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Division / Office	DCGT/OTAT
Committee Chair	Kimberly Schultz
Clinical Reviewer(s)	Megha Kaushal (Efficacy) Kavita Natrajan (Safety)
Project Manager	Kay Owosela, Zakaria Ganiyu
Priority Review	Yes
Reviewer Name(s)	Cong Wang
Review Completion Date / Stamped Date	
Supervisory Concurrence	Zhenzhen Xu, Ph.D. Team Leader, FDA/CBER/OBE/DB/TEB
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBE/DB/TEB
	John Scott, Ph.D. Director, FDA/CBER/OBE/DB
Applicant	Juno Therapeutics, a Celgene Company
Established Name	Lisocabtagene Maraleucel
(Proposed) Trade Name	Breyanzi (JCAR017)
Pharmacologic Class	CD 19-directed genetically-modified autologous T cell
Formulation(s), including Adjuvants, etc	75% (v/v) Cryostor® CS10 [containing 7.5% dimethylsulfoxide (v/v)], 24% (v/v) Multiple Electrolytes for Injection, Type 1, and 1% (v/v) of 25% albumin (human)
Dosage Form(s) and Route(s) of Administration	Single or two intravenous infusion(s)
Dosing Regimen	A single dose of 50 to 110 × 10 ⁶ CAR+ viable T cells
Indication(s) and Intended Population(s)	Treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies

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GLOSSARY

Abbreviation	Definition
2L+	Second-line or later
3L+	Third-line or later
AESI	Adverse event of Special Interest
ALL	Acute lymphoblastic leukemia
BLA	Biologics Licensure Application
BOR	Best overall response
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CR	Complete Response
CRS	Cytokine release syndrome
DLBCL	Diffuse large B-cell lymphomas
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FL	Follicular lymphoma
FL3B	Follicular lymphoma Grade 3B
HGL	High-grade lymphoma
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
IRC	Independent Review Committee
IND	Investigational new drug
KM	Kaplan-Meier
MCL	Mantle cell lymphoma
NA	Not applicable
NHL	Non-Hodgkin lymphoma
NR	Not reached
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial response
R/R	Relapsed or refractory
SAE	Serious adverse event
SC	Steering Committee
SD	Stable Disease
SRC	Safety review committee
STD	Standard deviation
tFL	transformed follicular lymphoma
US	United States

1. EXECUTIVE SUMMARY

JCAR017 is a CD19-directed genetically modified autologous cellular immunotherapy. This Biologics License Application (BLA) seeks licensure of JCAR017 for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies, including diffuse large B cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade lymphoma (HGL), and primary mediastinal large B-cell lymphoma (PMBCL).

The primary source of evidence to support this application is the DLBCL cohort of a Phase 1, single-arm, open-label and multicenter study (Study 017001). The DLBCL cohort enrolled subjects with DLBCL de novo, transformed follicular lymphoma (tFL), HGL, PMBCL and follicular lymphoma Grade 3B (FL3B). In this cohort, a total of 344 subjects underwent leukapheresis. Of these 344 subjects, 269 were treated with JCAR017. 256 of the 269 treated subjects in the DLBCL cohort were efficacy-evaluable and therefore their results constituted the primary evidence of efficacy for the product. The pre-specified primary efficacy endpoint is overall response rate (ORR), which is defined as the proportion of subjects with a best overall response (BOR) of either complete response (CR) or partial response (PR), as assessed by Independent Review Committee (IRC)-FDA algorithm. Results summarized in this memo are based on a data cut-off date of August 12, 2019.

The ORR as assessed by the IRC-FDA algorithm was 71.5% (183/256; 95% CI: 65.5%, 76.9%) and the lower limit of the 95% exact Clopper-Pearson confidence interval was 65.5% which was above the pre-specified null hypothesis rate of 40%. One hundred and thirty-six (53.1%) subjects had a best response of CR, and 47 (18.4%) subjects had a best response of PR. The median duration of response (DOR) was 16.7 months (95% CI: 6.0, NR) for all responders with a median follow-up time of 12.9 months (95% CI: 11.3, 17.0). The median DOR for the partial responders was 2.0 months (95% CI: 1.2, 2.4) and for complete responders, was not reached yet as of the data cut-off date (95% CI: 16.8, NR). Among the subjects in the DLBCL efficacy set, the median progression-free survival (PFS) was 3.5 months (95% CI: 3.0, 8.8) with a median follow-up time of 12.8 months (12.1, 17.7) and the median overall survival (OS) was 21.1 months (95% CI: 13.3, NR) with a median follow-up time of 17.5 months (95% CI: 13.2, 17.9). The majority of efficacy-evaluable subjects (192/256; 75%) received the study drug at the recommended dose (i.e., a single dose of 50 to 110×10^6 CAR+ viable T cells). In these 192 subjects, the ORR as assessed per IRC-FDA algorithm was 73.4% (95% CI: 66.6%, 79.5%) with a CR rate of 54.2% (95% CI: 46.8%, 61.4%).

Deaths occurred in 50.9% (137/269) of treated subjects in Study 017001 DLBCL cohort and most deaths reported after the first JCAR017 infusion were due to disease progression (116; 116/137=84.7%). In the Study 017001 DLBCL treated set, 122 of 269 subjects (45.4%) reported treatment-emergent serious adverse events (SAEs). The most frequently reported treatment-emergent SAEs were cytokine release syndrome (CRS) (44; 44/122=36.1%) and encephalopathy (14; 14/122=11.5%).

Study 017001 DLBCL cohort met the efficacy criteria for the ORR primary endpoint with the rejection of the pre-specified null hypothesis rate of 40%. The statistical analysis results provide sufficient evidence to support the safety and effectiveness of JCAR017 for the proposed indication in this BLA.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

B-cell malignancies are a heterogeneous group of neoplasms that include chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL) and Non-Hodgkin lymphoma (NHL). NHL cancers further can be classified as aggressive NHL diseases and include DLBCL, PMBCL, mantle cell lymphoma (MCL), follicular lymphoma (FL) and tFL.

NHL is the seventh most common cancer in adults in the United States (US), accounting for 4.2% of new cancers and 3.3% of all cancer-related deaths (Howlader, 2019)¹. Diffuse large B-cell lymphomas represent the most common NHL subtype worldwide, accounting for 30% of all adult NHL cases (Chao, 2013)². An estimated 150,000 people worldwide are diagnosed with DLBCL each year (Ferlay, 2019)³. The incidence of DLBCL is known to increase with age, with approximately half of all cases occurring in adults ages ≥ 65 years of age (Howlader, 2019)¹. There are other less common large B-cell lymphoma subtypes, for example, PMBCL accounts for only 2% to 3% of B-cell NHL and 10% of large B-cell lymphomas, while FL3B comprised only 1% of NHL cases. While the prevalence of each of the less common subtypes is relatively small compared with DLBCL not otherwise specified, collectively they represent a considerable number of patients with similarly limited options for control of R/R disease, and therefore are an important subgroup of the R/R large B-cell lymphoma population.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently available FDA approved therapies for R/R third-line or later (3L+) large B-cell lymphoma include Yescarta (regular approval) with an ORR of 72% (95% CI: 62%, 81%), Kymriah (regular approval) with an ORR of 50% (95% CI: 38%, 62%), Polivy (accelerated approval) with an ORR of 45% for polatuzumab vedotin-piiq + bendamustine + a rituximab product; an ORR of 18% for bendamustine + a rituximab product, and Keytruda (accelerated approval) with an ORR of 45% (95% CI: 32%, 60%) for PMBCL.

