% CI: 6.0, 23.3) months.

Among the 88 subjects who have received conforming liso-cel product, there were 44 (50.0%) deaths, and 47 (53.4%) subjects experienced treatment-emergent serious adverse events.

10.2 Conclusions and Recommendations

I have verified all the efficacy results for Study 017001 on a descriptive basis. Because the threshold for hypothesis testing was not agreed upon for any endpoint, there is no inferential statistical procedure to apply to the efficacy data. Therefore, the sufficiency of these data to provide substantial evidence of effectiveness is deferred to the clinical review team.

REFERENCES

1. Rule, S. The modern approach to mantle cell lymphoma. Hematological Oncology 2019.
2. Kumar, A, F Sha, A Toure, A Dogan, A Ni, CL Batlevi, MLM Palomba, C Portlock, DJ Straus, A Noy, SM Horwitz, A Moskowitz, P Hamlin, CH Moskowitz, MJ Matasar, AD Zelenetz, and A Younes, 2019, Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: progressive shortening in response duration and survival after each relapse, Blood Cancer J, 9(6):50.