BLA Clinical Review and Evaluation

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Application Type	Original BLA
Application Number(s)	125773/0
Priority or Standard	Priority
Submit Date(s)	March 27, 2023
Received Date(s)	March 27, 2023
PDUFA Due Date	February 24, 2024
Division/Office	DCEO/OCE/CBER
Review Completion Date	February 6, 2024
Established Name	Lifileucel
(Proposed) Trade Name	AMTAGVI
Pharmacologic Class	Tumor-derived autologous T cell immunotherapy
Code name	LN-144
Applicant	Iovance Biotherapeutics Inc
Formulation(s)	Intravenous infusion
(Proposed) Dosing Regimen	AMTAGVI (b) (4) viable cells suspended in a cryopreserved medium and provided in up to 4 patient-specific intravenous infusion bags.
FDA Recommended Dosing Regimen	AMTAGVI 7.5 x 10^9 to 72 x 10^9 viable cells suspended in a cryopreserved medium and provided in 1 to 4 patient-specific intravenous infusion bags.
Applicant Proposed Indication(s)/Population(s)	The treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.
Recommendation on Regulatory Action	OCE MORE Team recommends Accelerated Approval.
Recommended Indication(s)/Population(s) (if applicable)	The treatment of adult patients with unresectable or metastatic melanoma previously treated a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

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Reviewers of Clinical Review and Evaluation

Regulatory Project Manager	Catherine Tran
CMC Chair	Karin Knudson
CMC Primary	Brian Niland
CMC DCT1	Heba Degheidy
CMC	Liz Lessey-Morillon
Pharmacology/Toxicology Reviewer(s)	Yongjie Zhou
Pharmacology/Toxicology Team Leader(s)	Sandhya Sanduja
Office of Clinical Pharmacology Reviewer(s)	Million Tegenge
Office of Clinical Pharmacology Team Leader(s)	Xiaofei Wang
Clinical Reviewer	Lianne Hu
Clinical Team Leader	Chaohong Fan
Clinical Branch Chief	Peter Bross
Safety Analyst (if applicable)	Elin Cho
Statistical Reviewer	Qianmiao (Ann) Gao
CMC Statistical Consult	Tianjiao Dai
Statistical Team Leader	Zhenzhen Xu
Bioinformatics	Cinque Soto
OBPV/DPV	Douglas Rouse
Advertising and Promotional Labeling Branch	Benjamin Cyge
DBSQC: LMIVTS (review of BET, Mycoplasma and Sterility assays)	Seth Schulte
DBSQC: Regulatory Coordinator	Marie Anderson
DMPQ	Hector Carrero
DMPQ RPM	Jana Highsmith,
BIMO	Char-Dell Edwards
BIMO	Peter Lenahan
TEB Consult	Wojtek Tutak
TEB Consult	Carolina Panico
Facility	Hector Carrero
OPPT Consult	Andrey Safafanov

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OCE MORE Team Leader	Jaime Brewer
Division Director (DCEO)	Asha Das
OCE Director (or designated signatory authority)	Marc Theoret
Office Director (or designated signatory authority)	Nicole Verdun

Abbreviations: BIMO = bioresearch monitoring; CMC = Chemistry, Manufacturing, and Controls; DBSQC = Division of Biological Standards and Product Quality; DCEO = Division of Clinical Evaluation Oncology; DMPQ = Division of Manufacturing and Product Quality; DPV = Division of Pharmacovigilance; MORE = Medical Oncology Review and Evaluation; OBPV = Office of Biostatistics and Pharmacovigilance; OCE = Oncology Center of Excellence; OOD = Office of Oncologic Diseases; OPPT = Office of Plasma Protein Therapeutics; RPM = Regulatory Project Manager; TEB = Therapeutics Evaluation Branch

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Glossary

AA	Accelerated Approval
AE	adverse event
AF	atrial fibrillation
AJCC	American Joint Committee on Cancer
BIMO	bioresearch monitoring
BLA	Biologics License Application
BOR	best overall response
BRAF	proto-oncogene B-Raf
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CLS	capillary leak syndrome
CMC	Chemistry, Manufacturing, and Controls
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CR	complete response
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte antigen 4
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOA	end-of-assessment
EOP2	End-of-Phase 2
EORTC	European Organization for Research and Treatment of Cancer
FAS	Full Analysis Set: Applicant's definition for FAS included subjects who received lifileucel that met the product manufacturing specifications
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
Gen	Generation
H_0	null hypothesis
H_a	alternative hypothesis
HLH	hemophagocytic lymphohistiocytosis
HNSCC	head-and-neck squamous cell carcinoma

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HRQoL	health-related quality of life
HSV	herpes simplex virus
ICANS	immune effector cell-associated neurotoxicity syndrome
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IL-2	interleukin-2
IND	Investigational New Drug (application)
iPSP	initial pediatric study plan
IR	information request
IRC	Independent Review Committee
IU	International Units
IV	intravenous
KM	Kaplan-Meier
LAG-3	lymphocyte activation gene-3
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated extracellular signal-regulated kinase
MOA	mechanism of action
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMA-LD	nonmyeloablative lymphodepletion
NME	new molecular entity
NR	not reached
NSCLC	non-small cell lung cancer
OCP	Office of Clinical Pharmacology
ORR	objective response rate
OS	overall survival
OSI	Office of Scientific Investigation
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reactions
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PD-(L)1	programmed cell death protein-1/programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement

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PR	partial response
PREA	Pediatric Research Equity Act
pre-IND	pre-Investigational New Drug (application)
PRO	patient-reported outcome
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-C30
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RMAT	Regenerative Medicine Advanced Therapy
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	stable disease
SEER	U.S. Surveillance, Epidemiology, and End Results
SITC	Society for Immunotherapy of Cancer
SMQ	Standardized MedDRA Query
SoD	sum of diameters
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TE SAE	treatment-emergent serious adverse event
TH	tumor harvest
TIL	tumor-infiltrating lymphocytes
ULN	upper limit of the normal range
USPI	U.S. prescribing information

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1 Executive Summary

1.1. Product Introduction

AMTAGVI (hereafter referred to as lifileucel; LN-144) is an autologous tumor-derived T cell immunotherapy [Note: the Applicant uses the term "tumor infiltrating lymphocytes (TIL)" throughout this assessment aid) composed primarily of (b) (4) lymphocytes obtained from resected tumor material and expanded ex vivo in the presence of the cytokine interleukin-2 (IL-2), anti-CD3 (OKT3) antibody, and (b) (4) feeder cells (b) (4) (b) (4) The final product is supplied in 1 to 4 intravenous infusion bag(s), with each bag containing approximately 100 to 125 mL of cryopreserved suspension of viable tumor-derived T cells.

The Applicant's proposed indication is for the treatment of unresectable or metastatic melanoma previously treated with a PD1 blocking antibody and, if proto-oncogene B-Raf (BRAF) V600 mutation positive, a BRAF inhibitor with or without a mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor. The review team recommends Accelerated Approval (AA) of lifileucel for the treatment of unresectable or metastatic melanoma previously treated with a PD1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

The U.S. Food and Drug Administration (FDA)-approved lifileucel treatment regimen includes a nonmyeloablative lymphodepletion (NMA-LD) regimen with cyclophosphamide 60 mg/kg intravenously (IV) with mesna daily for 2 days followed by fludarabine 25 mg/m^2 IV daily for 5 days preceding lifileucel infusion, and then a single dose of lifileucel with all manufactured viable cells (FDA-approved dose range for commercial release: 7.5 x 10^9 to 72 x 10^9) infused IV followed by IL-2 (aldesleukin) at 600,000 International Units (IU)/kg IV every 8 to 12 hours starting 3 to 24 hours post lifileucel infusion for up to 6 doses over a period of up to 4 days.

In support of this application, the Applicant submitted safety and efficacy data from the clinical study, C-144-01. Study C-144-01 is a single-arm, Phase 2, multicenter, multiregional trial that enrolled patients ≥18 years of age with unresectable or metastatic melanoma who had progressed following ≥1 prior systemic therapy, including a PD-1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. A total of 156 subjects from Cohorts 2 (N=67) and 4 (N=89) who received cryopreserved lifileucel (generation [Gen] 2) constitute the primary safety analysis set. Of the 89 subjects in Cohort 4, 82 subjects who received lifileucel manufactured at (b) (4) facility and met the release specifications were included in the primary efficacy analysis (N=82). Efficacy results from Cohort 2 (N=66, excluded 1 subject who received less than 1 x 10^9 viable cells due to a serious anaphylactic reaction) and pooled Cohort 2 and 4 (N=153) from Cohort 2 (N=66) and Cohort 4 (N=87) provide supporting efficacy evidence.

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1.2. Conclusions on the Substantial Evidence of Effectiveness

Study C-144 was a multi-cohort, multicenter, multiregional (U.S. and Europe) study. Cohort 4 provided primary evidence of effectiveness and Cohort 2 provided supportive evidence of effectiveness of lifileucel in the intended population, based on objective response rate (ORR) and duration of response (DOR). Among the 82 subjects included in the primary efficacy analysis, the median age was 57 years, the majority race was White at 95.1%, and the median number of prior therapies was 3 (range: 1 to 8) with a median number of 2 prior lines of anti-PD1 containing therapy. All subjects had received prior anti-PD1 therapy, 84.1% had received prior anticytotoxic T-lymphocyte antigen 4 (CTLA-4) therapy, 56.1% had received prior combination therapy with anti-PD1 plus anti-CTLA-4, 29.3% had BRAF V600 mutation positive tumor and had received a BRAF ± MEK inhibitor, and 7.3% had received prior IL-2 therapy. All subjects had documented disease progression on or after their last prior therapy. All but 1 subject (98.8%) had Stage IV melanoma at study entry; 62.2% had M1c and 12.2% had M1d disease; and 52.4% had liver and/or controlled brain metastases as assessed by the Independent Review Committee (IRC).

At enrollment, subjects underwent tumor harvest (TH) for manufacturing lifileucel. The manufacturing of lifileucel required 22 days. The lifileucel treatment regimen included a NMA-LD regimen [cyclophosphamide (60 mg/kg with mesna) for 2 days starting on Day -7 followed by fludarabine (25 mg/m^2) for 5 days starting on Day -5], followed by 1 dose of lifileucel infusion containing 1 x 10^9 to 150 x 10^9 viable cells on Day 0 and an abbreviated course of IL-2 (600,000 IU/kg started within 3 to 24 hours following lifileucel, every 8 to 12 hours for up to 6 doses over a period of up to 4 days).

Baseline tumor assessment occurred at a median of 21 days (range: 7 to 39 days) after TH. Follow-up tumor assessments occurred every 6 weeks for the first 6 months, then every 3 months thereafter for up to 5 years.

The primary endpoint of Study C-144-01 was confirmed ORR assessed by a central IRC using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) guidelines. The key secondary endpoint FDA assessed was duration of response (DOR) as assessed by the IRC using RECIST v1.1.

Efficacy

The primary efficacy analysis was performed in 82 subjects treated in Cohort 4. The ORR was 28.0% with a 95% confidence interval (CI) of 18.7% to 39.1% (N=82); complete response (CR) in 3 (3.7%) subjects and partial response (PR) in 20 (24.4%) subjects. The median DOR was not reached (NR, 95% CI: 4.1, NR). Among the 23 responders, durable response at 6, 9, and 12 months was 56.5%, 47.8%, and 43.5%, respectively.

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Safety

For the safety profile, the Applicant focused on characterizing treatment-emergent adverse events (TEAEs) occurring during the first 30 days post lifileucel infusion among subjects who received lifileucel (N=156). The Applicant assessed most life-threatening and fatal adverse events (AEs) as known risks attributed to the NMA-LD regimen and/or IL-2. However, given that lifileucel treatment is a multi-component regimen, FDA was unable to separate the contribution of individual components of the lifileucel regimen to the overall safety profile of the regimen. For this reason, FDA disagreed with the Applicant's attribution of some of the life-threatening and fatal adverse events. Therefore, for severe, life-threatening, and fatal events, FDA assessed the contribution of the lifileucel regimen as one entity.

Study C-144 was the primary source for the safety data. A total of 156 subjects with unresectable or metastatic melanoma who had previously received at least one anti-PD1-based systemic therapy and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor were treated with lifileucel. Grade 3 or higher adverse reactions occurred in 96.9% of subjects who initiated the lifileucel regimen (N=160) including 93.8% non-laboratory adverse reactions. Among 156 subjects included in the primary safety analysis set, the most common (incidence of ≥10%) Grade 3 or higher non-laboratory adverse reactions were febrile neutropenia (46.8%), infection (13.5%), hypotension (12.2%), and hypoxia (12.2%). There were 10 cases (6.4%) of infusion-related reaction and 2 cases (1.3%) of anaphylactic reaction considered as an identified risk for lifileucel.