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

Table 1 summarizes the major pre- and post-submission regulatory activities associated with this BLA.

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

Date	Milestone
05/29/2015	IND 16506 submission
04/27/2016	Orphan Designation granted for the treatment of DLBCL
12/15/2016	Breakthrough Therapy designation granted for the treatment of R/R aggressive large B-cell NHL
09/07/2017	Orphan designation granted for the treatment of FL
10/20/2017	Regenerative Medicine Advanced Therapy designation granted for the treatment of R/R aggressive large B-cell NHL
07/12/2018	Orphan designation granted for the treatment of PMBCL
08/05/2019	Pre-BLA meeting
12/18/2019	BLA 125714 submission
02/14/2020	BLA filed. Filing letter issued to the Applicant
03/16/2020	Safety 3-month update
11/1/2020	PDUFA action due date

(Source: Module 1.6.3 Meeting correspondence Table 1; FDA statistical reviewer's summary)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting an in-depth and 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 the Study 017001 DLBCL cohort, which is the focus of this review memo.

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

The basis of this statistical memo includes the review of

- Clinical study reports and data sets submitted in modules 2 and 5 of BLA 125714/0.2
- Safety 3-month update submitted in BLA 125714/2.0

5.3 Table of Studies/Clinical Trials

A robust global safety dataset was provided in this BLA for a total of 357 subjects treated with JCAR017, which included both subjects with R/R large B-cell lymphoma and those with other B-cell malignancy indications from Study 017001 and 7 supportive ongoing JCAR017 clinical studies (6 interventional studies and 1 long-term follow-up study).

Table 2 summarizes the 8 studies included in the BLA submission. Results from Study

017001 formed the primary evidence of safety and efficacy of JCAR017 for this BLA application.

Table 2. Studies in the BLA application

Study code	Study population	Study design	# of subjects treated*
017001 (pivotal)	Adult 3L+ large B-cell lymphoma and 2L+ MCL	Phase 1, open-label, single-arm, multicohort, multicenter, monotherapy, seamless design trial	286**
JCAR017-BCM-001 (EU and Japan)	Adult 3L+ large B-cell lymphoma	Phase 2, open-label, single-arm, multicohort, multicenter, monotherapy trial	20
017007	Adult 3L+ large B-cell lymphoma	Phase 2, open-label, single-arm, multicenter, monotherapy trial	0
JCAR017-BCM-002	Adult 3L+ large B-cell lymphoma	Phase 1/2, open-label, multi-arm, parallel, multicohort, multicenter combination therapy trial	23
017006	Adult 2L+ transplant-noneligible large B-cell lymphoma	Phase 2, open-label, single-arm, multicenter, monotherapy trial	5
017004	Adult with R/R CLL or small lymphocytic lymphoma	Phase 1/2, open-label, single arm, multicenter monotherapy and combination therapy trial	23
JCAR017-BCM-004	Pediatric and young adult R/R B-cell ALL and B-cell NHL	Phase 1/2, open-label, single-arm, multicohort, multicenter, 2-stage design monotherapy trial	1
GC-LTFU-001 (Long-term follow-up)	Adult and pediatric treated with a Juno/Celgene CAR T-cell therapy, including JCAR017	Global, non-interventional, multicenter trial	19

* Data cutoff date = August 12, 2019 for Study 017001; data cutoff date = February 22, 2019 for other supportive studies

** Including 269 subjects in the DLBCL cohort and 17 subjects in the MCL cohort (Source: Clinical Overview Table 33, p. 123; FDA statistical reviewer’s summary)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study # 017001

Study 017001 was the pivotal study that constitutes the primary evidence of safety and efficacy of JCAR017 in the treatment of adult subjects with R/R large B-cell lymphoma after at least 2 prior therapies.

6.1.1 Objectives

Primary:

- To evaluate the safety of JCAR017
- To assess the antitumor activity of JCAR017 (i.e., measured by ORR)

Secondary objectives included assessing the CR rate and durability of antitumor activity, estimating the PFS and OS of subjects treated with JCAR017, characterizing the PK profile, assessing health-related quality of life (HRQoL) and outcomes research.

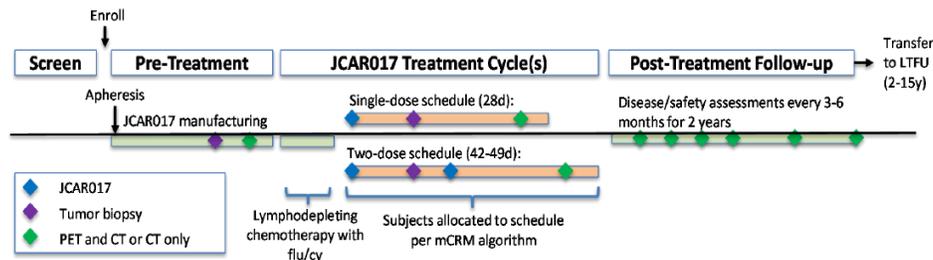
6.1.2 Design Overview

Study 017001 was an open-label, multicenter, multicohort, seamless designed, Phase 1 study to determine the safety, antitumor activity, and PK of JCAR017 in 2 disease cohorts: adult subjects with 3L+ DLBCL cohort and second-line or later (2L+) MCL cohort. The DLBCL cohort enrolled the subjects with DLBCL de novo, tFL, HGL, PMBCL and FL3B; and who were treated with an anthracycline and rituximab (or other CD20-targeted agent) and had relapsed or refractory disease after at least 2 lines of therapy or after auto-Hematopoietic stem cell transplantation (HSCT). The MCL cohort enrolled the subjects with MCL who received at least one prior line of MCL therapy.

Each cohort includes a dose finding group used to evaluate and refine the dose and schedule of JCAR017; a dose escalation group used to assess the efficacy and safety of JCAR017 at a given dose regimen; and a dose confirmation group used to further assess the safety and efficacy of JCAR017 at the regimen selected by the Steering Committee (SC) for further evaluation in Study 017001.

The DLBCL cohort is the focus of the JCAR017 BLA application. Figure 1 below gives the overview of design schematic.

Figure 1. Study design schematic



CT = computed tomography; d = days; flt/cy = fludarabine/cyclophosphamide; LTFU = long-term follow-up; mCRM = modified continual reassessment method; PET = positron emission tomography.

(Source: Original BLA 125714/0.1 Module 2 Clinical Efficacy Overview Figure 1, p.18)

6.1.3 Population

Key elements of eligibility criteria for Study 017001 are listed below.

- Eligible subjects were ≥ 18 years of age and must have relapsed or been refractory to at least 2 lines of therapy or relapsed after auto-HSCT.
- Subjects were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Note: An ECOG performance status of 2 was allowed until Protocol Amendment 5).

- Patients with primary central nervous system lymphoma were excluded from the study, although patients with secondary central nervous system involvement of lymphoma were permitted.
- Patients with prior allogeneic hematopoietic stem cell transplant (allo-HSCT) were permitted.

6.1.4 Study Treatments or Agents Mandated by the Protocol

- Dose Level 1: 50 x10⁶ CAR+ T cells (single-dose and 2-dose regimens tested: DL1S and DL1D, respectively)
- Dose Level 2: 100 x10⁶ CAR+ T cells (single-dose regimen only; DL2S)
- Dose Level 3: 150 x10⁶ CAR+ T cells (single-dose regimen only; DL3S)

Per agreement of the SC, based on the preliminary evidence for an efficacy dose-response, as well as acceptable safety in both DL1S and DL2S to date, a recommended regimen of a single dose of 100 x10⁶ CAR+ T cells (DL2S) was selected for the DLBCL cohort dose confirmation group.

