Application Type	Original BLA
STN	125773
CBER Received Date	March 27, 2023
PDUFA Goal Date	February 23, 2024
Division / Office	CBER/OTP
Committee Chair	Karin Knudson
Clinical Reviewer(s)	Lianne Hu
Project Manager	Catherine Tran
Priority Review	Yes
Reviewer Name(s)	Qianmiao Gao
Review Completion Date / Stamped Date	November 9, 2023
Supervisory Concurrence	Zhenzhen Xu, Ph.D. Team Leader, FDA/CBER/OBPV/DB/TEB1
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBPV/DB/TEB1
	John Scott, Ph.D. Director, FDA/CBER/OBPV/DB
Applicant	Iovance Biotherapeutics, Inc.
Established Name	LIFILEUCEL
(Proposed) Trade Name	AMTAGVI
Pharmacologic Class	Autologous tumor-infiltrating lymphocytes (TIL) obtained from resected individual patient's tumor and expanded ex vivo through cell culture in the presence of the cytokine interleukin-2 (IL-2) and muromonab CD3, a monoclonal antibody (mAb) to human CD3 (OKT3).
Formulation(s), including Adjuvants, etc	The cryopreserved investigational product is formulated in CryoStor® CS10 cryopreservation media and Plasma-Lyte A® containing 0.5% human serum albumin (HSA) and 300 IU/mL IL-2.
Dosage Form(s) and Route(s) of Administration	Cell suspension IV infusion
Dosing Regimen	Single dose of between (b) (4) viable cells

Indication(s) and Intended Population(s)	Unresectable or metastatic melanoma. Patients with unresectable or metastatic melanoma who progressed following treatment on at (b) (4) (b) (4) including a PD-1 blocking antibody, and if BRAF V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor in combination (b) (4) MEK inhibitor.

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GLOSSARY

Abbreviation	Definition
AE	Adverse Event
BOR	Best Overall Response
CI	Confidence Interval
CIBMTR	Center For International Blood And Marrow Transplant Research
CR	Complete Response
DCR	Disease Control Rate
DOR	Duration Of Response
DSMB	Data And Safety Monitoring Board
FAS	Full Analysis Set
IL-2	interleukin-2 (also known as Aldesleukin or Proleukin®)
IRC	Independent Review Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IV	Intravenous(Ly)
Lifileucel	Autologous Tumor-Infiltrating Lymphocytes; LN-144
LN-144	lifileucel; Autologous Tumor-Infiltrating Lymphocytes
Kg	Kilogram
Max	Maximum
MEK	Mitogen-Activated Extracellular Signal-Regulated Kinase
Min	Minimum
NE	Non-Evaluable
NMA-LD	Nonmyeloablative Lymphodepletion
NR	No Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PR	Partial Response
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
TIL	Tumor-Infiltrating Lymphocytes

1. EXECUTIVE SUMMARY

Lifileucel is an autologous tumor infiltrating lymphocyte (TIL) therapy. The product is composed of autologous TIL obtained from resected individual patient's tumor and expanded ex vivo. This Biologics Licensure Application (BLA) seeks licensure of lifileucel for the treatment of unresectable or metastatic melanoma in adult patients who progressed following treatment (b) (4) Primary analysis results were based on the data cutoff date of September 15, 2021.

The primary source of evidence to support efficacy and safety evaluation is from a Phase 2, nonrandomized, multicenter, multicohort study (Study C-144-01). The study started with a single cohort (Cohort 1) and subsequently incorporated three additional cohorts. Cohort 2 was introduced in the protocol amendment (Version 5, Feb 4, 2017), while Cohort 4 was integrated in another amendment (Version 8, Dec 20, 2018). Because the hypothesis testing procedure and sample size and power calculation were only pre-specified for Cohort 4, the primary efficacy analysis was conducted solely on the data from Cohort 4. The pre-specified primary efficacy endpoint, objective response rate (ORR), was evaluated by binomial exact test. Of the 82 subjects in the primary efficacy analysis set, there were 23 responders corresponding to an estimated ORR of 28% (95% CI: 18.7%, 39.1%). The pre-specified null hypothesis of ORR ≤ 0.1 in Cohort 4 was rejected (p-value < 0.0001). Supplemental analysis results including pooling data from Cohort 2 and Cohort 4 were consistent with the primary efficacy analysis.