Study treatment-related death rate was 7.5% (12/160) among all subjects who initiated the lifileucel regimen, including 10 deaths that occurred after lifileucel infusion and 2 deaths that occurred during NMA-LD. The death rate in the first 30 days following receiving any component of the study treatment was 5% (8/160).

In the primary safety analysis set (N=156), 87.8% (137/156) experienced at least one Grade 4 TEAE; 25.0% (39/156) had at least one Grade 3 or 4 TEAE unresolved to Grade 2 or lower at the time of death, some of which were related to death; 45.5% (71/156) had ≥ Grade 3 cytopenia for more than 30 days post lifileucel infusion or did not resolve to Grade 2 or lower. Among 89 subjects who received lifileucel in Cohort 4, 23.6% (21/89) were transferred to intensive care unit (ICU) post infusion for non-infusion-related activities such as managing serious adverse events, stabilizing, and monitoring study subjects. The median non-infusion ICU stay among these subjects was 12 days.

The overall safety profile of the lifileucel regimen identified in Study C-144-01 was consistent across lifileucel trials among patients with other solid tumors, except that pulmonary toxicities were more prevalent in study subjects with lung cancer.

FDA has not identified new serious risks emerging in lifileucel trials that were previously unknown to NMA-LD, IL-2, or other immunotherapies published in the literature.

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Conclusions

Accelerated Approval may be considered for an investigational product that addresses an unmet medical need based on an intermediate clinical endpoint reasonably likely to predict clinical benefit. The ORR observed in Study C-144, supported by the durability of response, serves as an intermediate clinical endpoint that is reasonably likely to predict clinical benefit in this patient population with a high unmet need for new therapies.

Based on the overall efficacy and safety results from Study C-144-01, FDA concludes that the Applicant has demonstrated substantial evidence of effectiveness of lifileucel, and the established overall benefit of lifileucel outweighs the risks to the intended patient population. In Study C-144-01, 93.6% (146/156) of study subjects had Stage IV disease previously treated with a median two lines of anti-PD1-based therapies and a BRAF inhibitor if BRAF V600 positive, 53.8% had also received an anti-PD1/anti-CTLA4 combination therapy, and over 80% had not responded to prior first-line anti-PD1 therapy; such patients have no FDA-approved therapy available.

Therefore, the review team recommends granting AA of lifileucel for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

Risk mitigation strategies will be instituted in the U.S. prescribing information (USPI) via the Boxed Warning and Warnings and Precautions sections and infusion and management guidelines, as well as via patient information for patients to be treated with the lifileucel regimen.

For products granted AA, a postmarketing confirmatory trial is generally required to verify the clinical benefit. The Applicant is conducting a confirmatory trial (IOV-MEL-301) as a postmarketing requirement (PMR), which is an ongoing open-label, randomized, controlled, multicenter, multiregional global trial to compare the efficacy and safety of the lifileucel regimen plus pembrolizumab with pembrolizumab alone in subjects with newly diagnosed unresectable or metastatic melanoma. Progression-free survival (PFS) and ORR are dual primary endpoints and overall survival (OS) is the key secondary endpoint. Continued approval of lifileucel in this indication is contingent upon verification of the clinical benefit of lifileucel in improving PFS without a detriment to OS via the confirmatory trial (IOV-MEL-301).

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Data from the U.S. Surveillance, Epidemiology, and End Results (SEER) registry estimated approximately 97,610 new cases of melanoma and 7,990 melanoma related deaths in 2023, which represent approximately 5% of all new cancer cases and 1.3% of all cancer-related deaths in the U.S. in 2023. The 1-year and 5-year relative survival for patients with metastatic melanoma is approximately 50% and 35%, respectively (NCI-SEER 2023).

FDA-approved therapies prior to the development of immune checkpoint inhibitors (ICIs) include dacarbazine, interferon, IL-2, and talimogene laherparepvec, none of which has demonstrated a survival benefit. The toxicities associated with these therapies have made them less desirable treatment options. Treatment outcomes have been drastically improved with ICIs. The first FDA-approved ICI for advanced and metastatic melanoma was ipilimumab, an anti-CTLA4 agent, with improvement in progression free survival (PFS) and overall survival (OS) via a randomized controlled trial (RCT). Following the approval of ipilimumab in 2011 for the treatment of unresectable or metastatic melanoma, several other ICIs have been approved as first line systemic therapies for unresectable, advanced, or metastatic melanoma including pembrolizumab, nivolumab, nivolumab plus ipilimumab, and nivolumab plus relatlimab, an anti-LAG3 agent. The approvals of these anti-PD1 agents with or without combination with another ICI were based on improvement in PFS and/or OS via RCTs (i.e., KEYNOTE 006 for pembrolizumab versus ipilimumab; CheckMate 067 for nivolumab plus ipilimumab or nivolumab alone versus ipilimumab; and RELATIVITY 047 for nivolumab plus relatlimab versus nivolumab alone).

Based on results from KEYNOTE 006, CheckMate 067, and RELATIVITY 047, patients with previously untreated unresectable or metastatic melanoma initially treated with anti-PD1 with or without another ICI (ipilimumab or relatlimab) achieved ORR of 33%-50%. Specifically, ORR for pembrolizumab was 34% (95% CI: 28%-40%) for 10 mg/kg Q2W, and 33% (95% CI: 27%-39%) for 10 mg/kg Q3W; ORR was 40% (95% CI: 34%-46%) for nivolumab; ORR was 50% (95% CI: 44%-55%) for nivolumab plus ipilimumab; and ORR was 43% (95% CI: 38%-48%) for nivolumab plus relatlimab.

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However, ORR results from these trials suggest that at least 50% of patients do not respond to the first-line anti-PD1-based ICIs. Furthermore, the PFS results from these previous trials suggest that at least 50% of patients experienced progressive disease (PD) within a year (refer to FDA labels for approved anti-PD1-based ICIs for metastatic melanoma) and once PD occurs on or after an anti-PD1-based therapy, the prognosis is poor with no FDA-approved therapy. Therefore, for patients who do not respond to the first-line anti-PD1-based ICIs and patients who develop PD on or after the first-line anti-PD1-based ICIs, there is a high unmet medical need for new therapies.

The Applicant submitted data from Study C-144-01 to support an AA of lifileucel for the treatment of adult patients with unresectable, or metastatic melanoma previously treated with at least one systemic therapy, including a PD-1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. FDA concurs with the Applicant that Study C-144-01 has established clinically important improvement in ORR [28.0% (95% CI: 18.7%-39.1%), N=82].

The data submitted to support the safety review of lifileucel regimen are sufficient for FDA to characterize toxicity in patients with unresectable or metastatic melanoma. FDA found that the incidence of high-grade adverse reactions and study treatment related death rate were higher than those observed in patients treated with ICIs and were more comparable to chimeric antigen receptor (CAR) T therapies approved by FDA for hematological cancers.

However, a review of the safety dataset revealed that the types of adverse reactions observed with the lifileucel regimen were not unique and the frequency and severity were mostly expected and manageable based on the components of the regimen. Since patients with previously anti-PD1 treated unresectable or metastatic melanoma have no available FDA-approved therapies, the benefit-risk profile of the lifileucel regimen is acceptable as a treatment for these patients with a high unmet medical need.

The following table summarizes FDA assessment of benefit-risk of the lifileucel regimen.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Melanoma accounts for 5% of all cancers. • Estimated new cases of melanoma are 97,610 in 2023. • 1-year and 5-year survival for metastatic melanoma (stage IV) are approximately 50% and 35%, respectively. • Melanoma predominantly occurs in the White population. In the U.S., the incidence rate of melanoma is 63.1 per 100,000 age-adjusted population in non-Hispanic White, approximately 3.8 times higher than in American Indians/Alaskan Natives who have the second highest incidence (16.5 per 100,000 age-adjusted population), and 33.2 times higher than in African Americans (NCI-SEER 2023).	Melanoma is a serious and life-threatening condition. Historically, the prognosis for advanced melanoma has been poor. With the introduction of ICIs, outcomes have improved significantly. However, there exists a high unmet medical need for patients with disease progression after the first-line therapy containing an anti-PD1 agent.
Current Treatment Options	• Current treatment approach for patients with unresectable or metastatic melanoma includes ICIs such as pembrolizumab, nivolumab, nivolumab plus ipilimumab, and nivolumab plus relatlimab. • Relapses following the treatment with ICI are challenging to treat. • Several kinase inhibitors targeting BRAF V600 mutations including dabrafenib plus trametinib, vemurafenib plus cobimetinib, encorafenib plus binimetinib, and atezolizumab plus cobimetinib plus vemurafenib. • However, at least 50% of patients do not respond to the first line therapy, and approximately 50% of patients develop PD within a year (refer to FDA labels for the above first line therapies). • There is no FDA-approved subsequent lines of systemic therapy after FDA-approved first line ICIs and biomarker targeted therapies. • Principles of subsequent treatment recommended by best clinical practice guidelines include: 1) another approved anti-PD1, or different class (e.g., anti-CTLA4); 2) combination therapy if first line was monotherapy (e.g., nivolumab + relatlimab; nivolumab + ipilimumab); 3)	Given that at least 50% of patients either do not respond or experience PD within a year after the first line anti-PD1-based therapies, there is a high unmet medical need for developing safe and effective treatments for patients with progressive disease following anti-PD1-based first line therapies.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	re-induction with the same agent or same class if patients previously achieved at least SD and relapsed more than 3 months after treatment discontinuation; and 4) IL-2, chemotherapy (e.g., carboplatin and paclitaxel, temozolomide, dacarbazine). • These recommended subsequent lines of treatment options are mostly based on lower-level clinical evidence and prior treatment history. Overall response rate varies from 3% to 20% assessed by local investigators and depending on intensity of prior treatment (Hersh et al. 2010; Hersh et al. 2015; Buchbinder et al. 2016).	
Benefit	• In the primary efficacy analysis set of Study C-144-01 (Cohort 4, N=82), lifileucel demonstrated a clinically meaningful ORR of 28.0% (95% CI: 18.7%-39.1%, N=82) including CR in 3 (3.7%) and PR in 20 (24.4%) subjects, assessed by IRC using RECIST v1.1. • The duration of objective responses (n=23) ranged from 1.4 to 26.3 months, with the median DOR not reached. • Among subjects in the primary efficacy analysis set who achieved a confirmed CR or PR (n=23), 56.5%, 47.8%, and 43.5% maintained durable responses at 6, 9, and 12 months following the initial response. • The ORR result based on the Cohort 4 primary efficacy analysis set (N=82) was supported by ORR results based on Cohort 2 efficacy set (ORR =34.8%, 95% CI: 23.5%-47.6%, N=66) and pooled Cohort 2 and 4 efficacy set (ORR =31.4%, 95% CI: 24.1%-39.4%, N=153), assessed by IRC using RECIST v1.1.	An ORR of 28.0% and durable response rate of 56.5%, 47.8%, and 43.5% at 6, 9, and 12 months, respectively, following initial response show clinically important and meaningful efficacy given that there is no FDA-approved systemic therapy for previously heavily treated patients with unresectable metastatic melanoma, and overall ORRs reported in the literature for this setting were generally less than 20%. Therefore, FDA concurs with the Applicant that Study C-144-01 met its primary objective.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety population included 160 subjects (156 received lifileucel) with melanoma from Study C-144-01, and an additional 184 subjects (173 received lifileucel) with other solid tumors from the following lifileucel studies and cohorts where lifileucel was a monotherapy: Study C-145-03 Cohort 2 (HNSCC, n=18), C-145-04 Cohort 1+2+4 (cervical cancer, n=107), IOV-LUN-002 Cohort 1+2, and IOV-COM-202 Cohort 3B (NSCLC, n=59). • Study treatment-related death rate in Study C-144-01 was 7.5% (12/160) including 2 deaths during NMA-LD period, 6 deaths within 30 days following lifileucel infusion, and 4 deaths within 38-150 days following lifileucel infusion. • Primary safety analysis was based on 156 subjects from Study C-144-01 who received Gen 2 lifileucel (primary safety analysis set). Significant risks based on this primary safety analysis set are summarized below: – Most common (≥10%) Grade 3 or 4 TEAEs (occurring during the first 30 days post lifileucel as defined by the Applicant) in descending order were thrombocytopenia (79.5%), neutropenia (70.5%), anemia (66.7%), febrile neutropenia (47.4%), leukopenia (47.4%), lymphopenia (43.6%), hypophosphatemia (31.4%), infection (20.5%), hypoxia (13.5%), hypotension (12.2%), and pyrexia (12.2%). – Overall, 95.5% (149/156) of subjects experienced at least one Grade 3 TEAE and 87.8% (137/156) experienced at least one Grade 4 TEAE. FDA notes that most of the high grade TEAEs were cytopenia and were manageable through standard of care. However, some high grade TEAEs were not resolved. FDA found that 25.0% (39/156) of subjects had one or multiple Grade 3 or 4 TEAE unresolved to Grade 2 or lower at the time of death, a few of which contributed to the	The occurrence rates of high-grade adverse reactions and study treatment-related deaths observed in Study-C-144-01 appear to be higher than FDA-approved ICIs for unresectable or metastatic melanoma. The study treatment-related death rate in Study C-144-01 appears to be comparable with or slightly higher than FDA-approved CAR T therapies for hematological cancers. However, FDA did not find significant new risks in lifileucel trials specific to lifileucel which were previously unknown to NMA-LD, IL-2, or other immunotherapies. The frequency and severity of adverse reactions observed in Study C-144-01 were mostly expected based on the components of the lifileucel regimen. Due to the multi-component nature of the lifileucel regimen, FDA is unable to parse out the contribution of lifileucel to these known risks or determine if these known risks have been potentiated by the addition of lifileucel. REMS was not recommended for lifileucel