Reviewer Comments:

1. According to the clinical review team, the dose range between 50 x10⁶ CAR+ T cells and 110 x10⁶ CAR+ T cells was determined to be the recommended regimen of dose for this product. Please see the clinical review memo for details.

6.1.6 Sites and Centers

Fourteen (14) study sites in US.

6.1.7 Surveillance/Monitoring

An independent Data Safety Monitoring Board (DSMB) reviewed cumulative study data from Study 017001 approximately every 3 months over the course of the study to evaluate safety, protocol conduct, and the scientific validity and integrity of the trials. Ad hoc meetings of the DSMB were held if safety events occurred which either the DSMB or the sponsor felt required urgent evaluation by the DSMB members.

A safety review committee (SRC), comprising all Principal Investigators who had treated subjects (or qualified designee) and the Sponsor's medical monitor, statistician, and safety representative, regularly assessed the safety and efficacy of JCAR017 administration throughout the trial. The SRC was allowed to recommend overriding the Bayesian algorithm's dose allocation decision, by either allocating subjects to a dose regimen that was estimated to be safer, or to a higher dose level if the escalated dose level appeared likely to be efficacious and safe enough.

6.1.8 Endpoints and Criteria for Study Success

In Study 017001, the primary endpoint was ORR, which was defined as the proportion of subjects with a BOR of either CR or PR, as assessed by IRC-FDA algorithm. All subjects who did not meet the criteria for an objective response by the analysis cut-off date were considered as non-responders.

The study protocol also included several secondary efficacy endpoints:

- a. CR rate, defined as the proportion of subjects with a BOR of CR per IRC-FDA algorithm.
- b. DOR, defined as the time from first response (CR or PR) to progressive disease (PD) or death, whichever occurs earlier, per IRC-FDA algorithm.
- c. PFS, defined as the time from first infusion of JCAR017 to PD, per IRC-FDA algorithm, or death, whichever occurs earlier.
- d. PFS ratio, defined as the ratio of PFS events on the most recent line of therapy prior to JCAR017 to those on JCAR017.
- e. OS, defined as the time from treatment with JCAR017 to the date of death.
- f. Measurement of HRQoL changes as assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and the (b) (4)

Reviewer Comments:

1. In the Applicant's submission, the response was assessed by IRC based on the Lugano 2014 criteria. However, per clinical review team request, we used the IRC-FDA algorithm as the primary method to assess response in this memo.
2. CRR, DOR, PFS and OS were major secondary efficacy endpoints in the BLA application.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol are described in the following:

Statistical hypothesis:

The analysis of the primary efficacy endpoint was performed by testing $H_0: \pi \leq 40\%$ vs. $H_a: \pi > 40\%$, where π is the ORR per IRC-FDA assessment.

The null hypothesis rate of 40% is justified as follows. The previous clinical trial results showed that the ORR in patients with large aggressive B-cell lymphomas who have received at least 2 prior therapies were low, ranging from 12% to 46% (Pettengell 2012⁴, Rigacci 2012⁵, Mounier 2013⁶, Nagle 2013⁷, Wang 2013⁸, Czuczman 2014⁹, Jacobsen 2015¹⁰, Van Den Neste 2016¹¹). A meta-analysis conducted based on those studies using a random-effects model led to an estimated ORR at 30% (95% CI: 24%, 38%).

Therefore, the Applicant specified the ORR of 40% under the null hypothesis, which is slightly above the upper limit of 95% CI obtained from the meta-analysis.

Analysis populations:

- *Leukapheresed Set* included all subjects in the DLBCL cohort who had signed informed consent, who met all inclusion/exclusion criteria, and who underwent leukapheresis.
- *JCAR017-treated Analysis Set* included all subjects in the DLBCL cohort who received at least 1 dose of JCAR017 cell product. JCAR017-treated analysis set was used for safety analyses in this BLA application.
- *JCAR017-treated Efficacy Analysis Set* (i.e., *DLBCL Efficacy Set*) included all subjects in the JCAR017-treated Analysis Set who had PET-positive disease present before JCAR017 administration based on IRC-FDA assessment. The *DLBCL Efficacy Set* was used for efficacy analyses in this BLA application.

- *Primary Analysis Set (PAS)* included subjects in the dose finding, dose escalation and dose confirmation groups who failed at least 2 therapies in the DLBCL cohort with DLBCL de novo or tFL, or HGL with myelocytomatosis oncogene and B-cell lymphoma gene 2 or 6 rearrangements with DLBCL histology, treated at 1 recommended regimen.
- *Per Protocol (PP) DLBCL Analysis Set* represented a subset of the JCAR017-treated analysis Set, including subjects in the DLBCL cohort who were compliant with the major requirements of the study protocol.

Statistical methods:

Efficacy analyses were conducted on the DLBCL Efficacy set. For the primary analysis, IRC-FDA assessment of disease status would be used.

Primary endpoint

The primary efficacy endpoint, ORR, was calculated along with the 2-sided 95% exact Clopper-Pearson confidence interval (CI). The number and proportion of subjects who were evaluated as CR, PR, stable disease (SD), PD, non-PD, or not evaluable/not done were also tabulated.

Secondary endpoints

- a. CR rate: CR rate was calculated along with the 2-sided 95% exact Clopper-Pearson CI.
- b. DOR: The Kaplan-Meier (KM) method was used to estimate the median DOR along with the 95% CI. The reverse KM method was used to estimate the median follow-up time for DOR with the 95% CI.
- c. PFS: The analysis of PFS was conducted similarly to the analysis of DOR.
- d. OS: The OS analysis included all available survival information with long-term follow-up data. Data from surviving subjects were censored at the last time that the subject was known to be alive. The distribution function of OS would be estimated using KM method and the median OS along with 95% CI would be presented.

Interim analyses:

The study protocol originally planned to divide the overall one-sided alpha level of 0.025 between the interim analysis with an alpha level of 0.01 and the primary analysis with an alpha level of 0.021, using interpolated spending function based on the PAS. However, as the primary analysis set was changed to a broader population based on FDA's recommendations, the interim analysis was actually not performed, and all the alpha (i.e., one-sided 0.025) was preserved for the primary analysis.

Note: The Agency review team had no objections regarding the interim analysis change because the originally interim analysis plan on the PAS was no longer applicable to the current broader population.

Sample size and power calculation:

The study was originally designed to focus the primary efficacy analysis solely on the subjects in the dose confirmation group of PAS. A sample size of 75 subjects was calculated to provide approximately 98% of study power to exclude a 40% overall response rate if the true rate was 65% at a one-sided alpha level of 0.025.

Further, the FDA clinical review team requested the applicant to extend the primary analysis population from PAS to DLBCL Efficacy Set by incorporating the subjects with other types of large B-cell lymphoma (e.g., PMBCL and FL3B) and treated with more than one dose regimens in the dose finding group and dose escalation group, in addition to those in the dose confirmation groups, leading to a total of 256 subjects for the primary analysis. No formal sample size and power calculation was conducted based on the DLBCL Efficacy Set.

Sensitivity analyses:

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

- The response determined by IRC assessment in the DLBCL Efficacy set
- The Leukapheresed set per IRC-FDA algorithm and IRC assessment, respectively
- The JCAR017-treated analysis set per IRC-FDA algorithm and IRC assessment, respectively

Subgroup analyses:

In the DLBCL Efficacy set, subgroup analyses were performed on the following variables based on patient's baseline status:

- Age: < 65 vs. \geq 65 years at the time of the first JCAR017 infusion
- Sex: male vs. female
- Ethnicity: Hispanic or Latino vs. not Hispanic or Latino
- Race: White vs. Other races
- Dose range
- ECOG score at screening: 0 vs. 1 vs. 2
- Prior HSCT status: yes vs. no
- Prior response status: refractory vs. relapsed to last prior therapy.
- Anticancer therapy for disease control: yes vs. no
- Disease burden

Note: Some grouping of classes was considered if there were too few subjects in some subgroups.