The primary population for safety evaluation includes the 156 subjects in the pooled population of Cohort 2 and Cohort 4 in Study C-144-01 who received lifileucel. There were 105 deaths occurring afterlifileucel infusion was (67.3% of the safety population). Among those, 85 deaths were primarily attributed to progressive disease, 12 deaths were primarily attributed to adverse event, and 8 deaths were primarily attributed to other causes.

Study C-144-01 met its primary efficacy objective. The statistical analysis results provide sufficient evidence to support the applicant's proposed indication of lifileucel in this BLA.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

In 2020, there were approximately 96,445 cases of melanoma with 7201 deaths in the U.S.[1] It has been estimated that approximately 4% of new cases diagnosed in the US will have metastatic melanoma.[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 for BLA 125773

Date	Milestone
09/11/2018	Type B End-of-Phase 2 (EOP2) meeting (CRMTS# 11302)
01/24/2019	Type B CMC-focused meeting (CRMTS# 11581)
06/26/2019	Type B RMAT multidisciplinary meeting (CRMTS# 11801)
09/29/2020	Type B CMC-focused meeting (CRMTS# 12796)
09/15/2021	Type B CMC-focused meeting (CRMTS# 13557)
03/04/2022	Type B CMC-focused meeting (CRMTS# 13881)
07/29/2022	Type B Pre-BLA meeting (CRMTS# 14161)
08/01/2022	BLA Rolling Review Request
03/27/2023	BLA 125773 received
05/11/2022	BLA Filing Meeting
07/27/2023	Applicant Mid-cycle Review Meeting
09/07/2023	Major Amendment Acknowledgement Letter issued to the applicant. Goal date extended to February 24, 2024.
12/07/2023	Applicant Late-cycle Review Meeting
02/23/2024	FDA Action Letter Due

(Source: adapted from BLA 125773/0.1 Module 1.5 Correspondence Regarding Meetings; 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 Cohort 2 and Cohort 4 of Study C-144-01. This review memo is focused on these two cohorts.

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 125773/0.1; and IR response under BLA 125773/0.28.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study C-144-01

Study C-144-01 has four cohorts that were to comprise the following:

- **Cohort 1**: Patients infused with non-cryopreserved lifileucel product.
- **Cohort 2**: Patients infused with cryopreserved lifileucel product.
- **Cohort 3**: Patients who were previously treated in Cohort 1, Cohort 2, or Cohort 4, had progressed, and opted to be rescreened and retreated with the lifileucel regimen, using cryopreserved lifileucel product.
- **Cohort 4**: Patients infused with cryopreserved lifileucel product.

The non-cryopreserved product infused in Cohort 1 is no longer in clinical use. Cohorts 2, 3, and 4 used the same manufacturing process to generate cryopreserved lifileucel product. The patient populations in Cohort 2 and Cohort 4 were aligned with the intended indication, and therefore are the source of primary and supportive evidence of efficacy. The patients in Cohort 2 and Cohort 4 met the same primary eligibility criteria, had the same assessments, and had received the same regimen and lifileucel that was produced using the same cryopreserved TIL manufacturing process, release criteria, and product formulation.

This section focuses on Cohort 2 and Cohort 4. Cohort 2 was added in the fifth amendment of the protocol (Feb 4, 2017) without any formal hypothesis testing plan. Cohort 4 was added in the eighth amendment (Dec 20, 2018) with prespecified hypothesis testing procedure on the primary endpoint of objective response rate (ORR). Therefore, the primary efficacy analysis was conducted solely on the data from Cohort 4. Pooled data from Cohort 2 and Cohort 4 were used as supportive evidence for efficacy.

6.1.1 Objectives

Primary:

- Evaluate the efficacy of lifileucel in patients with unresectable or metastatic melanoma using the objective response rate (ORR).

Secondary:

- Evaluate the efficacy of lifileucel using duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).
- Characterize the safety profile of lifileucel.