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	deaths of study subjects as assessed by FDA. – Most serious adverse reactions (SARs) included acute respiratory failure, renal failure, cardiac arrhythmia, severe infections including pneumonia, sepsis and septic shock and encephalitis, internal organ hemorrhage, ascites and liver injury, and bone marrow failure. These SARs were at least possibly related to 12 deaths (12/160=7.5%) among subjects in Study C-144-01 who initiated the lifileucel regimen. – Based on additional data submitted by the Applicant, FDA found that 23.6% (21/89) of study subjects who received lifileucel in Cohort 4 of Study C-144-01 were transferred to ICU for non-infusion related activities such as managing adverse events and stabilizing study subjects post infusions. • Hemophagocytic lymphohistiocytosis (HLH) was a rare event in all lifileucel trials. However, it was related to the death of two subjects with NSCLC after receiving lifileucel. • Safety profile of lifileucel regimen was consistent across lifileucel trials except that pulmonary toxicity-related deaths was more prevalent (30-day death rate was ~12%) among study subjects with NSCLC based on preliminary trial data.	due to the lack of specific serious risks. To mitigate serious risks associated with the lifileucel regimen, the following risk mitigation measures are taken through the FDA-approved label (USPI): 1) disclosing significant risks associated with the lifileucel regimen; 2) mitigating risks through Boxed Warning and Warnings and Precautions; 3) mitigating risks by administering the lifileucel regimen in a hospital inpatient setting to ensure that patients have immediate access to ICU. 4) including a patient information in USPI. FDA recommends that healthcare providers assess benefit/risk ratio for each patient before and during the treatment course, and in the event of a SAR, re-assess the benefit over risk of completing the treatment course.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Section 8.1.1.3 Study endpoints]
		☐	Patient-reported outcome (PRO) Patient-reported outcomes for HRQoL were assessed using the EORTC QLQ-C30 v3.0 instrument and analyzed per the published evaluation manual. Baseline scores, post-Baseline scores, and change from baseline for each scale and single item measure were descriptively tabulated (number, mean, SD, median, min, max) at each timepoint	
		☐	Observer-reported outcome (ObsRO)	
		☐	Clinician-reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that was not submitted in the application but was considered in this review.			

The FDA's Assessment:

No specific patient experienced data were used to support this BLA review. Also refer to Sections 2.1, 8.1.1.3, and 8.1.2.11.

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2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position

Melanoma is the fifth most commonly diagnosed form of cancer in the United States (U.S.) (Siegel et al. 2022). This represents approximately a third of newly diagnosed melanoma cancer cases worldwide (99,780 in the U.S. (Siegel et al. 2022) and 324,635 worldwide (Sung et al. 2021) in 2022). In the U.S. in 2020, it was estimated that 4% of patients have metastatic melanoma at the time of diagnosis (Howlader et al. 2020). In 2022, the mortality rates for melanoma were 7,650 in the U.S. and 99,780 worldwide.

While in situ and locally invasive melanomas are curable by surgery, metastatic disease is difficult to treat and remains a significant public health concern (Steininger et al. 2021). Despite advances in front-line treatment that include immune checkpoint inhibitor (ICI) therapies administered alone or in combination, targeted therapies, and therapies such as the fixed-dose combination of nivolumab/relatlimab (programmed cell death protein-1 [PD-1 blocking antibody]/lymphocyte activation gene-3 [LAG-3] blocking antibody)(National Comprehensive Cancer Network (NCCN) 2022), the majority of patients do not achieve long-term benefit from these therapies (Larkin et al. 2015; Luke et al. 2017; Gide et al. 2018; Long et al. 2022). A large observational study followed 383 consecutive patients receiving PD-1/programmed death-ligand 1 (PD-[L]1) blocking antibodies for advanced melanoma, among whom 247 patients experienced disease progression (Patrinely et al. 2020). Despite a variety of different treatment approaches employed, the median survival after progression was 6.8 months and responses to subsequent systemic therapy were meaningful only for those eligible for BRAF-targeted therapy as a subsequent line. Patients with metastatic melanoma who are progressing after treatment with ICIs (including combination therapies) and/or targeted agents, when appropriate, thus represent a population with limited therapeutic options, low response rates to currently used treatments, and short survival.

The FDA's Assessment

FDA concurs with the Applicant. More than 50% of patients with unresectable or metastatic melanoma do not respond to FDA-approved first line anti-PD1-based immunotherapies as monotherapies or in combination or experience progressive disease (PD) within a year after the first-line therapies. The prognosis for these patients after PD is poor. FDA agrees that there is a high unmet medical need for developing safe and effective treatments for this patient population.

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2.2. Analysis of Current Treatment Options

The Applicant's Position

Unresectable or metastatic melanoma is a life-threatening condition that is difficult to treat and, despite recent advances in treatment, there remains a significant unmet medical need. Currently there are no therapies approved by the FDA for the treatment of unresectable or metastatic melanoma progressing after treatment with ICIs. Guidelines from the National Comprehensive Cancer Network (NCCN) recommend the use of therapies whose mechanism of action (MOA) differs from prior lines of therapy that resulted in poor response, disease progression, or unacceptable toxicity. Agents listed by the NCCN panel for second-line or subsequent therapy include PD-1 blocking antibodies (pembrolizumab, nivolumab), CTLA-4 blocking antibodies (ipilimumab), cytotoxic chemotherapy, and, if BRAF mutation-positive, BRAF inhibitors (dabrafenib, vemurafenib, encorafenib) in combination with MEK inhibitors (trametinib, cobimetinib, binimetinib) with the caveat that rechallenge with a therapy from the same therapeutic class is unlikely to be successful.

The eligibility criteria for Study C-144-01 required that the patients had progressed after PD-1 blocking antibody therapy and a BRAF inhibitor or BRAF inhibitor in combination with a MEK inhibitor, if appropriate. Prior treatment with a CTLA-4 blocking antibody either as a separate line or in combination was allowed. There were no restrictions with regard to the maximum number of prior therapies. As such, NCCN guideline-recommended therapies (i.e., ICIs in monotherapy or combination) are generally not treatment options for this patient population, given their prior exposure to or progression on such agents. Remaining available treatment options are currently limited to IL-2 and dacarbazine (both FDA-approved for use in melanoma) and clinical trials or best supportive care. There are currently no published prospective clinical trial data for use of IL-2 after prior ICI.

The response rates to dacarbazine after ICI are low [i.e., 10%, (Goldinger et al. 2022)]. The ORR to dacarbazine or investigators' choice chemotherapy (including agents not specifically FDA-approved for melanoma) from the control arms of the KEYNOTE-002 and CheckMate-037 clinical trials were 4% to 11% (Weber et al. 2015b; Hamid et al. 2017b).

Data on response rates to FDA-approved agents that have been explored in the second line after progression on PD-1 blocking therapy are limited and derived from control arms of prospective randomized studies, smaller retrospective case series or meta-analyses of such data, real world evidence, or limited numbers of prospectively treated patients with investigator-assessed responses (Table 1). There are several caveats with the latter, including the response criteria used (Response Evaluation Criteria in Solid Tumors [RECIST] or the modified RECIST for immune-based therapeutics [iRECIST] criteria) and inclusion of only CTLA-4 naïve patients. Another caveat is the inclusion of a significant proportion of patients progressing after PD-1 exposure in the adjuvant setting alone [e.g., (Olson et al. 2021;

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Vanderwalde et al. 2022)]. With these limitations, the available data are summarized in Table 1. The response rates to these therapies are unsatisfactory and thus a high unmet need exists in this patient population.

Table 1. Applicant – Response Rates of FDA-Approved Melanoma Therapies in Previously ICI-treated Unresectable or Metastatic Melanoma Patients

Therapy	Patient Population	Response Rates (Range)	Study Type	Comment References
Cytotoxic Chemotherapy				
Dacarbazine	PD-1 exposed patients receiving dacarbazine (N=118)	10.2%	Retrospective	(Goldinger et al. 2022)
Investigator choice agents	Second-line therapy in metastatic melanoma where chemotherapy was the control arm N=179 (Hamid) N=133 (Weber)	4%-11%	Randomized prospective trials (KEYNOTE 002; CheckMate 037)	(Weber et al. 2015a; Hamid et al. 2017a)
PD-1 Blocking Antibody Monotherapy Retreatment after Progression				
PD-1 monotherapy after progression on a PD-1 blocking antibody	Compilation of PD-1 rechallenge case series (N=85); U.S. single center series (N=34)	15%-16%	Retrospective series compilation	(Betof Warner et al. 2020; Reschke and Ziemer 2020)
Ipilimumab Monotherapy/Ipilimumab+PD-1 Blocking Antibody Combination				
Ipilimumab monotherapy after pembrolizumab	Follow-up of the KEYNOTE 006 trial (N=97)	4%-14%	Prospectively enrolled	(Long et al. 2017)
Ipilimumab + a PD-1 blocking antibody after progression on a PD-1 blocking antibody	N=70 (Olson) N=70 (Vanderwalde) N=37 (Zimmer) N=19 (Gaughan)	11%-28%	Combination of prospective and retrospective studies	RECIST criteria not used; investigator-assessed responses; significant heterogeneity in inclusion criteria (Gaughan et al. 2017; Zimmer et al. 2017; Olson et al. 2021; Vanderwalde et al. 2022)
Ipilimumab after first line a PD-1 blocking antibody	N=116	8%	Real world evidence	(Cybulska-Stopa et al. 2020)
Relatlimab + Nivolumab Combination				
Relatlimab/nivolumab combination after progression on a PD-1 blocking antibody	N=43; efficacy reported in 31 patients	16%	Prospective trial	(Ascierto et al. 2017)

Abbreviations: FDA = Food and Drug Administration; ICI = immune checkpoint inhibitor; PD-1 = programmed cell death protein-1; RECIST = Response Evaluation Criteria in Solid Tumors

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The FDA's Assessment

There is no FDA-approved treatment for unresectable or metastatic melanoma which has progressed after the first line of systemic therapy with an FDA-approved anti-PD1-based ICI, and biomarker targeted therapies (if applicable). In the clinical setting, treatment for these patients may include: 1) another approved anti-PD1 or different class (e.g., anti-CTLA4); 2) combination therapy if the first line was a monotherapy (e.g., nivolumab + relatlimab, nivolumab + ipilimumab); 3) re-induction with the same agent or same class if patients previously achieved at least stable disease (SD) and relapsed more than 3 months after treatment discontinuation; and 4) IL-2, chemotherapy (e.g., carboplatin and paclitaxel, temozolomide, dacarbazine).

However, based on published literature as indicated in Applicant Table 1, overall tumor response rates of these subsequent systemic therapies were less than 20%, most of which were based on retrospective cohort studies, investigator-initiated trials not regulated by FDA, and tumor responses assessed by local investigators instead of central independent reviewers.