Missing data:

All subjects who did not meet the criteria for an objective response by the analysis cut-off date were considered as non-responders. For assessment of DOR, PFS and OS, loss to follow-up subjects would be censored at the date of the last adequate disease assessment on or prior to the earliest censoring event.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

For analyses of efficacy and safety in Study 017001 DLBCL cohort, Table 3 summarizes the study analysis sets. Leukapheresed set included 344 subjects. Of 344 subjects, 269 (78.2%) subjects received JCAR017 that constituted the safety analysis set, and 256 (74.4%) subjects were efficacy evaluable that constituted the primary efficacy set.

Table 3. Analysis sets

Analysis Set	N (%)
Screened set	347
Leukapheresed set	344*
Eligible set	341
JCAR017-treated analysis set	269 (78.2)
DLBCL Efficacy set	256 (74.4)

* More subjects were included in the Leukapheresed set than the Eligible set due to subjects having enrolled in the study although they did not meet eligibility criteria. In some cases, the subjects were allowed on study after discussion with the Applicant and in other cases the deviations were identified retrospectively.

(Source: FDA statistical reviewer’s summary)

6.1.10.1.1 Demographics

Table 4 shows the demographic information for subjects in the Leukapheresed set, JCAR017-treated analysis set and DLBCL Efficacy set, respectively. Subjects’ demographics in these three analysis sets were similar.

Table 4. Demographics for Leukapheresed set, Safety and Efficacy analysis sets

	Leukapheresed set n=344	Treated analysis set n=269	DLBCL Efficacy set n=256
Age (years)			
Mean (STD)	60.0 (13.1)	60.1 (13.3)	60.3 (13.3)
Median (min, max)	62 (18, 86)	63 (18, 86)	63 (18, 86)
Sex n (%)			
Female	122 (35.5%)	95 (35.3%)	87 (34.0%)
Male	222 (64.5%)	174 (64.7%)	169 (66.0%)
Race n (%)			
White	294 (85.5%)	232 (86.2%)	219 (85.5%)
Black or African American	17 (4.9%)	12 (4.5%)	12 (4.7%)
Asian	13 (3.8%)	11 (4.1%)	11 (4.3%)
Other	20 (5.8%)	14 (5.2%)	14 (5.5%)
Ethnicity n (%)			
Hispanic or Latino	34 (9.9%)	26 (9.7%)	24 (9.4%)
Other	310 (90.1%)	243 (90.3%)	232 (90.6%)

(Source: FDA statistical reviewer’s summary)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 5 shows the baseline characteristics for subjects in the Leukapheresed set, JCAR017-treated analysis set and DLBCL Efficacy set, respectively. There were no outstanding differences with respect to subject baseline characteristics among these three analysis sets.

Table 5. Baseline characteristics for Leukapheresed set, Safety and Efficacy analysis sets

	Leukapheresed set n=344	Treated analysis set n=269	DLBCL Efficacy set n=256
Age at initial diagnosis (years)			
n	344	269	256
Mean (STD)	57.9 (13.1)	58.0 (13.4)	58.2 (13.4)
Median (min, max)	60 (18, 82)	60 (18, 82)	60.5 (18, 82)
BMI (kg/m^2)			
n	302	269	256
Mean (STD)	26.4 (5.5)	26.4 (5.4)	26.5 (5.4)
Median (min, max)	25.4 (15.7, 51.6)	25.6 (15.7, 51.6)	25.6 (15.7, 51.6)
Weight (kg)			
n	304	269	256
Mean (STD)	78.6 (19.8)	78.6 (19.4)	79.0 (19.7)
Median (min, max)	76.0 (40.1, 182.2)	76.1 (40.1, 182.2)	76.2 (40.1, 182.2)
ECOG score at screening n (%)			
0	126 (36.6%)	110 (40.9%)	104 (40.6%)
1	210 (61.1%)	155 (57.6%)	148 (57.8%)
2	8 (2.3%)	4 (1.5%)	4 (1.6%)
CrCl pre-LDC n (%)*			
< 60 mL/min	58 (16.9%)	51 (19.0%)	49 (19.1%)
≥ 60 mL/min	240 (70.0%)	218 (81.0%)	207 (80.9%)
LVEF at screening n (%)*			
≥ 40% to < 50%	19 (5.5%)	13 (4.8%)	13 (5.1%)
≥ 50%	311 (90.4%)	256 (95.2%)	243 (94.9%)

BMI = body mass index; CrCl = creatinine clearance; LDC = lymphodepleting chemotherapy; LVEF = left ventricular ejection fraction.

*There were 46 subjects with missing baseline CrCl pre-LDC data and 14 subjects with missing baseline LVEF data in Leukapheresed set.

(Source: FDA statistical reviewer's summary)

6.1.10.1.3 Subject Disposition

At the time of the data cutoff date 08/12/2019, out of the 269 subjects in the DLBCL cohort JCAR017-treated analysis set who received treatment with JCAR017, 35 had completed the study, 103 were still on study in the follow-up portion of the study, and 131 had discontinued. Among the 131 subjects who discontinued, the most common reason for discontinuation was death (N = 121).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Table 6 shows the best response per IRC-FDA algorithm for Leukapheresed set, JCAR017-treated analysis set and DLBCL Efficacy set, respectively. Additionally, the responses were also presented in the dose range between 50 and 110 x10⁶ CAR+ T cells as recommended by clinical review team.

Table 6. Best response per IRC-FDA algorithm (Leukapheresed set, Treated and Efficacy analysis sets)

	Leukapheresed set, n=344	Treated analysis set, n=269	DLBCL Efficacy set, n=256	Dose range 50 -110x10 ⁶ , n=192
ORR (CR+PR), n (%)	203 (59.0%)	190 (70.6%)	183 (71.5%)	141 (73.4%)
95% CI	(53.6%, 64.3%)	(64.8%, 76.0%)	(65.5%,76.9%)	(66.6%,79.5%)
Complete response rate, n (%)	148 (43.0%)	140 (52.0%)	136 (53.1%)	104 (54.2%)
95% CI	(37.7%, 48.4%)	(45.9%, 58.1%)	(46.8%,59.4%)	(46.8%,61.4%)
Partial response rate, n (%)	55 (16.0%)	50 (18.6%)	47 (18.4%)	37 (19.3%)
95% CI	(12.3%, 20.3%)	(14.1%, 23.8%)	(13.8%,23.7%)	(13.9%,25.6%)
Stable disease, n (%)	14 (4.1%)	11 (4.1%)	11 (4.3%)	8 (4.2%)
Progressive disease, n (%)	63 (18.3%)	56 (20.8%)	54 (21.1%)	37 (19.3%)
Non-progressive disease, n (%)	7 (2.0%)	6 (2.2%)	2 (0.8%)	0
Not evaluable, n (%)	57 (16.6%)	6 (2.2%)	6 (2.3%)	6 (3.1%)

(Source: FDA statistical reviewer's analysis)

In the DLBCL Efficacy set of 256 subjects, 183 subjects (71.5%) had a best overall response of CR or PR, as determined by IRC-FDA algorithm. The lower limit of the 95% exact Clopper-Pearson confidence interval for ORR was 65.5% which is well above the pre-specified null hypothesis rate of 40%. Among the 183 responders, 136 subjects (53.1%) had a best response of CR, and 47 (18.4%) subjects had a best response of PR.