6.1.2 Design Overview

This is an ongoing Phase 2 trial to assess the efficacy and safety of lifileucel for the treatment of metastatic melanoma. The study includes 4 cohorts. The primary efficacy analysis was conducted on the data from Cohort 4. There was no planned statistical comparison between cohorts.

6.1.3 Population

Patients with unresectable or metastatic melanoma who progressed following treatment with at least 1 systemic therapy, including a programmed cell death protein-1 (PD-1) blocking antibody and, if proto-oncogene B-Raf (BRAF) V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor with mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor.

6.1.4 Study Treatments or Agents Mandated by the Protocol

For both Cohort 2 and Cohort 4, NMA-LD + lifileucel + IL-2, specifically:

- NMA-LD: Cyclophosphamide IV (60 mg/kg × 2 doses) over 2 days with mesna (15 mg/kg over the first 2 hours followed by mesna 3 mg/kg/hour over the remaining 22 hours). Followed by fludarabine IV (25 mg/m2 × 5 doses) over 5 days.
- Lifileucel infusion: After completion of NMA-LD
- IL-2 IV (600,000 IU/kg) approximately every 8-12 hours (maximum of 6 doses) with the first dose within 3-24 hours after the completion of the lifileucel infusion

6.1.6 Sites and Centers

A total of 50 clinical sites, 23 in the US and 27 in Europe, screened patients for participation in this study. Patients were enrolled at 42 clinical sites in the U.S. (N = 21) and Europe (N = 21).

6.1.7 Surveillance/Monitoring

An Independent Data Monitoring Committee (IDMC) provided oversight of the study.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint:
ORR, defined as the proportion of patients who had a BOR of CR or PR among the patients in the FAS, as assessed by the IRC per RECIST v1.1.

Secondary Endpoints:

- DOR, defined as the time (in months) from the timepoint at which the initial measurement criteria per RECIST v1.1 were met for a CR or PR, whichever response was observed first, until the first date that PD was objectively documented, or the patient expired.
- DCR, defined as the proportion of patients who had a BOR of CR, PR, stable disease, or non-CR/non-PD, where non-CR/non-PD is only for patients without target lesions identified by the IRC.
- PFS was defined as the time (in months) from the date of lifileucel infusion to PD or death due to any cause, whichever occurred earlier.
- OS was defined as the time (in months) from the date of lifileucel infusion to death due to any cause.

Study Success Criteria

The study was to be considered to have met its primary objective if the primary null hypothesis (H_{01}: ORR <= 10%) for Cohort 4 is rejected.

Reviewer's note:
The null hypothesis of 10% ORR was prespecified based on historical control in the eighth amendment (Dec 20, 2018), when Cohort 4 was originally added to the study. In the clinical reviewer's opinion, 10% may have been reasonable at the time based on available treatment options. However, the clinical reviewer has indicated that her assessment of the effectiveness of this product is not based on a 10% threshold.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol and statistical analysis plan are described in the following:
Design features:
This was an open-label, nonrandomized study, with no comparison between cohorts.

Statistical hypothesis:

- Primary hypothesis testing was on ORR in Cohort 4. H_{01}: ORR ≤ 10% vs. H_{a1}: ORR > 10%
- Second hypothesis testing was on ORR in the pooled Cohorts 2 and 4. H_{02}: ORR ≤ 10% vs. H_{a2}: ORR > 10%

Multiplicity Adjustment:
A fixed-sequence testing procedure was to be used to control the overall Type I error rate at two-sided 0.05. The second null hypothesis (H_{02}) was to be tested only if the primary null hypothesis (H_{01}) was rejected, in order to reinforce the evidence for efficacy in the targeting patient population.