A recently published randomized controlled trial (RCT, N=168 with 1:1 randomization) conducted in the Netherlands compared an autologous TIL product to ipilimumab among subjects with Stage IIIC to IV melanoma (Rohaan et al. 2022). The results from this trial suggest a significantly improved PFS and ORR among subjects treated with TIL [median PFS =7.2 (95% CI: 4.2 to 13.1) months; ORR =49% (95% CI: 38% to 60%)] compared with subjects treated with ipilimumab [median PFS =3.1 months (95% CI: 3.0 to 4.3) and ORR =21% (95% CI: 13% to 32%)]. Of note, although most subjects (89%) enrolled in this trial had received one line of prior anti-PD1, 11% had not received systemic therapy prior to the trial enrollment. Additionally, tumor responses were assessed by investigators instead of a central IRC. In contrast, all subjects enrolled to Study C-144-01 received at least one prior line of anti-PD1-based therapy and a median of two lines of prior anti-PD1-based therapies. Additionally, Study C-144-01 implemented IRC for tumor assessments to support the marketing application, per FDA request (also refer to FDA Table 3 in Section 3.2).

FDA concludes that there is a high unmet medical need for a safe and effective subsequent treatment for patients with unresectable or metastatic melanoma which has progressed after FDA-approved anti-PD1-based systemic therapies and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position

Lifileucel is not currently registered or approved in the U.S. or any other country.

The FDA's Assessment

FDA concurs that lifileucel is not currently registered or approved in the U.S. or any other country in the world.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position

A pre-Investigational New Drug application (pre-IND) meeting was held on 7/20/2012, at which FDA agreed that no additional nonclinical studies were needed to support the initiation of Study C-144-01. The original IND was then submitted (IND 16317) and the trial was initiated on 12/30/2014.

Lifileucel has been granted both Fast Track (8/29/2017) and Regenerative Medicine Advanced Therapy (RMAT, 8/24/2018) designations for the treatment of advanced melanoma. The Sponsor and the Agency subsequently met on several occasions to discuss the lifileucel development program (Table 2).

Table 2. Applicant – Key Regulatory Meetings for the Lifileucel Development Program

Date	Meeting Description	Key Outcomes
9/11/2018	Type B EOP2 meeting (CRMTS# 11302)	FDA and the Sponsor agreed on the following preliminary description for the indication: "Patients with unresectable or metastatic melanoma who have previously been treated with (b) (4) (b) (4) including a PD-1 blocking antibody and if BRAF V600 mutation positive, a BRAF inhibitor or BRAF inhibitor (b) (4) MEK inhibitor." In addition, it was acknowledged that lifileucel registration for this indication could be supported by a single-arm study.
6/26/2019	Type B RMAT multidisciplinary meeting (CRMTS# 11801)	At the RMAT multidisciplinary meeting, FDA indicated that results from Study C-144-01 Cohort 4 may provide primary evidence of effectiveness for a BLA submission, and Cohort 2 could provide supportive data. During this meeting, the Sponsor agreed to submit certain information addressing specific CMC topics.

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Date	Meeting Description	Key Outcomes
7/29/2022	Type B Pre-BLA Meeting (CRMTS# 14161)	At the pre-BLA meeting, FDA indicated that an Accelerated Approval pathway is feasible and recommended requesting a rolling BLA submission in order to allow for further agreement on the CMC components of the BLA. The FDA also requested inclusion of additional safety data from other ongoing Iovance-sponsored TIL studies in the BLA. In general, there was agreement on the overall format and content of the proposed BLA.
9/29/2022	Type B Pre-Phase 3 Meeting (CRMTS#14304)	FDA and the Sponsor agreed on the key elements of the proposed Phase 3 confirmatory study design, including primary endpoints and key secondary endpoints. Additional discussion was held on the patient population to be enrolled, timing of tumor resection, and statistical considerations

Abbreviations: BLA = Biologics License Application; BRAF = proto-oncogene B-Raf; CMC = Chemistry, Manufacturing, and Controls; CRMTS = Center for Biologics Evaluation and Research Regulatory Meeting Tracking System; EOP2 = End-of-Phase 2; FDA = Food and Drug Administration; MEK = mitogen-activated extracellular signal-regulated kinase; PD-1 = programmed cell death protein-1; RMAT = Regenerative Medicine Advanced Therapy; TIL = tumor-infiltrating lymphocytes

The FDA's Assessment

FDA concurs with the Applicant regarding the regulatory history.

FDA notes that at the EOP2 meeting on 8/24/2018, the Applicant and FDA agreed to add Cohort 4 to ongoing Study C-144-01 and implement an IRC for the assessment of tumor responses. Furthermore, at the 6/26/2019 meeting, FDA and the Applicant agreed that Cohort 4 of Study C-144-01 may serve as the basis for providing primary efficacy evidence for a Biologics License Application (BLA) submission with the efficacy results from Cohort 2 as supporting evidence.

FDA notes that a new Phase 3 confirmatory trial (IOV-MEL-301) sponsored by the Applicant is now open for enrollment. Trial IOV-MEL-301 is an open-label, randomized, controlled, multicenter, multiregional trial to compare the efficacy and safety of the lifileucel regimen plus pembrolizumab with pembrolizumab alone in the front-line treatment setting for the treatment of untreated, unresectable, or metastatic melanoma. ORR and PFS are dual primary efficacy endpoints to be assessed by a blinded independent review committee. OS is the key secondary efficacy and safety endpoint. The confirmatory trial is required to demonstrate an improvement in the PFS outcome without a detriment to the OS outcome. Approximately 670 eligible study subjects are planned to be randomized at a 1:1 ratio into the lifileucel plus pembrolizumab arm and the pembrolizumab alone arm, respectively. Eligible subjects are either prior anti-PD1 treatment-naïve (~600 subjects) or only treated in adjuvant or neoadjuvant settings (~70 subjects).

Approximately 120 study sites in 22 countries are planned across U.S., Canada, Australia, United Kingdom, European Union, Israel, and South Korea. Of the 120 planned study sites, 101 have started site initiation process.

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As of 1/16/2024, five subjects have been randomized and two subjects have undergone tumor resection. All randomized subjects have initiated study therapy with pembrolizumab.

Per Applicant, 10 out of planned 120 study sites have been activated. Approximately 40 sites are projected to be open globally by 3/31/2024.

The primary analysis of PFS is expected in the third quarter of Year 2028 (3Q2028), and the final analysis of OS is expected in the first quarter of Year 2030 (1Q2030).

FDA notes that Trial IOV-MEL-301 is conducted under a postmarketing requirement. Refer to Section 14.

Refer to FDA Table 3 for additional regulatory history.

Table 3. FDA – Additional Important Regulatory History

Date	Milestone Activity
1/30/2015	IND Safe to proceed
6/9/2015	ODD granted for lifileucel for the treatment of malignant melanoma Stage IIB to IV.
3/31/2017	BTD request for the treatment of patients with metastatic melanoma following at least two systemic therapies denied mainly due to product comparability issues.
8/29/2017	FTD for the treatment of advanced melanoma granted
8/24/2018	RMAT designation for the treatment of advanced melanoma granted
12/272018	Cohort 4 added to Study C-144-01; IRC implemented
3/27/2023	Final module of rolling BLA submission received
5/26/2023	BLA filed. The filing met priority review criteria.
7/27/2023	Mid-cycle meeting with Applicant. Major CMC review issues were discussed. No substantial review issues identified by other review teams.
9/8/2023	FDA notified the Applicant that the Applicant's amendment submitted on 8/28/2023, contained a substantial amount of new data not previously submitted to or reviewed by FDA and a new analysis of studies not previously submitted to the BLA. FDA considered this amendment as a major amendment, which added additional 3 months for review. The new PDUFA due date was reset to 2/24/2024, in lieu of 11/24/2023.
11/20/2023	Late-cycle meeting with Applicant. Remaining major CMC issues were discussed with the Applicant. FDA notified the Applicant that no REMS was recommended for lifileucel.
1/24/2024	FDA revised USPI conveyed to the Applicant
2/24/2024	FDA action due date (ADD)

Abbreviations: BLA = Biologics License Application; CMC = Chemistry, Manufacturing, and Controls; FTD = Fast Track Designation; IND = investigational new drug; IRC = Independent Review Committee; ODD = Orphan Drug Designation; REMS = Risk Evaluation and Mitigation Strategy; RMAT = Regenerative Medicine Advancement Therapy

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Bioresearch Monitoring (BIMO)

FDA selected three clinical investigators for audit: Dr. Amod Sarnaik (Site 003), Dr. Harriet Kluger (Site 004), and Dr. Karl Lewis (Site 019). These study sites enrolled among the highest number of subjects, including Site 003 (30 subjects), Site 004 (16 subjects), and Site 019 (18 subjects). Sites 003 and 004 have had no prior inspections. Site 019 was previously inspected on 02/20/2015 with no findings.

During the inspection of Site 019, the following 483 inspectional observations were made:

- Observation 1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.
- Observation 2: Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.
- Observation 3: A copy of the written consent form, which had been approved by the institutional review board and signed and dated by the subject or the subject's legally authorized representative, was not provided to the subject or the subject's legally authorized representative at the time of consent.

The FDA inspectors did not identify significant issues in Sites 003 and 004. .

The FDA OSI concludes that issues identified during the inspections did not appear to have affected the interpretation of study data or biased the study results in favor of efficacy.

Based on the results of these inspections, the study appears to have been conducted adequately and the data generated by the inspected entities appear to be acceptable in support of this BLA.

See Section 8.1.2.1 for more details.

4.2. Product Quality

During the review process, the following issues were identified:

- The proposed process controls may not be sufficient to ensure control/consistency of the manufacturing process.
- The proposed product attributes may not be sufficient to ensure manufacturing consistency/control and distinguish a quality and potent drug product lot.

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- Adequate demonstration of comparability between (b) (4) iCTC manufacturing sites is necessary to utilize iCTC at launch.
- A formal simulated, (b) (4) study assessing cumulative leachables from all high-risk process components preceding the container closure system should be performed.

4.3. Clinical Microbiology

There were no Chemistry, Manufacturing, and Controls (CMC) concerns regarding clinical microbiology.

4.4. Devices and Companion Diagnostic Issues

No device or companion diagnostic were needed to support the benefit-risk assessment of this BLA Application.

5 Nonclinical Pharmacology/Toxicology

Refer to FDA Pharmacology/Toxicology review memo for this BLA.

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6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment

Please see FDA Clinical Pharmacology reviewer's memo for discussion of this section.

Analysis of the dose-efficacy relationship based on DOR (categorized as ≥12 months or <12 months) showed no association between DOR and total infused dose. The dose-efficacy analysis showed a weak positive trend with best overall response (BOR). The median dose resulting in complete response (CR) or partial response (PR) was 30.0 x 10^9 cells (range: 6.2 x 10^9 to 72 x 10^9) and a higher probability of CR or PR is expected with a higher dose. No significant correlation was found between exposure (i.e., persistence) and efficacy. Exploratory dose-exposure analysis showed a weak positive trend for increased persistence with a higher dose. The mean tumor-derived T cell persistence was 36±24% for subjects who received lower than the median lifileucel dose of 30.0 x 10^9 cells which yielded CR or PR, and 49±25% for subjects who received higher than the median lifileucel dose.

Overall, the clinical pharmacology analysis supports the Accelerated Approval of lifileucel for the treatment of unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

Refer to FDA Clinical Pharmacology review memo.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data

The relatively short and unselected process used to manufacture lifileucel is an optimal process to generate a diverse repertoire of memory T cells. This process ensures the inclusion of tumor-reactive T cells in the final product and results in a personalized autologous cell product to which conventional pharmacokinetic (PK) metrics do not apply. (b) (4) was used to verify the high polyclonality of the resulting lifileucel melanoma TIL product and to determine the magnitude and durability of TIL-associated clonotype abundance and persistence in patients for up to 1-year post-infusion.

In Vivo Persistence of the Lifileucel TIL Product

Individual TIL products and PBMC samples collected pre- and post-TIL infusion were studied using polymerase chain reactions (PCR) followed by (b) (4) of the

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(b) (4) of the variable region of the T cell receptor's (b) (4) Bioinformatics analysis was applied to characterize the TIL products and clonotypes present in the TIL and (b) (4) samples to document persistence at post-infusion timepoints.

TIL Product Characterization

Assessment of individual TIL product lots of Study C-144-01 Cohort 2 subjects revealed counts between 959 and 21,187 of unique T cell clones per lot, with a mean of 6,159 and median of 5,287 clonotypes per product. A total of 366,441 clones were identified across all TIL products. Of these clones, 349,221 (95.3%) were subject-specific, identified only in single subjects.

Assessment of individual TIL product lots of Study C-144-01 Cohort 4 subjects revealed counts between 491 and 14,904 of unique T cell clones per lot with a mean of 3,543 and median of 2,792 clonotypes per product. A total of 292,050 clones were identified across all TIL products. Of these clones, 281,134 (96.3%) were patient-specific, identified only in single subjects.