For analysis results of the primary endpoint ORR based on the Leukapheresed and JCAR017-treated analysis sets, the lower limits of the 95% exact Clopper-Pearson confidence intervals for ORR were 53.6% and 64.8%, respectively, which are both above the null hypothesis rate of 40%.

Table 7 shows the best response based on IRC assessment for Leukapheresed set, JCAR017-treated analysis set and DLBCL Efficacy set, respectively. Analysis of ORR including CR rate assessed by IRC results in the same conclusion as assessed by IRC-FDA algorithm.

Table 7. Best response per IRC assessment (Leukapheresed set, Treated and Efficacy analysis sets)

	Leukapheresed set, n=344	Treated analysis set, n=269	DLBCL Efficacy set, n=256
ORR (CR+PR), n (%)	207 (60.2%)	192 (71.4%)	185 (72.3%)
95% CI	(54.8%, 65.4%)	(65.6%, 76.7%)	(66.3%, 77.7%)
Complete response rate, n (%)	150 (43.6%)	140 (52.0%)	136 (53.1%)
95% CI	(38.3%, 49.0%)	(45.9%, 58.1%)	(46.8%, 59.4%)
Partial response rate, n (%)	57 (16.6%)	52 (19.3%)	49 (19.1%)
95% CI	(12.8%, 20.9%)	(14.8%, 24.6%)	(14.5%, 24.5%)
Stable disease, n (%)	32 (9.3%)	29 (10.8%)	28 (10.9%)
Progressive disease, n (%)	35 (10.2%)	30 (11.2%)	29 (11.3%)
Non-progressive disease, n (%)	5 (1.5%)	5 (1.9%)	4 (1.6%)
Not evaluable, n (%)	65 (18.9%)	13 (4.8%)	10 (3.9%)

(Source: FDA statistical reviewer’s analysis)

To evaluate the concordance in assessment of disease status, best overall response graded by IRC-FDA algorithm and IRC assessment for DLBCL Efficacy set was shown in Table 8.

Table 8. Concordance between IRC-FDA algorithm and IRC assessment in the evaluation of the best overall response for DLBCL Efficacy set

Frequency	IRC assessment						
	CR	PR	SD	PD	Non-PD	Not evaluable	Total
IRC-FDA algorithm							
CR	135	1	0	0	0	0	136
PR	1	46	0	0	0	0	47
SD	0	0	10	1	0	0	11
PD	0	2	18	28	2	4	54
Non-PD	0	0	0	0	2	0	2
Not evaluable	0	0	0	0	0	6	6
Total	136	49	28	29	4	10	256

(Source: FDA statistical reviewer’s summary)

The assessments based on IRC-FDA and IRC assessment made the same best overall response call in 88.7% (=227/256) of the cases. 181 subjects were determined to be responders by both IRC-FDA algorithm and IRC (135 CRs, 46 PRs) assessment. Among responders assessed by IRC-FDA algorithm, IRC assessment was in agreement in 98.9% (=181/183) of the cases. Among responders assessed by IRC, IRC-FDA algorithm was in agreement in 97.8% (=181/185) of cases.

6.1.11.2 Analyses of Secondary Endpoints

Duration of response (DOR)

Table 9 summarizes the DOR results for DLBCL Efficacy set per IRC-FDA and IRC assessments, respectively. [Additionally, the DOR results were also presented in the dose](#)

range between 50 and 110 x10⁶ CAR+ T cells per FDA algorithm as recommended by the clinical review team.

Table 9. DOR results for DLBCL Efficacy set (per IRC-FDA, IRC assessments)

	IRC-FDA algorithm	IRC assessment	Dose range 50-110x10 ⁶
Number of subjects achieved CR or PR, n	183	185	141
Number of events, n (%)	85 (46.5%)	78 (42.1%)	66 (46.8%)
Progression	83 (45.4%)	75 (40.5%)	64 (45.4%)
Death	2 (1.1%)	3 (1.6%)	2 (1.4%)
Censored, n (%)	98 (53.5%)	108 (57.9%)	75 (53.2%)
Ongoing	59 (32.2%)	60 (32.4%)	47 (33.3%)
Completed the Study	24 (13.1%)	24 (13.0%)	18 (12.8%)
Received a new anticancer therapy	13 (7.1%)	21 (11.4%)	9 (6.4%)
Proceeded to HSCT	2 (1.1%)	2 (1.1%)	1 (0.7%)
DOR (months)			
median	16.7	NR	16.7
95% CI	(6.0, NR)	(9.1, NR)	(6.0, NR)
Follow-up (months)			
median	12.9	12.0	16.4
95% CI	(11.3, 17.0)	(11.2, 16.7)	(11.7, 17.0)
Percentage of subjects with response duration (%)*			
≥6 months	56.9	60.4	57.1
≥12 months	52.0	54.7	52.8
≥18 months	48.3	52.1	48.3
≥24 months	48.3	52.1	48.3

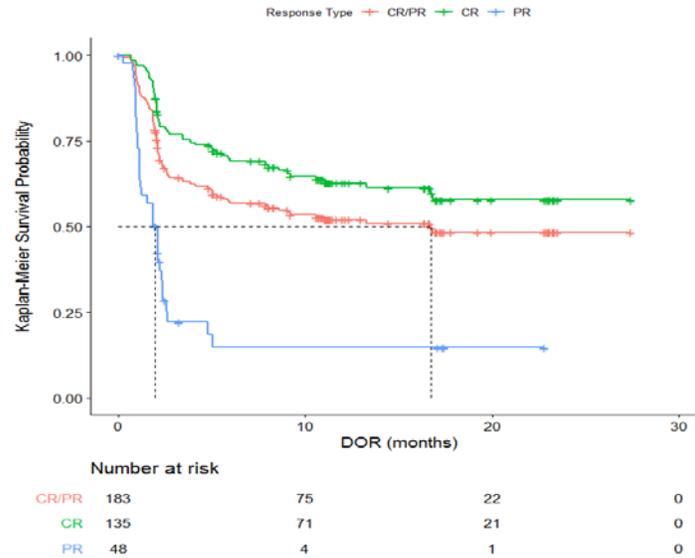
*The estimated percentage of subjects with response duration ≥ 6, 12, 18, and 24 months was presented with 95% CIs using the KM method.
(Source: FDA statistical reviewer’s analysis)

For analysis of DOR per IRC-FDA algorithm, the overall median was 16.7 months with a lower 95% limit of 6.0 months and an unattainable upper limit. The median follow-up time was 12.9 months (95% CI: 11.3, 17.0). For analysis per IRC assessment, the overall median of DOR was not reached with a lower 95% limit of 9.1 months and an unattainable upper limit. The median follow-up time was 12.0 months (95% CI: 11.2, 16.7). For the subjects in the recommended dose range 50 - 110 x10⁶ CAR+ T cells, the overall median of DOR was 16.7 months with a lower 95% limit of 6.0 months and an unattainable upper limit. The median follow-up time was 16.4 months (95% CI: 11.7, 17.0).

Figure 2 shows Kaplan-Meier curves of DOR per IRC-FDA algorithm by response type (CR or PR). Complete responders had substantially longer DOR than the partial responders. The median DOR for the partial responders was 2.0 months (95% CI: 1.2,

2.4) and the median DOR was not reached for complete responders (95% CI: 16.8, NR), leading to the median DOR for the complete responders and partial responders combined group as 16.7 months with an unattainable upper limit.