Analysis populations:
Tumor Harvested Set (TH Set, also referred to as the Enrolled Set) was defined as all patients who had tumor resected for the production of lifileucel, regardless of whether they received lifileucel or not.
Safety Analysis Set was defined as patients who received any lifileucel infusion.
Full Analysis Set (FAS) was defined as patients who had received lifileucel that met the manufacturing product specifications.
Efficacy Analysis Set 2 was defined as patients in the FAS who received lifileucel manufactured at (b) (4)

Statistical methods:
In the SAP and original BLA submission (125773/0.1), the applicant proposed to use FAS as primary analysis set. Based on comments from the FDA clinical review team, the primary analysis set for efficacy was revised to Efficacy Analysis Set 2 (n = 82) in Cohort 4 which excludes the 5 subjects whose lifileucel was not manufactured at (b) (4) from FAS due to the outstanding comparability issue among lifileucel manufactured in different manufacturing facilities. The FAS in the pooled Cohorts 2 and 4 (n=87 from

Cohort 4 and n=66 from Cohort 2) was used as the analysis set for supportive efficacy evidence.

Primary endpoint

ORR was to be analyzed by binomial exact test with a two-sided Type I error rate of 0.05.

Secondary endpoints

- DOR, PFS, OS: Kaplan–Meier estimator was to be used to estimate the survival function.
- DCR: Clopper-Pearson exact method was to be used for a point estimate and its two-sided 95% CIs

Interim Analyses:

No interim analysis for Cohort 4 was planned or performed.

Sample size and power calculation:

The sponsor assumed ORR of 10% in the null hypothesis, and ORR of 25% for TIL therapy in the target population. Therefore, based on a Type I error rate of two-sided 0.05 and 90% power using the binomial exact test, approximately 75 subjects were planned to be infused with lifileucel in Cohort 4. The actual number of subjects infused with lifileucel in Cohort 4 was 89.

Supplemental analyses:

ORR was to be estimated for the TH set.

Subgroup analyses:

Subgroup analysis of ORR by IRC was to be performed in the FAS for critical demographic and baseline disease characteristics, including age category (< 65 years vs. ≥ 65 years), gender (male vs. female), number of prior lines of therapy (1 to 3 vs. ≥ 4), etc.

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 Demographics for Cohort 4 and Cohort 2 (FAS)

	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled (N=153)
Gender, n (%)			
Female	43 (49.4)	27 (40.9)	70 (45.8)
Male	44 (50.6)	39 (59.1)	83 (54.2)
Age (years)			
n	87	66	153
Mean (SD)	55.4 (11.87)	54.3 (11.48)	54.9 (11.68)
Median	58.0	55.0	56.0
Min, Max	25, 74	20, 79	20, 79
Age, n (%)			
<40	9 (10.3)	7 (10.6)	16 (10.5)
>=40, <65	56 (64.4)	45 (68.2)	101 (66.0)
>=65	22 (25.3)	14 (21.2)	36 (23.5)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	1 (1.1)	2 (3.0)	3 (2.0)
Black or African American	2 (2.3)	1 (1.5)	3 (2.0)
White	83 (95.4)	63 (95.5)	146 (95.4)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (1.1)	0	1 (0.7)
Ethnicity, n (%)			
Hispanic or Latino	3 (3.4)	5 (7.6)	8 (5.2)
Not Hispanic or Latino	83 (95.4)	54 (81.8)	137 (89.5)
Unknown	1 (1.1)	7 (10.6)	8 (5.2)
Weight (kg)			
n	87	66	153
Mean (SD)	78.0 (18.7)	83.3 (19.0)	80.3 (19.0)
Median	76.0	81.0	78.7
Min, Max	44.9, 133.7	49.7, 141.9	44.9, 141.9
Region			
US	54 (62.1)	55 (83.3)	109 (71.2)
Europe	33 (37.9)	11 (16.7)	44 (28.8)

(Source: Adapted from BLA 125773/0.1 Module 5.3.5; c-144-01-14-tables-figures.pdf, p.14)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 3 Baseline Disease Characteristics for Cohort 4 and Cohort 2 (FAS)

	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled (N=153)
Stage at Study Entry, n (%)			
IIIC	1 (1.1)	9 (13.6)	10 (6.5)
IV	86 (98.9)	57 (86.4)	143 (93.5)
Disease metastasis at Study Entry, n (%)			
M0	0	NA	NA
M1a	9 (10.3)	NA	NA
M1b	12 (13.8)	NA	NA
M1c	54 (62.1)	NA	NA
M1d	11 (12.6)	NA	NA
Patients with Baseline Liver and/or Brain Lesions by IRC, n (%)	44 (50.6)	28 (42.4)	72 (47.1)
Patients with Mucosal Melanoma, n (%)	7 (8.0)	3 (4.5)	10 (6.5)