TIL Persistence In Vivo

Using the T cell receptor (TCR) repertoires established as described above for each lifileucel product lot, in vivo abundance of the individual clones that made up each lot could be assessed prior to TIL infusion and monitored after TIL infusion.

Substantial fractions of these clones were shown to persist in the blood of all infused subjects, for all timepoints assessed up to 1 year post TIL infusion; specifically, clones were detected in 100% of subjects (46/46 in Cohort 2 and 74/74 in Cohort 4) at Day 42, 100% of subjects (12/12 in Cohort 2 and 22/22 in Cohort 4) at Month 6, and 100% of subjects (11/11 in Cohort 2 and Cohort 4, each) who had PBMC samples available at Month 12. The proportion of TCR repertoire composed of clonotypes present in TIL and subject blood samples increased from 23% pre-infusion to an average of 93% at Day 4 in Cohort 2 subjects and from 12% pre-infusion to an average of 79% at Day 4 in Cohort 4 subjects, suggesting that the TIL product lot contributes T cell clones to the patient circulation that were not detectable pre-cell transfer.

The Applicant's Position

Lifileucel TIL products were highly polyclonal and patient-specific. Overall, while not amenable to classic PK and pharmacodynamic parameter calculations, 100% of the subjects showed in vivo persistence of the transferred T cells at all timepoints studied. Frequency of the persisting clones varied over time and across subjects but suggested that the TIL product lots contribute T cell clones to the patient circulation that were not detectable pre-cell transfer.

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The FDA's Assessment

Because of the nature of lifileucel, conventional studies on pharmacokinetics (absorption, distribution, metabolism, and excretion) are not applicable.

Most subjects received 6 doses of IL-2 (i.e., 53 out of 87 subjects in Cohort 4 full efficacy set, and 32 out of 66 subjects in Cohort 2 full efficacy set), suggesting that 6 doses of IL-2 were tolerated by most study subjects. However, some subjects did not tolerate 6 doses of IL-2. In Cohort 4, 9 subjects received 1 to 3 doses of IL-2 and 23 subjects received 4 to 5 doses of IL-2. The Applicant's data suggest that the lifileucel persistence data among these three subsets (1 to 3 versus 4 to 5 versus 6 IL-2 doses) were comparable. In addition, there appeared to be a trend for higher lifileucel persistence among those who received 1 to 4 doses versus 5 to 6 doses.

These lifileucel persistence data appear to indicate that patients to be treated in the future may still achieve clinical benefit with less than 6 doses of IL-2.

Overall, caution is needed in interpreting subgroup analyses of lifileucel persistence for different dosing regimens of IL-2 due to the higher variability of lifileucel persistence and small sample sizes of subjects who received less than 6 doses of IL-2. Based on the current lifileucel persistence data, the Applicant's proposed up to 6 doses of IL-2 based on tolerability is acceptable. FDA recommends that the Applicant continue to monitor safety, efficacy, and lifileucel persistence in the ongoing trials to further optimize IL-2 dosing regimens for various patient populations.

Refer to Section 6.3.2.3 "FDA Assessment of Appropriateness of Applicant-Selected Six Doses of IL-2 for Lifileucel Regimen.". Also refer to FDA Clinical Pharmacology review memo.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data and The Applicant's Position

Lifileucel is provided as a single dose in up to four patient-specific IV infusion bag(s). The entire dose is administered.

The FDA's Assessment

FDA concurs that lifileucel is autologous tumor-derived T cells suspended in a cryopreserved medium and provided as a single dose in up to four patient-specific IV infusion bags. The lifileucel dose range selected by the Applicant for the lifileucel trials was 1 x 10^9 to 150 x 10^9 viable cells. The upper limit was based on published literature (Dudley et al. 2005; Radvanyi et al. 2012) and the lower limit was based on data collected in the initial study subjects enrolled to

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Cohort 1 of Study C-144-01 and received Gen 1 product (refer to Applicant Table 5). Study subjects were expected to receive all manufactured viable cells that met the release criteria.

Refer to FDA comments in Section 8.1.2.10.3 for the actual lifileucel dose range administered to subjects enrolled to Cohort 2 and 4 of Study C-144-01.

6.2.2.2. Therapeutic Individualization

Data and The Applicant's Position

Not applicable.

The FDA's Assessment

FDA concurs with the Applicant.

6.2.2.3. Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data and The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA concurs with the Applicant.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Data and The Applicant's Position

Not applicable. Establishing classic PK and pharmacodynamic parameters is not feasible for TIL.

The FDA's Assessment

FDA concurs with the Applicant.

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6.3.2.2. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

Data

Study C-144-01 was not designed as a dose-response study because the entire individual patient-specific lot is administered. Formal tests of hypotheses or quantitative evaluation were not amenable given the patient-specific, autologous nature of lifileucel. Exploratory analyses evaluated dose-response using visual displays.

As illustrated in Figure 1 for the Full Analysis Set (FAS, defined as subjects who received lifileucel that met the manufacturing product specifications) of Cohort 4, the distribution of the TIL dose in the disease control (i.e., subjects with a BOR of CR, PR, or SD; N=72) and non-disease control (i.e., subjects with BOR of PD or not evaluable; N=15) groups was largely overlapping. Importantly, disease control was observed in subjects who had received cell doses that were lower than the lowest dose received in the non-disease control group (minimum cell dose of 1.34 x 10^9 in a subject with disease control and 5.34 x 10^9 in a subject with non-disease control).

For the FAS of Pooled Cohorts 2 and 4, the distribution of the TIL dose in in the disease control (N=120) and non-disease control (N=33) groups was also largely overlapping. Disease control was observed in subjects who had received low cell doses, with no meaningful difference of minimum doses in the groups with and without disease control identified. Lastly, non-disease control was observed in subjects who had received a high cell dose, with only a single subject who had achieved disease control having received a higher cell dose than any subject with non-disease control.

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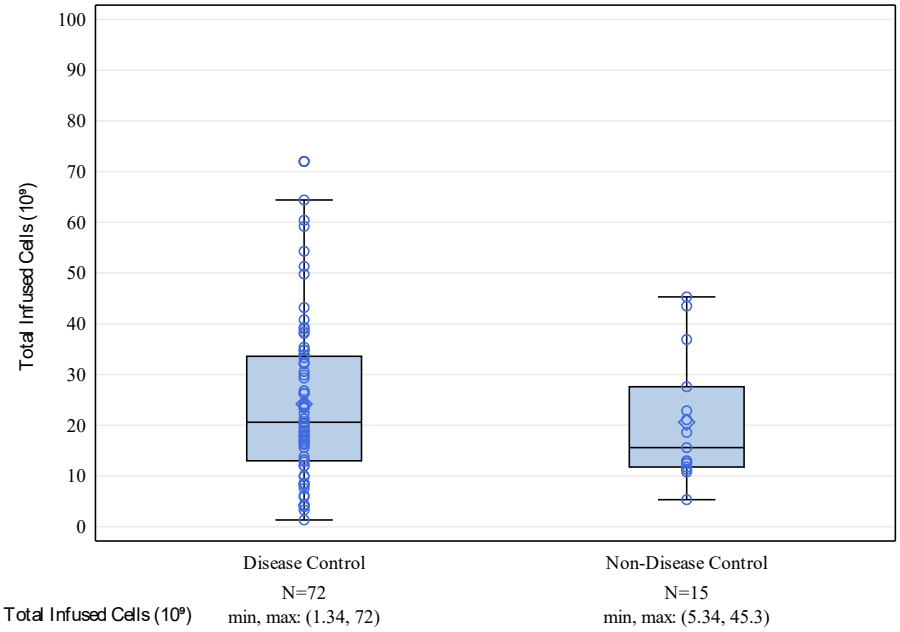
Figure 1. Applicant – Total Infused Cells by Disease Control as Assessed by the IRC per RECIST v1.1 for Cohort 4 (Full Analysis Set)



Source: C-144-01, Program: f14-2-7-1-box-til-orr-irc-c4-fas.sas, Data: ADSL and ADRS, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
NOTES: The subgroup of disease control includes subjects with a BOR of CR, PR, or SD and the subgroup of non-disease control includes subjects with a BOR of PD or NE.
Abbreviations: BOR = best overall response; CR = complete response; IRC = Independent Review Committee; max = maximum; min = minimum; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

An analysis of the dose received by best percent change in target lesion sum of diameters (SoD) from Baseline by disease/non-disease control groups was also performed for the FAS of Cohort 4 and Pooled Cohorts 2 and 4. Although linear regression analysis suggested a weak association between lifileucel dose and target lesion SoD change, tumor burden reductions were achieved across the entire range of doses administered in both analyses.

Finally, a subgroup analysis of ORR by median TIL dose was performed. The lower bound of the 95% CI exceeded the null hypothesis (H_0) of 10% ORR for both subgroups based on the pooled data indicating clinically and statistically meaningful efficacy results regardless of TIL dose.

There were no meaningful differences (defined as >10% difference in incidence) between the subject subgroups who received above (n=77) or below (n=79) the median number of total infused cells (21.09 x 10^9 cells as determined for the FAS) in the overall incidence of TEAEs and TEAEs leading to the discontinuation of lifileucel. Although there was a slightly greater than 10% difference between the subject subgroups for treatment-emergent serious adverse events (TE SAEs; 40.3% versus 29.1%, respectively), this was not considered to be meaningful given that there were no such imbalances at the individual SAE level that would suggest a trend for patients to experience a particular serious event or medical condition.

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The Applicant's Position

No consistent correlation between TIL dose and the efficacy and safety variables tested was observed.

The FDA's Assessment

FDA agrees that Study C-144-01 was not designed as a dose-response study.

Although there appears to be a trend that responders received higher lifileucel doses on average than non-responders (Figure 2), the correlation was weak and there were limited number of study subjects in various dose ranges (refer to Section 12 "Labeling Recommendations"). FDA also agrees that there is no consistent or meaningful correlation between lifileucel dose and safety observed in Study C-144-01. However, due to the autologous, patient-specific, and non-modification nature of lifileucel, FDA recommends that lifileucel dose-response and dose-safety relationships be interpreted with caution.

As shown in Applicant Figure 1, the Applicant compared dosing ranges between subjects with disease control and those without disease control. However, as explained in FDA comments on Dose/Dose Response in Section 8.1.2.10.3 and Applicant's labeling recommendations in Section 12, FDA is unable to interpret the relationship between stable disease and treatment effect in a single arm trial setting.

Therefore, FDA conducted additional analyses of dose-objective response. Although FDA was unable to detect strong correlation between lifileucel dose and objective response, or detect meaningful improvement of ORR by increasing lower dose limit (refer to results in Section 12 "Labeling Recommendations"), FDA Figure 2 below shows that overall, responders (left panels on the figure) received a higher number of viable cells (overall median =30.0, mean =31.1, range: 6.2 x 10^9 to 72.0 x 10^9 viable cells) than non-responders (right panels on the figure, median =17.8, mean =22.5, range: 1.2 x 10^9 to 99.5 x 10^9 viable cells).

FDA Figure 2 also suggests that the minimum number of viable cells received by responders (6.2 x 10^9 cells) was higher than that received by non-responders (1.2 x 10^9 cells) whereas the maximum number of viable cells received by responders (72.0 x 10^9 cells) was lower than that received by non-responders (99.5 x 10^9 cells). These results appear to suggest that the dose-response relationship for lifileucel is not consistent, although there appears to be a trend that responders received a higher dose on average compared with non-responders.

For more details of the FDA recommended lifileucel dose ranges accounting for dose-objective response relationship, MOA, and the complexity of lifileucel, refer to FDA assessments in Section 12 "Labeling Recommendations."