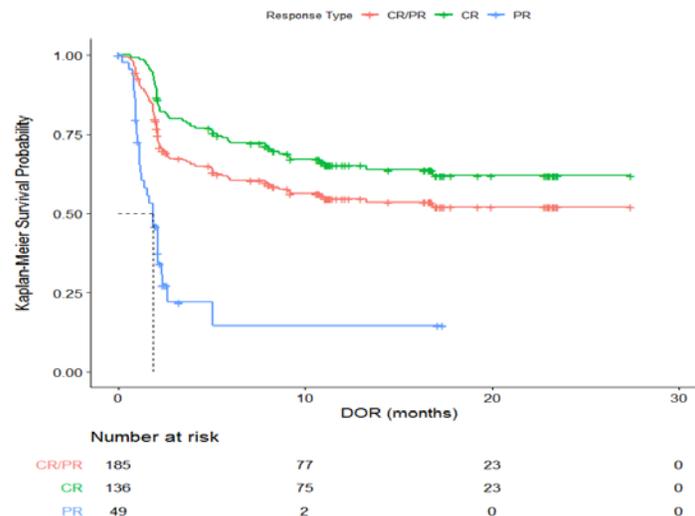
Figure 2. Kaplan-Meier curves of DOR per IRC-FDA algorithm by response type



(Source: FDA statistical reviewer’s analysis)

Figure 3 shows Kaplan-Meier curves of DOR per IRC assessment by response type (CR or PR). Similar to the results of DOR assessed by IRC-FDA algorithm, complete responders had substantially longer DOR than the partial responders. The median DOR for the partial responders was 1.9 months (95% CI: 1.2, 2.3) and the median DOR was not reached for complete responders (95% CI: NR, NR), leading to the median DOR for the complete responders and partial responders combined group not being reached.

Figure 3. Kaplan-Meier curves of DOR per IRC assessment by response type



(Source: FDA statistical reviewer’s analysis)

Progression-free Survival (PFS)

Table 10 summarizes the PFS results per IRC-FDA and IRC assessments, respectively.

Table 10. PFS results for DLBCL Efficacy set (per IRC-FDA, IRC assessments)

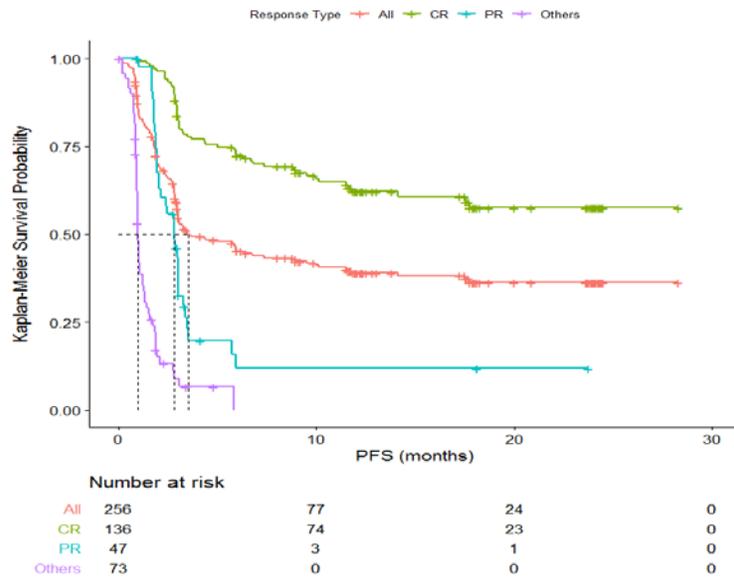
	IRC-FDA algorithm, n=256	IRC assessment, n=256
Number of events, n (%)	146 (57.0%)	126 (49.2%)
Progression	139 (54.3%)	114 (44.5%)
Death	7 (2.7%)	12 (4.7%)
Censored, n (%)	110 (43.0%)	130 (50.8%)
Ongoing	59 (23.0%)	61 (23.8%)
Completed the Study	24 (9.4%)	24 (9.4%)
Discontinued the Study	1 (0.4%)	1 (0.4%)
Received a new anticancer therapy	24 (9.4%)	42 (16.4%)
Proceeded to HSCT	2 (0.8%)	2 (0.8%)
PFS (months)		
median	3.5	6.8
95% CI	(3.0, 8.8)	(3.5, 17.7)
Follow-up (months)		
median	12.8	12.3
95% CI	(12.1, 17.7)	(12.0, 17.5)
Percentage of subjects with PFS at		
6 months	45.2	51.4
12 months	39.0	44.1
18 months	36.3	42.1
24 months	36.3	42.1

(Source: FDA statistical reviewer’s analysis)

For analysis of PFS per IRC-FDA algorithm, the overall median was 3.5 months with a lower 95% limit of 3.0 months and an upper limit of 8.8 months. The median follow-up time was 12.8 months (95% CI: 12.1, 17.7). For analysis per IRC assessment, the overall median of PFS was 6.8 months with a lower 95% limit of 3.5 months and an upper limit of 17.7 months. The median follow-up time was 12.3 months (95% CI: 12.0, 17.5).

Figure 4 shows Kaplan-Meier curves of PFS per IRC-FDA algorithm by response type (CR, PR or Non-responders). Complete responders had substantially longer PFS than the partial responders and non-responders. The median PFS was not reached for the complete responders, and reached at 2.8 months (95% CI: 2.0, 3.3) for the partial responders and 0.99 months (95% CI: 0.95, 1.2) for the non-responders, respectively.

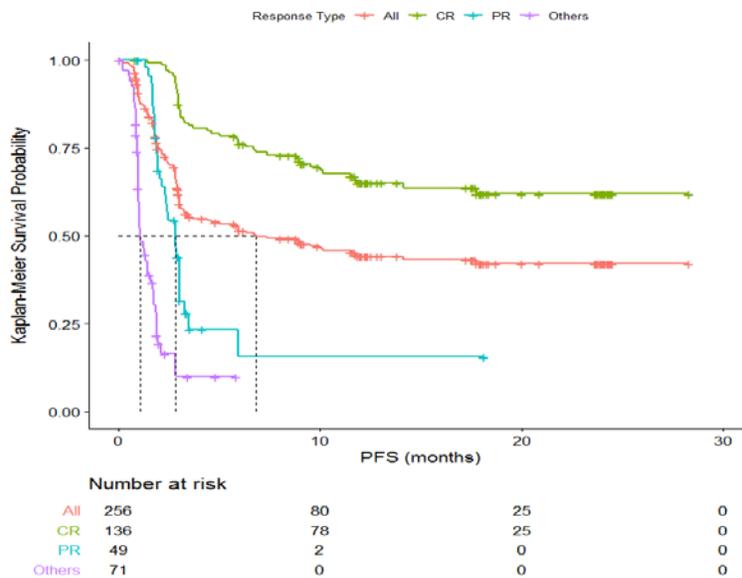
Figure 4. Kaplan-Meier curves of PFS per IRC-FDA algorithm by response type



(Source: FDA statistical reviewer’s analysis)

Figure 5 shows Kaplan-Meier curves of PFS per IRC assessment by response type (CR, PR or Non-responders). Similar to results of PFS assessed by IRC-FDA algorithm, complete responders had substantially longer PFS than the partial responders and non-responders. The median PFS was not reached for the complete responders, and reached at 2.8 months (95% CI: 2.3, 3.3) for the partial responders and 1.1 months (95% CI: 0.99, 1.7) for the non-responders, respectively.