(Source: Adapted from BLA 125773/0.1 Module 5.3.5; body report, p.78)

Table 4 Prior Anti-Cancer Therapy for Cohort 4 and Cohort 2 (FAS)

	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled (N=153)
Prior Therapy Category, n (%)			
Anti-PD-1/PD-L1	87 (100)	66 (100)	153 (100)
Anti-CTLA-4	72 (82.8)	53 (80.3)	125 (81.7)
Anti-PD-1/CTLA-4 Combo	48 (55.2)	34 (51.5)	82 (53.6)
BRAF/MEK Inhibitor [1]	24 (27.6)	15 (22.7)	39 (25.5)
IL-2	6 (6.9)	7 (10.6)	13 (8.5)
Radiotherapy	44 (50.6)	34 (51.5)	78 (51.0)
Surgery	86 (98.9)	65 (98.5)	151 (98.7)
Number of Adjudicated Prior Therapies			
n	87	66	153
Mean (SD)	3.2 (1.63)	3.3 (1.70)	3.3 (1.65)
Median	3.0	3.0	3.0

Min, Max	1, 8	1, 9	1, 9

(Source: Adapted from BLA 125773/0.1 Module 5.3.5; body report, p.82)

6.1.10.1.3 Subject Disposition

Table 5 Patient Disposition for Cohort 4, Cohort 2, and Pooled Cohorts 2 and 4 (Tumor Harvested Set)

	Cohort 4 (N=111) n (%)	Cohort 2 (N=78) n (%)	Pooled (N=189) n (%)
Tumor Harvested Set (Enrolled Set)	111 (100)	78 (100)	189 (100)
Safety Analysis Set	89 (80.2)	67 (85.9)	156 (82.5)
Full Analysis Set	87 (78.4)	66 (84.6)	153 (81.0)
Patients who received lifileucel of < 1 billion viable cells	0	1 (1.3)	1 (0.5)
Patients who received lifileucel out of specifications	2 (1.8)	0	2 (1.1)
Patients who did not receive lifileucel	22 (19.8)	11 (14.1)	33 (17.5)
Patients in Tumor Harvested Set Who Did Not Receive lifileucel [1]	22 (19.8)	11 (14.1)	33 (17.5)
Primary Reason for Not Receiving lifileucel			
Adverse Event	2 (1.8)	1 (1.3)	3 (1.6)
Death	3 (2.7)	2 (2.6)	5 (2.6)
Partial Withdrawal of Consent	1 (0.9)	0	1 (0.5)
TIL Not Available	6 (5.4)	2 (2.6)	8 (4.2)
Withdrawal by Subject	0	1 (1.3)	1 (0.5)
Progressive Disease	5 (4.5)	4 (5.1)	9 (4.8)
Start of a New Anti-cancer Therapy	2 (1.8)	0	2 (1.1)
COVID-19	0	0	0
Other	3 (2.7)	1 (1.3)	4 (2.1)
Patients in Full Analysis Set Who Discontinued Assessment Period [2]	77 (88.5)	55 (83.3)	132 (86.3)
Primary Reason for End of Assessment			
Adverse Event	2 (2.3)	0	2 (1.3)
Death	3 (3.4)	7 (10.6)	10 (6.5)
Lost to Follow-up	1 (1.1)	0	1 (0.7)
Physician Decision	0	1 (1.5)	1 (0.7)
Partial Withdrawal of Consent	2 (2.3)	0	2 (1.3)
Withdrawal by Subject	0	2 (3.0)	2 (1.3)