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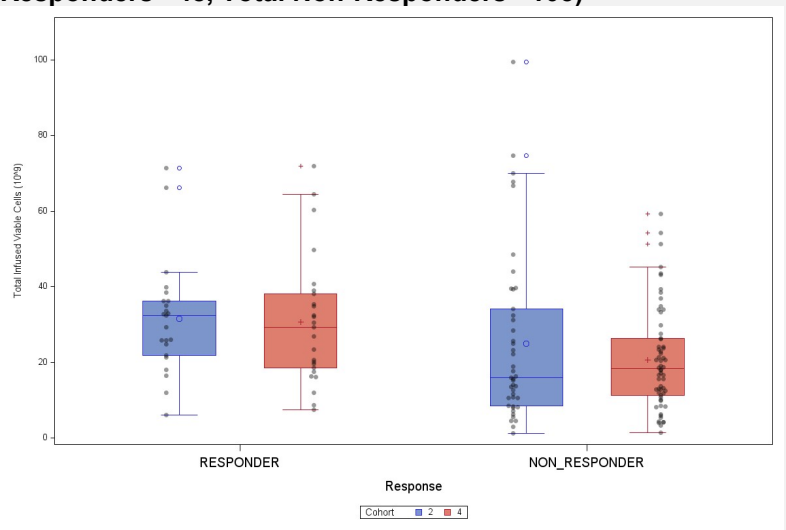
Figure 2. FDA – Box Plot of Total Infused Viable Lifileucel Cells by Objective Response Status (Assessed by IRC per RECIST v1.1) for Pooled Cohorts 2 and 4 Full Efficacy Analysis Set (Total Responders =48, Total Non-Responders =105)



Source: Datasets: ADSL, ADTTE
Abbreviations: IRC = Independent Review Committee; RECIST = Response Evaluation Criteria in Solid Tumors

6.3.2.3. FDA Assessment of Appropriateness of Applicant-Selected Six Doses of IL-2 for Lifileucel Regimen

Prior to the approval of ICIs, high-dose IL-2 was the first FDA-approved immune effector cell stimulator for the treatment of metastatic melanoma with a durable ORR of 16% (Rosenberg 2014). However, due to severe treatment-related toxicities, the use of high-dose IL-2 has been restricted to in-patient settings, where skilled providers and patient access to ICU are available.

As shown in Table 48, 42.3% of Grade 4 and 5 TEAEs in Study C-144-01 were assessed as related to IL-2 by the investigators, suggesting the need for selecting optimal IL-2 dosing to support the expansion of tumor-derived T cells and persistence without increasing IL-2 related toxicity (also refer to Applicant assessment in Section 8.2.4.8).

The IL-2 regimen (600,000 IU/kg for up to 6 doses within 4 days) selected for lifileucel studies was based on published studies of TIL conducted in Dr. Steven Rosenberg's lab at National Cancer Institute (NCI) in patients with metastatic melanoma (Dudley et al. 2002; Goff et al. 2016). Within the lifileucel regimen, the maximum potential cumulative IL-2 exposure was 3,600,000 IU/kg, significantly lower (by 79%) than the cumulative exposure demonstrating the efficacy of IL-2 as an independent monotherapy for advanced melanoma. The limited doses of IL-2 are not expected to have clinical efficacy in lymphodepleted hosts as demonstrated in other studies (Gunturu et al. 2010) but, instead, to support the expansion and persistence of TIL. Results from a trial conducted in Dr. Steven Rosenberg's lab (Goff et al. 2016) showed that subjects (n=39) who received 3 to 5 doses of IL-2 achieved slightly numerically higher CR and PR rates (CR rate =31% and PR rate =33%, respectively) than subjects (n=41) who received 6 to 8

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doses of IL-2 (CR rate =24% and PR rate =27%, respectively). This result suggests that increasing the number of IL-2 doses beyond 5 doses is not associated with improved tumor response to TIL therapy.

The Applicant's analysis results based on the full analysis set (N=153) suggest that ORR among subjects who received 1 to 4 doses of IL-2 [33.3% (95% CI: 19.6% to 49.5%), n=42] was similar to those who received 5 to 6 doses of IL-2 [31.2% (95% CI: 22.7% to 40.8%), n=109].

Additionally, the durability of ORR was numerically higher among responders who received 1 to 4 doses of IL-2 (78.6% at 6-month, and 71.4% at 12-month from initial response among responders, n=14) than those who received 5 to 6 doses of IL-2 (55.9% at 6-month and 47.1% at 12-month from initial response among responders, n=34). However, FDA notes that the ORR durability data were based on very small sample sizes of subgroup responders. These results were consistent across Cohort 2 and 4.

FDA compared the number of IL-2 doses for responders and non-responders. As shown in FDA Table 4, mean and median IL-2 doses received by responders and non-responders were no different (mean=~5 doses, median =6 doses). The results were consistent across Cohort 2 and 4 as shown in FDA Table 4.

FDA Table 4 also suggests that among all 48 responders from the pooled full efficacy analysis set (N=153), only 6 subjects received less than 4 doses of IL-2.

Based on the above analyses by both the Applicant and FDA, FDA concludes that there is no evidence to recommend against "up to 6 doses of IL-2" chosen by the Applicant for the lifileucel regimen.

However, FDA notes that Study C-144-01 was not designed to compare different IL-2 dosing regimens; receiving less than 6 doses of IL-2 merely indicated that study subjects were unable to tolerate successive IL-2 administration(s), or that more than 2 consecutive IL-2 doses were discontinued due to toxicities associated with the lifileucel regimen. Therefore, it remains uncertain whether 4 doses of IL-2 within the lifileucel regimen could be as effective as 5 or 6 doses. FDA recommends that the Applicant continue to optimize IL-2 dosing regimen through the ongoing lifileucel trials and other post-marketing studies.

Also refer to Section 6.2.1 regarding relationships between lifileucel persistence and IL-2 doses.

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Table 4. FDA – Number of IL-2 Doses in Responders and Non-Responders

Cohort Objective Response Status	Mean	Median	Minimum	Number of Subjects with IL-2<4 Doses
Pooled Cohort 2 and 4 (N=153)	-	-	-	-
Responder (n=48)	5.0	6.0	1.0	6
Non-Responder (n=105)	4.9	6.0	0.0	20
Cohort 4 (N=87)	-	-	-	-
Responder (n=25)	5.4	6.0	2.0	1 (2 doses of IL-2)
Non-Responder (n=62)	5.0	6.0	0.0	10
Cohort 2 (N=66)	-	-	-	-
Responder (n=23)	4.6	6.0	1.0	5 (three subjects had 1 dose, two subjects had 2 doses of IL-2)
Non-Responder (n=43)	4.7	5.0	1.0	10

Source: Dataset: ADSL
Abbreviations: IL-2 = interleukin-2

6.3.2.4. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors (e.g., Race, Ethnicity, Age, Performance Status, Genetic Subpopulations, etc.)?

Data and The Applicant's Position

Not applicable.

The FDA's Assessment

FDA concurs with the Applicant.

6.3.2.5. Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

Data and The Applicant's Position

Food-drug and drug-drug interactions are not relevant to lifileucel.

The FDA's Assessment

FDA concurs with the Applicant.

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data

The clinical portion of this BLA is based on the primary analysis of Study C-144-01, an ongoing Phase 2, global, multicenter, multicohort, open-label, single-arm clinical trial evaluating the efficacy and safety of treatment with lifileucel in adult patients with unresectable or metastatic melanoma (Table 5). A total of 42 sites enrolled subjects in this study: 21 in the U.S., 2 in France, 8 in Germany, 1 in Hungary, 5 in Spain, 1 in Switzerland, and 4 in the United Kingdom.

The primary analysis was performed on data that were reported up to 9/15/2021.
Study C-144-01 consists of 4 cohorts of which 2 form the basis of this submission: Cohort 4 (N=89, based on the safety analysis set, i.e., subjects who received the lifileucel infusion) and Cohort 2 (N=67). Cohort 2 and Cohort 4 subjects met the same primary eligibility criteria, had the same study assessments, and received the same treatment regimen and lifileucel that was produced using the same cryopreserved TIL manufacturing process (Gen 2) and product formulation.

Additional supportive safety data are presented from 344 subjects who received any component of the study regimen (i.e., NMA-LD, TIL, or IL-2) in a monotherapy cohort from the ongoing Iovance studies of Gen 2 TIL:

- Cervical cancer: C-145-04 Cohorts 1, 2, and 4
- Non-small cell lung cancer (NSCLC):
  - IOV-LUN-202 Cohorts 1 and 2
  - IOV-COM-202 Cohort 3B
- Head-and-neck squamous cell carcinoma (HNSCC): C-145-03 Cohort 2

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Table 5. Applicant – Listing of Clinical Trials Relevant to This BLA

Study Number ***ClinicalTrials.gov Identifier***	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s)/ Dosage Regimen/ Route of Administration**	**Number of Patients Infused with TIL**	**Patient Population**
Studies Supportive of Efficacy and Safety					
C-144-01 *NCT02360579*	<u>Primary Objective</u> Evaluate efficacy based on the ORR as assessed by the IRC per RECIST v1.1 <u>Secondary Objectives</u> Evaluate efficacy based on DOR, DCR, and PFS as assessed by the IRC per RECIST v1.1 Further evaluate efficacy based on ORR, DOR, DCR, and PFS as assessed by the Investigator per RECIST v1.1 Evaluate OS Characterize the safety profile	Open-label	NMA-LD+TIL (lifileucel)+ IL-2 **1) NMA-LD** Cyclophosphamide IV (60 mg/kg × 2 doses) with mesna over 2 days followed by fludarabine IV (25 mg/m^2 × 5 doses) over 5 days **2) TIL (lifileucel)** IV infusion after completion of NMA-LD (1 day) **3) IL-2** 600,000 IU/kg IV approximately every 8 to 12 hrs (maximum of 6 doses) with the first dose within 3 to 24 hrs after completion of the lifileucel infusion over up to 4 days	Cohort 1 (Gen 1): 23 Cohort 2 (Gen 2): 67 Retreatment Cohort 3 (Gen 2): 11 Cohort 4 (Gen 2): 89	Melanoma Adult patients with unresectable or metastatic melanoma (Stage IIIc or Stage IV) At least 1 prior systemic therapy, including a PD-1 blocking antibody; and if BRAF V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor in combination with MEK inhibitor

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Study Number ***ClinicalTrials.gov Identifier***	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s)/ Dosage Regimen/ Route of Administration**	**Number of Patients Infused with TIL**	**Patient Population**
Studies Supportive of Safety (Gen 2 TIL Monotherapy Cohorts)					
C-145-03 *NCT03083873*	Primary Objective Evaluate efficacy based on the ORR as assessed by the Investigator per RECIST v1.1 Secondary Objectives Evaluate efficacy based on DOR, DCR, and PFS as assessed by the Investigator per RECIST v1.1 Evaluate OS Characterize the safety profile	Open-label	NMA-LD+TIL (LN-145)+ IL-2 *Same regimen as Study C-144-01*	Cohort 2: 17	HNSCC Adult patients with recurrent and/or metastatic HNSCC who received 1 to 3 lines of prior systemic immunotherapy and/or chemotherapy for HNSCC with radiologically documented disease progression on or after the most recent prior treatment

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Study Number ***ClinicalTrials.gov Identifier***	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s)/ Dosage Regimen/ Route of Administration**	**Number of Patients Infused with TIL**	**Patient Population**
C-145-04 *NCT03108495*	**Cohorts 1 & 2:** Primary Objective Evaluate efficacy based on the ORR as assessed by the IRC per RECIST v1.1 Secondary Objectives Evaluate efficacy based on DOR, DCR, and PFS as assessed by the IRC per RECIST v1.1 Evaluate efficacy based on ORR, DOR, DCR, and PFS as assessed by the Investigator per RECIST v1.1 Evaluate OS Characterize the safety profile **Cohort 4:** Primary Objective Explore the efficacy and safety profile	Open-label	NMA-LD+TIL (LN-145)+ IL-2 *Same regimen as Study C-144-01.* The cyclophosphamide dose could be lowered to 30 mg/kg after consultation with the Medical Monitor	Cohorts 1, 2, and 4: 102	Cervical Cancer Adult patients with recurrent, metastatic, or persistent squamous cell carcinoma, adeno-squamous carcinoma, or adenocarcinoma of the cervix that Is not amenable to curative treatment with surgery and/or radiation therapy
IOV-COM-202 *NCT03645928*	Primary Objectives Evaluate efficacy based on the ORR as assessed by the Investigator using RECIST v1.1 Characterize the safety profile Secondary Objective Further evaluate the efficacy based on the CR rate, DOR, DCR, and PFS as assessed by the Investigator using RECIST v1.1, and OS	Open-label	NMA-LD+TIL (LN-145) + IL-2 *Same regimen as Study C-144-01*	Cohort 3B: 28	NSCLC Adult patients with Stage III or Stage IV NSCLC (squamous, adeno-carcinoma, large cell carcinoma) who have previously received systemic therapy with ICIs (e.g., anti-PD-1/anti-PD-L1)