Figure 5. Kaplan-Meier curves of PFS per IRC assessment by response type



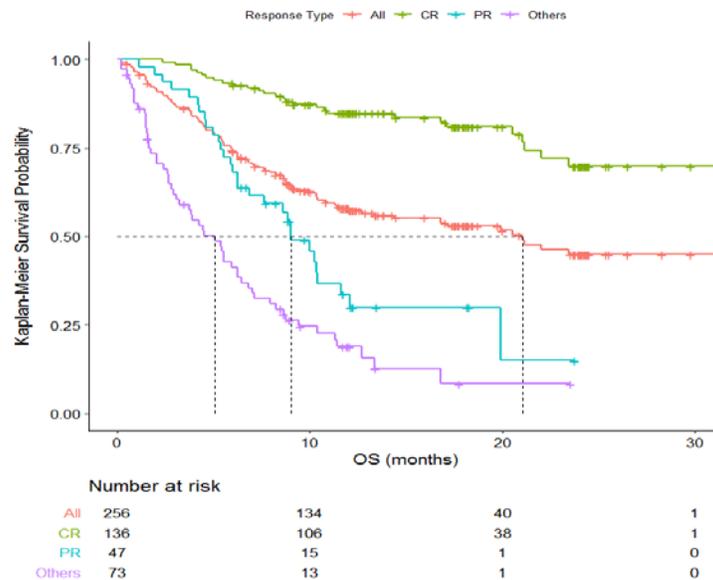
(Source: FDA statistical reviewer’s analysis)

Overall Survival (OS)

A total of 116 subjects (45.3%) died in the DLBCL Efficacy set (n=256). The overall median survival time was 21.1 months with a lower 95% limit of 13.3 months and an unattainable upper limit. The median follow-up time for OS assessment was 17.5 months (95% CI: 13.2, 17.9). The Kaplan-Meier estimated survival rate at 6-, 12-, 18- and 24-month was 51.4%, 44.1%, 42.1% and 42.1%, respectively.

Figure 6 shows Kaplan-Meier curves of OS per IRC-FDA algorithm by response type (CR, PR or Non-responders). Complete responders had substantially longer OS than the partial responders and non-responders. The median OS was not reached for the complete responders, and reached at 9 months (95% CI: 6.9, 12.1) for the partial responders and 1.25 months (95% CI: 0.99, 1.74) for the non-responders, respectively.

Figure 6. Kaplan-Meier curves of OS per IRC-FDA algorithm by response type

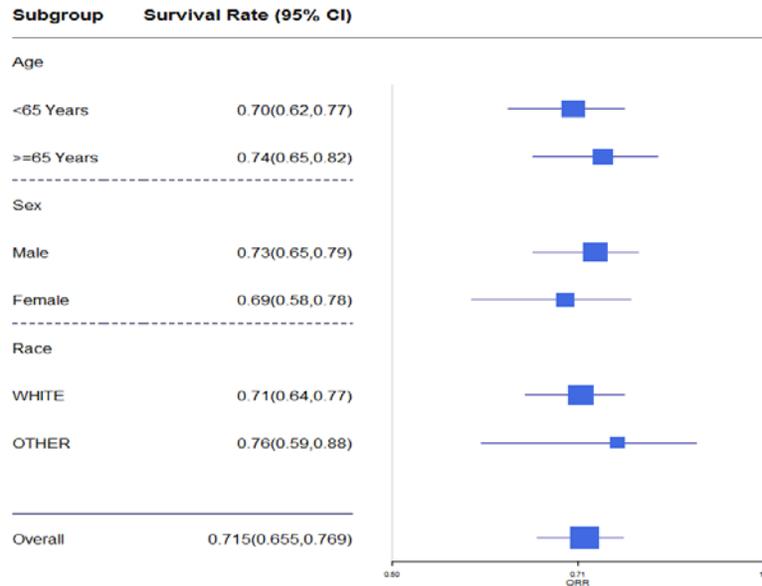


(Source: FDA statistical reviewer’s analysis)

6.1.11.3 Subpopulation Analyses

Figure 7 shows the forest plot of ORR in the DLBCL Efficacy set by age group, sex and race. Results of ORR appear to be generally consistent among subgroups. The lower limit of 95% exact Clopper-Pearson confidence interval for ORR is above the null hypothesis rate of 40% for each subgroup.

Figure 7. Forest plot of ORR by subgroups



(Source: FDA statistical reviewer’s analysis)

Table 11 shows the subgroup analysis of ORR in the DLBCL Efficacy set by dose range. The lower limits of 95% exact Clopper-Pearson confidence intervals are all above the pre-specified ORR null hypothesis rate of 40% for dose ranges 50-60 and 70-110 (unit: $\times 10^6$ CAR+ T cells). The number of subjects in the dose range of 60-70 was too small to make conclusions. These results support the clinical review team’s recommendation regimen of dose range from 50 to 110 $\times 10^6$ CAR+ T cells for this product.

Table 11. Subgroup analysis of ORR by dose range

Dose range ($\times 10^6$ CAR+T cells)	# Subjects in range	ORR, n (%)	Lower limit of 95% CI
40-50	20	12 (60.0%)	36.1%
50-60	26	19 (73.1%)	52.2%
60-70	4	3 (75.0%)	19.4%
70-80	16	11 (68.8%)	41.3%
80-90	55	43 (78.2%)	67.2%
90-100	70	49 (70.0%)	59.2%
100-110	21	16 (76.2%)	52.8%
110-120	9	5 (55.6%)	21.2%
120-130	16	11 (66.8%)	41.3%
130-140	13	9 (69.2%)	38.6%
140-150	5	4 (80.0%)	28.4%
150-160	1	1 (100%)	NA
Overall	256	183 (71.5%)	65.5%

(Source: FDA statistical reviewer’s analysis)

6.1.11.4 Dropouts and/or Discontinuations

Table 12 summarizes subjects' dropouts and discontinuations status from the study. The reasons for dropouts and discontinuations included deaths, disease-related complication, no longer meeting eligibility criteria, manufacturing failure, content withdrawal, lost to follow-up and others. Among the 269 treated subjects in the DLBCL cohort, 35 subjects have completed the study and 103 subjects have ongoing follow-up currently.

Table 12. Subject dropouts and discontinuations

Leukapheresed set, n (%)	344 (100%)
Discontinued before JCAR017 treatment	50 (14.5%)*
Death	33 (9.6%)
Disease-related complication	6 (1.7%)
No longer meet eligibility criteria	5 (1.5%)
Manufacturing failure	2 (0.6%)
Withdrew content	2 (0.6%)
Others	2 (0.6%)
JCAR017 treated	269 (78.2%)
Complete the study	35 (10.2%)
Follow-up ongoing	103 (29.9%)
Death	121 (35.2%)
Withdrew content	7 (2.0%)
Lost to follow-up	2 (0.6%)
Others	1 (0.3%)

* 25 subjects received non-conforming product at the first infusion.

(Source: Summary of Clinical Safety 3-month safety update Table 14.1.1. a; FDA statistical reviewer's summary)

6.1.12 Safety Analyses

This section summarizes safety results of Study 017001 DLBCL cohort.

6.1.12.1 Methods

Descriptive statistic was used to summarize safety data for Study 017001 DLBCL cohort. The safety analysis set in this section included a total of 269 subjects who received at least one dose of JCAR017.

6.1.12.3 Deaths

Deaths reported in the study are listed in Table 13. Among the 344 leukapheresed subjects, 44 (12.8%) subjects died before JCAR017 treatment. Among the 269 treated subjects, 137 (50.9%) subjects died anytime post the first infusion.