Progressive Disease	63 (72.4)	42 (63.6)	105 (68.6)
Start of a New Anti-cancer Therapy	5 (5.7)	3 (4.5)	8 (5.2)
COVID-19	0	0	0
Other	1 (1.1)	0	1 (0.7)
Patients in Full Analysis Set Who Discontinued from Study [2]	61 (70.1)	47 (71.2)	108 (70.6)
Primary Reason for End of Study			
Death	57 (65.5)	45 (68.2)	102 (66.7)
Lost to Follow-up	1 (1.1)	2 (3.0)	3 (2.0)
Withdrawal by Subject	3 (3.4)	0	3 (2.0)
COVID-19	0	0	0

[1] Percentages are calculated using Tumor Harvested Set.
[2] Percentages are calculated using Full Analysis Set
(Source: Adapted from BLA 125773/0.1 Module 5.3.5; body report, p.72)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

The primary null hypothesis (H_{01}) on ORR was tested in Efficacy Analysis Set 2 of Cohort 4 (refer to Section 6.1.9 Statistical methods). Of the 82 subjects in this set, there were 3 CR and 20 PR. The ORR was 28% (95% CI: 18.7%, 39.1%). H_{01} was rejected with a binomial exact test (p-value < 0.0001).

The second null hypothesis (H_{02}) on ORR was tested in the FAS of the Pooled Cohorts 2 and 4. Of the 153 subjects in this set, there were 8 CR and 40 PR. The ORR was 31.4% (95% CI: 24.1%, 39.4%). H_{02} was rejected with a binomial exact test (p-value < 0.0001).

6.1.11.2 Analyses of Secondary Endpoints

Table 6 summarizes the analysis on DOR (Per RECIST v1.1 assessed by IRC) in Efficacy Analysis Set 2 of Cohort 4. The median time to first response was 1.5 months (min, max: 1.3, 4.2).

Table 6: DOR in Efficacy Analysis Set 2 in Cohort 4

Endpoint	N=82
Duration of Response[a]	
Median DoR in months (95% CI)[b]	NR (4.1, NR)[c]
Range[d]	(1.4+, 26.3+)
Patients with DoR ≥ 6 months, n (%)	13 (56.5)
Patients with DoR ≥ 9 months, n (%)	11 (47.8)
Patients with DoR ≥ 12 months, n (%)	10 (43.5)
Median follow-up for DOR in months	18.6

[a] The number of responders was N=23.
[b] Kaplan-Meier estimate
[c] NR, not reached
[d] A + sign indicates a censored value
(Source: Statistical Review)

Table 7 summarizes the analysis on DOR (Per RECIST v1.1 assessed by IRC) in FAS of Pooled Cohort 2 & 4. The median time to first response was 1.4 months (min, max: 1.3, 4.2).

Table 7: DOR in FAS in Pooled Cohort 2 & 4

Endpoint	N=153
Duration of Response[a]	
Median DoR in months (95% CI)[b]	NR (8.3, NR)[c]
Range[d]	(1.4+, 45.0+)
Patients with DoR ≥ 6 months, n (%)	30 (62.5)
Patients with DoR ≥ 9 months, n (%)	27 (56.3)
Patients with DoR ≥ 12 months, n (%)	26 (54.2)
Median follow-up for DOR in months	21.5

[a] The number of responders was N=48.
[b] Kaplan-Meier estimate
[c] NR, not reached
[d] A + sign indicates a censored value
(Source: Statistical Review)

6.1.11.3 Subpopulation Analyses

The review team determined the recommended AMTAGVI dosing range at 7.5 to 72.0 × 10^9 viable cells, based on the outcome that among the 82 patients in the primary efficacy analysis set (i.e., Efficacy Analysis Set 2 in Cohort 4). Nine patients received AMTAGVI at a dose less than 7.5 × 10^9 viable cells and did not achieve an objective response. Therefore, analysis on ORR and DOR was repeated in the subpopulation in Efficacy Analysis Set 2 of Cohort 4 who received the recommended AMTAGVI dosing range (n=73 subjects), as shown in Table 8. The median time to first response to AMTAGVI was 1.5 months (min, max: 1.3, 4.2). The findings do not show any substantial difference from the primary analysis.