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Study Number ***ClinicalTrials.gov Identifier***	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s)/ Dosage Regimen/ Route of Administration**	**Number of Patients Infused with TIL**	**Patient Population**
IOV-LUN-202 *NCT04614103*	<u>Primary Objective</u> Evaluate efficacy based on the ORR as assessed by the IRC using RECIST v1.1 <u>Secondary Objectives</u> Evaluate efficacy based on the ORR as assessed by the Investigator using RECIST v1.1 Further evaluate the efficacy based on the CR rate, DOR, DCR, and PFS as assessed by the IRC and the Investigator using RECIST v1.1; and OS Characterize the safety profile	Open-label	NMA-LD+TIL+ IL-2 *Same regimen as Study C-144-01 except that the fludarabine dosing was concurrent with the cyclophosphamide dosing*	Cohorts 1 and 2: 26	**NSCLC** Adult patients with histologically or pathologically confirmed diagnosis of metastatic Stage IV NSCLC (squamous, nonsquamous, adenocarcinoma, large cell, or mixed histologies) without EGFR, ALK, or ROS genomic alterations progressing on or after prior therapy including ICI and platinum-based chemotherapy with or without bevacizumab and targeted therapy when applicable

Abbreviations: ALK = anaplastic lymphoma kinase; BLA = Biologics License Application; BRAF = proto-oncogene B-Raf; CR = complete response; DCR = disease control rate; DOR = duration of response; EGFR = epidermal growth factor receptor; Gen = generation; HNSCC = head-and-neck squamous cell carcinoma; hrs = hours; ICI = immune checkpoint inhibitor; IL-2 = interleukin-2; IRC = Independent Review Committee; IU = International Units; IV = intravenous; MEK = mitogen-activated extracellular signal-regulated kinase; NCT = National Clinical Trial; NMA-LD = nonmyeloablative lymphodepletion; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death protein-1; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; ROS = ROS proto-oncogene 1; TIL = tumor-infiltrating lymphocytes

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The Applicant's Position

Data from Study C-144-01 are provided as the basis of the efficacy and safety analyses and is supported by additional safety data from four studies of Gen 2 TIL monotherapy in patients with HNSCC, cervical cancer, and NSCLC. In total, efficacy was assessed in 153 subjects across Study C-144-01 Cohorts 2 (N=66) and 4 (N=87). Safety was assessed in 344 subjects who received any component of the study regimen (i.e., NMA-LD, TIL, or IL-2) in a Gen 2 TIL monotherapy cohort (including the subjects from Study C-144-01 Cohorts 2 and 4). This represents a large dataset from which to derive the supporting analyses.

The FDA's Assessment

FDA concurs that data from multi-cohort Study C-144-01 with Cohort 4 as the primary efficacy cohort and Cohort 2 as the supporting cohort provide the basis for the efficacy and safety analyses, and safety summaries from the additional four ongoing or completed lifileucel trials (refer to Table 5) sponsored by the Applicant among patients with HNSCC (Study C-145-03), cervical cancer (Study C-145-04), or NSCLC (Study IOV-COM-202 and Study IOV-LUN-202) provide additional information for the assessment of the safety of the lifileucel regimen.

Due to unresolved product comparability issues between different manufacturing facilities, FDA's assessment of primary efficacy evidence was based on Cohort 4 data from 82 out of 87 subjects whose lifileucel was manufactured at the (b) (4) facility and met product release criteria (i.e., primary efficacy analysis set). Efficacy data from Cohort 2 (N=66) and pooled Cohort 2 and 4 (N=153) were assessed by FDA as supporting efficacy evidence.

FDA notes, the Applicant's safety analyses were mainly focused on the 156 subjects from Study C-144-01 who received any lifileucel (N=89 from Cohort 4, and N=67 from Cohort 2). However, FDA's assessment of main safety evidence was based on all subjects enrolled to Study C-144-01 (N=189, TH set) starting from tumor harvest for lifileucel manufacturing. Among these 189 subjects in the TH set, 160 initiated lifileucel regimen and received at least 1 dose of NMA-LD and 156 received lifileucel (primary safety analysis set). Additionally, FDA's assessment of safety information from the other four lifileucel trials among patients with other solid tumors was focused on safety summaries.

The following FDA Table 6 provides information regarding the number of subjects with each solid tumor included in the safety assessment by FDA.

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Table 6. FDA – Number of Study Subjects in Gen 2 Lifileucel Monotherapy Trials for Safety Assessment

Safety Population	C-144-01 Cohorts 2+4 (melanoma)[a]	C-145-04 Cohorts 1+2+4 (cervical)[b]	IOV-LUN-202 Cohorts 1+2 + IOV-COM-202 Cohort 3B (NSCLC)[c]	C-145-03 Cohort 2 (HNSCC)[d]	Total
Safety population who received any component of lifileucel regimen	160	107	59	18	344
Safety population who received lifileucel	156	102	54	17	329

Source: 90-day safety updated report by Applicant (6/21/2023)
a. final data cutoff: 15-SEP-2021)
b. ongoing, cutoff: 29-JAN-2023)
c. ongoing cutoff: 29-JAN-2023
d. cutoff at final data extraction: 12-OCT-2022
Abbreviations: HNSCC = head-and-neck squamous cell carcinoma; NSCLC = non-small cell lung cancer.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study C-144-01

The primary evidence of efficacy and safety for lifileucel is based on data from the ongoing Phase 2 Study C-144-01.

8.1.1.1. Trial Design

The Applicant's Description

Study C-144-01 is a Phase 2, global, multicenter, multicohort, open-label, single-arm clinical trial evaluating the efficacy and safety of lifileucel in adult patients with advanced melanoma (American Joint Committee on Cancer [AJCC] version 7.0 staging system Stage IIIC or Stage IV). The lifileucel regimen was investigated as a one-time treatment and included an NMA-LD preparative regimen followed by a single infusion of lifileucel and post-infusion administration of IL-2. This study is closed to enrollment of new patients.

Study C-144-01 consists of the following cohorts:

- **Cohort 1** (N=23), which was administered non-cryopreserved TIL product
- **Cohort 2** (N=67), which was administered cryopreserved lifileucel product (i.e., the product being pursued for registration)
- **Cohort 4** (N=89), which was administered cryopreserved lifileucel product

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An additional cohort, **Cohort 3** (N=11), comprises subjects who were previously treated in Cohort 1, Cohort 2, or Cohort 4. These subjects had PD and then opted to be retreated with the lifileucel regimen using the cryopreserved lifileucel product.

The same manufacturing process was used to generate cryopreserved lifileucel product across Cohorts 2, 3, and 4.

Data from Cohort 1 are not presented because the non-cryopreserved product is no longer in clinical use, is not considered comparable to the cryopreserved product being pursued for clinical development or evaluated in the hypothesis testing of Study C-144-01, and is not the intended commercial formulation. Summaries of the data for subjects in the retreatment cohort (i.e., Cohort 3) are also not presented because the small number of subjects (N=11) limits interpretation of possible retreatment-associated findings.

After signing the informed consent form, subjects were screened during a Screening Period of up to 28 days (Figure 3 and Table 7). Eligible subjects were then enrolled, and their tumor procured for the manufacture of lifileucel. Subsequently, the Treatment Period (i.e., Day -7 to the end-of-treatment visit/Day 28) began with the NMA-LD preparative regimen, followed by the lifileucel infusion on Day 0 and post-TIL infusion administration of IL-2.

Subjects were first evaluated for efficacy at Week 6 (Day 42) during the Assessment Period, then every 6 weeks until Month 6 (Week 24), and then every 3 months (12 weeks) for up to 5 years from Day 0 or until disease progression or the start of a new anticancer therapy. At that time, the end-of-assessment (EOA) visit was completed. After the EOA visit, the OS Follow-up Period began and continued for up to 5 years from enrollment or until discontinuation from the study, with telephone contact every 3 months to obtain survival status and subsequent anticancer therapy information.

Figure 3. Applicant – Study Flow Chart

Abbreviations: EOA = end-of-assessment; ICF = informed consent form; IL-2 = interleukin-2; NMA-LD = nonmyeloablative lymphodepletion; OS = overall survival.
Note: Cohort 3 patients (ie, patients who were previously treated in Cohort 1, 2, or 4, had progressed, and opted to be retreated with the lifileucel regimen) may have had a second tumor resection, if needed, especially when new lesions were available and feasible for resection.

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Table 7. Applicant – Schedule of Assessments

	Screening, Enrollment, & Baseline Period			Treatment Period (All Visit Dates Were Calculated From Lifileucel Infusion [Day 0])														Assessment Period (All Visit Dates Were Calculated From Lifileucel Infusion [Day 0])			OS Follow-Up Period[a]
Assessments	**Screening (≤28 days From ICF Signature)**	**Enrollment/Tumor Resection**	**Baseline (Day -21 to Day -10)**	**Day -7**	**Day -6**	**Day -5**	**Day -4**	**Day -3**	**Day -2**	**Day -1**	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 14 (±3 days)**	**End-of-Treatment Visit Day 28 (±3 days)**	**Every 6 Weeks (Week 6 [+7 Days], Week 12 [±3 Days], and Week 18 [±3 Days])**	**Every 3 Months (±1 Week) (Starting at Month 6)**	**EOA Visit**	**Every 3 Months (±3 Weeks)**
Informed consent	X																				
Inclusion/Exclusion	X		X																		
Collection of demographic and medical history information	X																				
ECOG performance status	X		X	X												X		X	X	X	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs [b]	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	
Eye examination (slit lamp) [c]	X																	X			
Cardiac and pulmonary evaluations	X		ECG																		
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival status/anti-cancer therapy [a]																					X

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Assessments	Screening, Enrollment, & Baseline Period			Treatment Period (All Visit Dates Were Calculated From Lifileucel Infusion [Day 0])														Assessment Period (All Visit Dates Were Calculated From Lifileucel Infusion [Day 0])			OS Follow-Up Period[a]
	Screening (≤28 days From ICF Signature)	Enrollment/Tumor Resection	Baseline (Day -21 to Day -10)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (±3 days)	End-of-Treatment Visit Day 28 (±3 days)	Every 6 Weeks (Week 6 [+7 Days], Week 12 [±3 Days], and Week 18 [±3 Days])	Every 3 Months (±1 Week) (Starting at Month 6)	EOA Visit	Every 3 Months (±3 Weeks)
Tumor assessment by imaging and physical examination: evaluation and measurement of skin and palpable lesions[e], tumor assessment, CT – chest, abdomen, pelvis, MRI – brain	X		X															X	X	X	
Hematology & chemistry	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid panel	X															X				X	
ß-HCG pregnancy test[f]	X		X	X							X						X	X	X	X	
Infectious disease screening[g]	X	X																			
Tumor resection		X																			

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	Screening, Enrollment, & Baseline Period			Treatment Period (All Visit Dates Were Calculated From Lifileucel Infusion [Day 0])													Assessment Period (All Visit Dates Were Calculated From Lifileucel Infusion [Day 0])			OS Follow-Up Period[a]
Assessments	**Screening (≤28 days From ICF Signature)**	**Enrollment/Tumor Resection**	**Baseline (Day -21 to Day -10)**	**Day -7**	**Day -6**	**Day -5**	**Day -4**	**Day -3**	**Day -2**	**Day -1**	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 14 (±3 days)**	**End-of-Treatment Visit Day 28 (±3 days)**	**Every 6 Weeks (Week 6 [+7 Days], Week 12 [±3 Days], and Week 18 [±3 Days])**	**Every 3 Months (±1 Week) (Starting at Month 6)**	**EOA Visit**	**Every 3 Months (±3 Weeks)**
Supportive care	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Immune monitoring		X		X								X			X	X		X	X	
HRQoL			X															X	X	X

a. OS Follow-up begins when a patient completes the EOA visit (last efficacy assessment) and continues for up to 5 years from Enrollment/tumor resection or until discontinuation from the study. Patients who have tumor resection but do not receive lifileucel for any reason perform an EOA visit and transition directly into the OS Follow-up Period. Patients or designees are contacted every 3 months by telephone to obtain survival status and subsequent anti-cancer therapy information.
b. On Day 0 (lifileucel infusion), vital signs are monitored every 30 minutes during infusion, then hourly (±15 minutes) for 4 hours, and then routinely (every 4 to 6 hours). For up to approximately 24 hours post-lifileucel infusion.
c. Slit-lamp eye examination in patients with history of uveitis. Day 84 is required if clinically indicated. Eye examination performed within 28 days prior to signing the ICF is allowed.
d. All concomitant medications taken within 28 days prior to signing the ICF are collected, and subsequently throughout the duration of study.
e. Evaluation and measurement of skin and palpable lesions may be performed (if applicable).
f. Serum pregnancy test for women of childbearing potential only. Serum pregnancy testing continues to Month 12 (Week 52) or EOA, whichever occurs first.
g. Serology for HIV-1, HIV-2, HbsAg, anti-HBc, HCV Ab, and syphilis are required at tumor resection or within 7 days after tumor resection, for tumor samples acquired in Europe.
Abbreviations: AE = adverse event; anti-HBc = hepatitis B virus core antibody; CT = computerized tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOA = end-of-assessment; HbsAg = hepatitis B virus surface antigen; β-HCG = beta human chorionic gonadotropin; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; ICF = informed consent form; MRI = magnetic resonance imaging; OS = overall survival; SAE = serious adverse event

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The FDA's Assessment

FDA concurs that Study C-144-01 is the primary basis of efficacy and safety to support this BLA for an AA of lifileucel for the treatment of advanced or metastatic melanoma after disease progression following prior anti-PD1-based therapy and molecular-target therapy if positive for BRAF V600 mutation. Specifically, ORR and DOR results from 82 study subjects from Cohort 4 who received lifileucel manufactured at (b) (4) facility that met lot release specifications provide the basis for primary efficacy analysis. Of note, five subjects from Cohort 4, whose lifileucel was manufactured at (b) (4) facility, were excluded from the primary efficacy dataset due to product comparability issues between manufacturing facilities. ORR and DOR results from Cohort 2 (N=67) and pooled Cohort 2 and 4 (N=153) who received lifileucel that met lot release specifications provide supporting efficacy analysis. The basis of safety evidence is from all subjects enrolled to Cohort 2 or 4 of Study C-144-01 who underwent tumor harvest for lifileucel manufacturing (N=189). Among these enrolled 189 subjects, 160 initiated lifileucel treatment regimen by receiving at least 1 dose of lymphodepleting chemotherapy; 156 received lifileucel including 153 subjects included in the pooled full efficacy set, 2 subjects who received lifileucel that was out of specification (OOS) and 1 subject who received less than one billion viable cells due to a life-threatening anaphylactic reaction.