Table 13. Deaths reported

Leukapheresed set, n (%)	344 (100%)
Subjects who died before the infusion	44 (12.8%)
Primary cause of death	
Disease progression	37 (10.8%)
Adverse event	1 (0.3%)
Unknown/Others	6 (1.7%)
JCAR017 treated, n (%)	269 (100%)
Subjects who died anytime post the infusion	137 (50.9%)
Primary cause of death	
Disease progression	116 (43.1%)
Adverse event	12 (4.5%)
Unknown/Others	9 (3.3%)

(Source: Summary of Clinical Safety 3-month safety update Table 14.3.1.16.a)

6.1.12.4 Nonfatal Serious Adverse Events

The Applicant reported 122 (45.4%) subjects who had at least one treatment-emergent non-fatal SAEs in the safety analysis set (n=269). The most frequently reported treatment-emergent SAEs were CRS (44, 16.4%) and encephalopathy (14, 5.2%). Table 14 summarizes the treatment-emergent non-fatal SAEs reported in at least 1.5% of treated subjects (i.e., 4 subjects) by preferred term.

Table 14. Treatment-emergent non-fatal SAEs reported in $\geq 1.5\%$ of treated subjects

Preferred term	N (%)
Subjects with at least one treatment-emergent SAEs	122 (45.4%)
Cytokine release syndrome	44 (16.4)
Encephalopathy	14 (5.2%)
Neutropenia	11 (4.1%)
Febrile neutropenia	10 (3.7%)
Pyrexia	10 (3.7%)
Thrombocytopenia	10 (3.7%)
Aphasia	9 (3.3%)
Confusional state	8 (3.0%)
Hypotension	8 (3.0%)
Pneumonia	8 (3.0%)
Mental status changes	7 (2.6%)
Anaemia	5 (1.9%)
Agitation	4 (1.5%)
Sepsis	4 (1.5%)
Syncope	4 (1.5%)

(Source: Summary of Clinical Safety 3-month safety update Table 14.3.1.11.1.a)

6.1.12.5 Adverse Events of Special Interest (AESI)

Table 15 summarizes the AESI post JCAR017 treatment. CRS occurred most frequently in 42.0% (=113/269) of treated subjects.

Table 15. Adverse events of special interest (AESI) reported

Term	N (%)
Cytokine release syndrome	113 (42.0%)
Neurological toxicity	80 (29.7%)
Infusion related reaction	3 (1.1%)
Tumor lysis syndrome	2 (0.7%)

(Source: Summary of Clinical Safety 3-month safety update Table 14.3.2.1.a; FDA statistical reviewer’s summary)

9. ADDITIONAL STATISTICAL ISSUES

9.1 Special Populations

Subjects could have received more than one dose of JCAR017, but only under three pre-specified situations described below. In these descriptions, the word “dose” refers to infusion of JCAR017 product, while the word “cycle” refers to repeating the complete lymphodepleting chemotherapy, JCAR017 product infusion, and most, if not all, study eligibility and evaluations from pretreatment through Day 29. Allowed treatment with multiple doses included:

- Two-dose schedule: This was a protocol-defined schedule into which a subject may have been assigned at study enrollment to receive 2 doses of JCAR017 approximately 14 days apart as their treatment cycle.
- Retreatment cycles: Subsequent JCAR017 cycles may have been administered to a subject only if PD occurred following CR to JCAR017.
- Additional cycles: Additional JCAR017 cycles may have been administered to a subject only if SD or PR was their BOR after the initial response assessment.

In the DLBCL Efficacy set (n=256), 7 subjects had additional cycles and 16 subjects were retreated. Table 16 shows the best response results for DLBCL Efficacy set excluding the 23 subjects with retreatment cycles and additional cycles per IRC-FDA and IRC assessments, respectively.

Table 16. ORR result excluding the subjects with retreatment and additional cycles per IRC-FDA and IRC assessments

	IRC FDA algorithm n=233	IRC assessment n=233
ORR (CR+PR), n (%)	164 (70.4%)	166 (71.2%)
95% CI	(64.1%, 76.2%)	(65.0%, 77.0%)
Complete response rate, n (%)	118 (50.6%)	118 (50.6%)
95% CI	(44.0%, 57.2%)	(44.0%, 57.2%)
Partial response rate, n (%)	46 (19.7%)	48 (20.6%)
95% CI	(14.8%, 25.4%)	(15.6%, 26.4%)

(Source: FDA statistical reviewer’s summary)

For analysis in the set excluding subjects in additional cycles and retreatment cycle, the lower limits of the 95% exact Clopper-Pearson confidence intervals for ORR were 64.1% and 65.0%, respectively, which are both above the null hypothesis rate of 40%. The conclusion was the same as analysis for all 256 subjects in the DLBCL Efficacy set.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

JCAR017 is a CD19-directed genetically modified autologous cellular immunotherapy. This BLA seeks licensure of JCAR017 for the treatment of adult patients with R/R large B-cell lymphoma after at least 2 prior therapies.

The primary source of evidence to support this application is the DLBCL cohort of a Phase 1, single-arm, open-label and multicenter study (Study 017001). A total of 344 subjects underwent leukapheresis. Of 344 subjects, 269 subjects were treated by a single or two intravenous infusion with JCAR017 at the dose range of 44×10^6 to 156×10^6 CAR+ T cells. As requested by clinical review team, the dose range of 50×10^6 to 110×10^6 CAR+ T cells is the recommended regimen of dose for this BLA approval. 256 of the 269 treated subjects in the DLBCL cohort were efficacy-evaluable and therefore constituted the primary evidence of efficacy for the product.

The primary efficacy endpoint, ORR as assessed per IRC-FDA algorithm, was 71.5% (95% CI: 65.5%, 76.9%) in the DLBCL Efficacy set. The lower limit of the 95% exact Clopper-Pearson confidence interval was greater than the pre-specified null hypothesis rate of 40%. One hundred and thirty-six (136; 53.1%) subjects had a best response of CR, and 47 (18.4%) subjects had a best response of PR. In addition, the median DOR was 16.7 months (95% CI: 6.0, NR) for all responders with a median follow-up time of 12.9 months (95% CI: 11.3, 17.0). The median DOR for the partial responders was 2.0 months (95% CI: 1.2, 2.4) and the median DOR was not reached for complete responders (95% CI: 16.8, NR). The median PFS was 3.5 months (95% CI: 3.0, 8.8) for the subjects in the DLBCL efficacy set with a median follow-up time of 12.8 months (12.1, 17.7). The median OS was 21.1 months (95% CI: 13.3, NR) with a median follow-up time of 17.5 months (95% CI: 13.2, 17.9). The majority of efficacy-evaluable subjects (192/256; 75%) received the study drug at the recommended dose (i.e., a single dose of 50 to 110×10^6 CAR+ viable T cells). In these 192 subjects, the ORR as assessed per IRC-FDA algorithm was 73.4% (95% CI: 66.6%, 79.5%) with a CR rate of 54.2% (95% CI: 46.8%, 61.4%).

Deaths occurred in 50.9% (=137/269) of treated subjects in Study 017001 DLBCL cohort and most deaths reported after the first JCAR017 infusion were due to disease progression (116; 116/137=84.7%). In the Study 017001 DLBCL treated set, 122 of 269 subjects (45.4%) reported treatment-emergent SAEs. The most frequently reported treatment-emergent SAEs were CRS (44; 44/122=36.1%) and encephalopathy (14; 14/122=11.5%).

10.2 Conclusions and Recommendations

Study 017001 DLBCL cohort met the efficacy criteria for the ORR primary endpoint with the rejection of the pre-specified null hypothesis rate of 40%. The statistical analysis results provide evidence to support the Applicant's proposed indication for Breyanzi (JCAR017) in this BLA.

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