Table 8: ORR and DOR in Subjects Who Received AMTAGVI Dose Range of 7.5-72.0 × 10^9 Viable Cells in Efficacy Analysis Set 2 of Cohort 4

Endpoint	**N=73**
Objective Response Rate	
ORR, % (95% CI)	31.5 (21.1-43.4)
Complete response rate, n (%)	3 (4.1)
Partial response rate, n (%)	20 (27.4)
Duration of Response[a]	
Median DoR in months (95% CI)[b]	NR (4.1, NR)[d]
Range[c]	(1.4+, 26.3+)
Patients with DoR ≥ 6 months, n (%)	13 (56.5)
Patients with DoR ≥ 9 months, n (%)	11 (47.8)
Patients with DoR ≥ 12 months, n (%)	10 (43.5)
Median follow-up for DOR in months	18.6

[a] Number of responders was N=23.
[b] Kaplan-Meier estimate in months among all responders.
[c] + sign indicates a censored value
[d] NR, not reached
(Source: Statistical Review)

Table 9 summarizes the subgroup analysis of ORR on age, gender, and prior lines of therapy in Efficacy Analysis Set 2 of Cohort 4. The findings do not show any substantial difference from the primary analysis.

Table 9: ORR by subgroup in Cohort 4 (Efficacy Analysis Set 2, N=82)

Objective Response Rate by Subgroup	n/N (%)	95% CI
Age Group		
<65	19/ 62 (30.6)	(19.6, 43.7)
>=65	4/ 20 (20.0)	(5.7, 43.7)
Gender		
Male	12/ 41 (29.3)	(16.1, 45.5)
Female	11/ 41 (26.8)	(14.2, 42.9)
Prior Lines		
1-3	17/ 55 (30.9)	(19.1, 44.8)
>=4	6/ 27 (22.2)	(8.6, 42.3)

(Source: Adapted from BLA 125773/0.1; module 5.3.5 5353-273-sce-tfls.pdf, p.86)

6.1.11.4 Dropouts and/or Discontinuations

Refer to Section 6.1.10.1.3 Subject Disposition.

6.1.12 Safety Analyses

6.1.12.1 Methods

Descriptive statistics were used to summarize safety data. The primary population for safety evaluation includes the 156 subjects in Study C-144-01 who received lifileucel.

6.1.12.3 Deaths

Among the 156 subjects in Study C-144-01 who received lifileucel, 105 subjects (67.3%) died after lifileucel infusion. Of those, 85 deaths were primarily attributed to progressive disease, 12 deaths were primarily attributed to adverse event, and 8 deaths were primarily attributed to other causes.

6.1.12.4 Nonfatal Serious Adverse Events

Of the 156 subjects, 54 (34.6%) had at least one SAE that started from lifileucel infusion to 30 days post lifileucel infusion, and 29 (18.6%) had at least one SAE that started 30

days post-lifileucel infusion through 6 months post-lifileucel infusion or up to the start of a new anti-cancer therapy, whichever occurred first.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Lifileucel is an autologous tumor infiltrating lymphocyte (TIL) therapy. This Biologics Licensure Application (BLA) seeks licensure of lifileucel for the treatment of unresectable or metastatic melanoma in adult patients.

The primary source of evidence to support the effectiveness of lifileucel in this population is Cohort 4 from a Phase 2, nonrandomized, multicenter, multicohort study (Study C-144-01). A total of 82 subjects were included in the primary efficacy analysis set. The primary null hypothesis of ORR ≤ 0.1 in Cohort 4 was rejected by binomial exact test (p-value < 0.0001). There were 23 responders corresponding to an estimated ORR of 28% (95% CI: 18.7%, 39.1%). The efficacy evidence was supported by the second hypothesis testing of ORR in the Pooled Cohorts 2 and 4 from the same study, with a p-value < 0.0001, under a fixed-sequence testing procedure.

There were 105 deaths among the 156 subjects who received lifileucel in Study C-144-01. Of those, 85 deaths were primarily attributed to progressive disease, and 12 deaths were primarily attributed to adverse events.

10.2 Conclusions and Recommendations

Study C-144-01 met its primary efficacy objective: the pre-specified null hypothesis on the primary efficacy endpoint was rejected. The statistical analysis results provide sufficient evidence to support the applicant's proposed indication of lifileucel in this BLA.

REFERENCES

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