Supporting safety evidence is based on safety summaries from other ongoing or completed lifileucel trials where Gen 2 lifileucel was also a monotherapy for 3 other disease indications: Cohort 1+2+4 of Study C-145-04 in patients with cervical cancer (n=107, data cutoff on 1/29/2023), Study C-145-03 in patients with HNSCC (n=18, final data extracted on 10/12/2022), and Cohort 1+2 of Study IOV-LUN-202 and Cohort 3B of Study IOV-COM-202 in subjects with NSCLC (n=54, data cutoff on 1/29/2023). Refer to FDA Figure 4.

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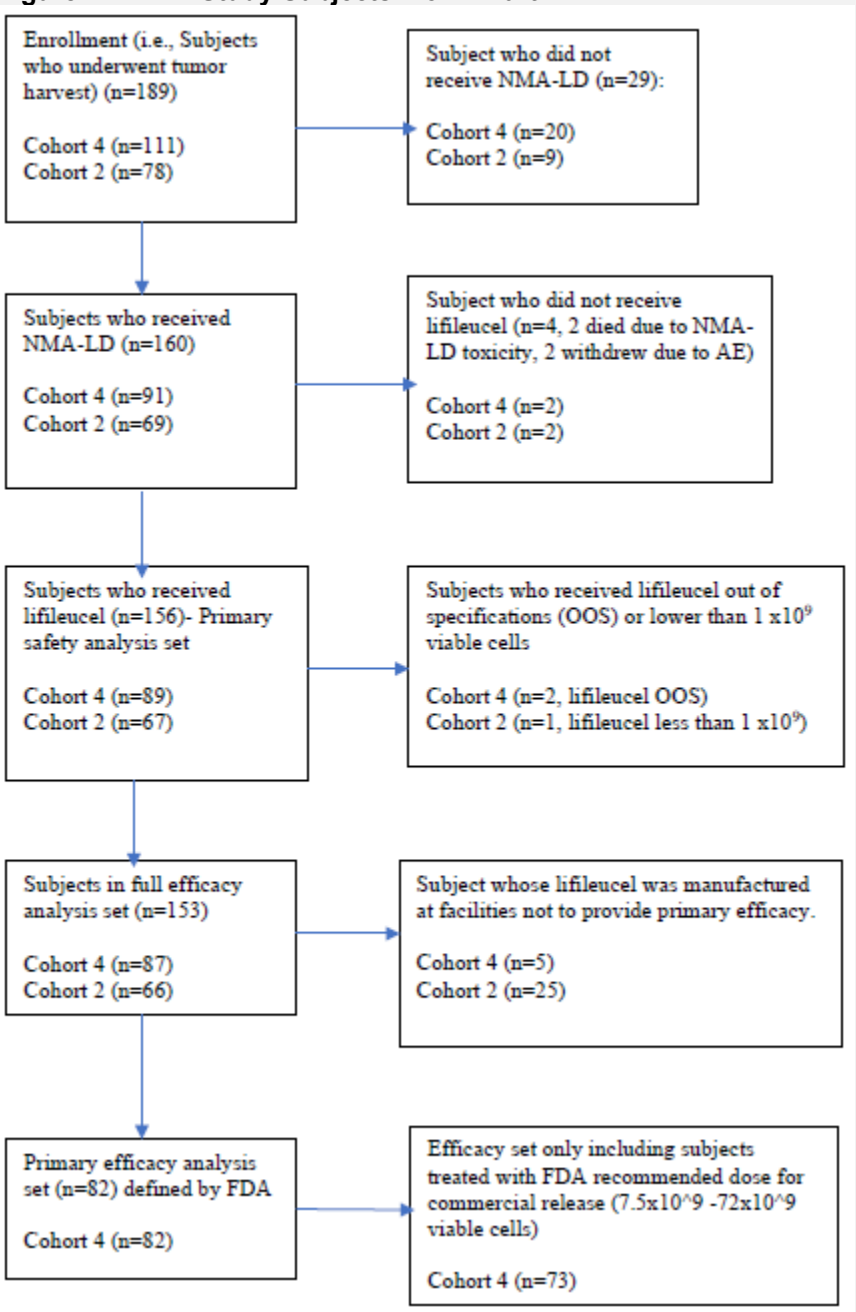
Figure 4. FDA – Study Subjects Flow Chart



Source: Datasets: ADSL ADBL ADDS
Abbreviations: AE = adverse event; NMA-LD = nonmyeloablative lymphodepletion; OOS = out of specification

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8.1.1.2. Eligibility Criteria

The Applicant's Description

Adult patients with a diagnosis of unresectable or metastatic melanoma (Stage IIIC or Stage IV; per the AJCC staging manual, 7th edition) were eligible to participate in this study if they had progressed following ≥1 prior systemic therapy, including a PD-1 blocking antibody, and if BRAF V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor in combination with a MEK inhibitor. Prior treatment with a CTLA-4 blocking antibody, PD-1/CTLA-4 blocking antibody combinations, as well as more than 1 line of prior therapy with ICI(s) was allowed and there were no restrictions with regard to the maximum number of prior therapies (including combination therapies).

Eligible patients also had documentation of radiological disease progression after the most recent therapy, with at least 1 measurable target lesion, as defined by RECIST v1.1; at least 1 resectable lesion (or aggregate of lesions resected) of a minimum 1.5 cm in diameter post-resection to generate TIL; surgical removal with minimal morbidity; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and an estimated life expectancy of ≥3 months; and acceptable hematologic parameter values and adequate organ function. Patients with symptomatic and/or untreated brain metastases were excluded, with the exception that patients with definitively treated brain metastases may have been considered for enrollment and must have been stable for ≥14 days prior to beginning the NMA-LD preparative regimen.

The FDA's Assessment

Overall, the eligibility criteria set for Study C-144-01 are acceptable. Several limitations of protocol-defined eligibility described below suggest potential baseline heterogenicity of the study population:

a. The Study C-144-01 protocol did not define the treatment setting for prior anti-PD1 containing therapies, adequate prior anti-PD1 treatment, or minimal treatment duration for prior anti-PD1 therapies. Therefore, FDA considers study subjects enrolled to Study C-144-01 as those previously treated with anti-PD1 therapies, irrespective of the treatment setting, treatment plan, and objective response to the anti-PD1 therapies (also refer to FDA assessment regarding "Number of Prior Lines of anti-PD1 Therapies and Longest Treatment Duration on a Single Line" in Section 8.1.2.6)
b. The Study C-144-01 protocol required that after tumor harvest for lifileucel manufacturing, eligible subjects must have had at least one remaining measurable target lesion for tumor response assessment. Based on FDA's assessment, this eligibility criterion was determined by the investigators, not the IRC. FDA identified one subject from Cohort 4 (b) (6) and three subjects from Cohort 2 (b) (6) who did not have a target lesion at baseline per IRC.

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c. The protocol-defined PD at study entry was based on radiographical documentations from patients' medical records. The baseline PD status was not confirmed by the IRC. Additionally, patients who experienced PD during and after prior anti-PD1 therapy were both eligible for enrollment; patients who either responded or did not respond to prior anti-PD1 were both eligible for enrollment.

8.1.1.3. Study Endpoints

The Applicant's Description

The study endpoints and definitions are presented in Table 8 and the statistical methods used to analyze the data are presented below in the "Statistical Analysis Plan and Amendments" in Section 8.1.1.4.

Table 8. Applicant – Study Endpoints

Endpoints	Definitions
Primary	-
ORR as assessed by the IRC per RECIST v1.1	ORR was defined as the proportion of patients who had a BOR of CR or PR by the IRC per RECIST v1.1.
Secondary	-
DOR, DCR, and PFS as assessed by the IRC per RECIST v1.1	DOR was defined as the time, in months, from the time point 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 was defined as the proportion of patients who had a BOR of CR or PR, SD, or non-CR/non-PD, where non-CR/non-PD was only for patients without target lesions. PFS was defined as the time, in months, from the date of the lifileucel infusion to PD or death due to any cause, whichever occurred earlier.
ORR, DOR, DCR, and PFS as assessed by the Investigator per RECIST v1.1	As presented above.
OS	OS was defined as the time, in months, from the date of the lifileucel infusion to death due to any cause.
Safety evaluations	Safety was assessed based on the incidence, severity, seriousness, relationship to study treatment, and characteristics of TEAEs, including AEs leading to early discontinuation from treatment or withdrawal from the Assessment Period, and AEs resulting in deaths. Changes in numeric laboratory values and graded laboratory abnormalities were assessed and graded according to CTCAE v4.03.

Abbreviations: AEs = adverse events; BOR = best overall response; CR = complete response; CTCAE v4 = Common Terminology Criteria for Adverse Events version 4.03; DCR = disease control rate; DOR = duration of response; IRC = Independent Review Committee; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease; TEAEs = treatment-emergent adverse events

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The FDA's Assessment

The primary endpoint of Study C-144-01 was ORR, further supported by DOR. ORR is an intermediate endpoint that is reasonably likely to predict clinical benefit. Therefore, ORR along with DOR provide the basis of primary efficacy evidence to support a marketing application of lifileucel under an AA. However, FDA requires that the Applicant conduct a well-controlled randomized trial in subjects with unresectable or metastatic melanoma to verify the clinical benefit of lifileucel measured by PFS and OS.

8.1.1.4. Statistical Analysis Plan and Amendments

The Applicant's Description

The Study C-144-01 final statistical analysis plan (SAP) version 3.0 was dated 9/13/2021 and was submitted to FDA on 9/15/2021 (SN0253). There were no changes to the planned analyses in the SAP.

The statistical analyses of efficacy and safety data were performed for Cohort 2, Cohort 4, and Pooled Cohorts 2 and 4 in order to evaluate cryopreserved TIL product. The FAS was the primary set for the efficacy analyses and was defined as subjects who received lifileucel that met the manufacturing product specifications. The primary set for the safety analyses was the safety analysis set and was defined as subjects who received a lifileucel infusion. Primary efficacy endpoint and AE analyses were also performed on the TH Set, which was defined as all subjects who had a tumor resected for the production of lifileucel, regardless of whether they received lifileucel or not. The primary analysis was performed on data that were reported up to 9/15/2021, thereby providing efficacy data with at least 6 months of follow-up after the initial IRC-assessed response for confirmed responders in Cohort 4.

The study endpoints are presented in Table 8.

The primary efficacy endpoint, ORR, was expressed as a binomial proportion and was summarized using a point estimate and its 2-sided 95% CI based on the Clopper-Pearson exact method. Statistical hypothesis testing of the primary efficacy endpoint was performed for the FAS of Cohort 4 using a null hypothesis (H_{01}) of an ORR ≤10% versus an alternative hypothesis (H_{a1}) of an ORR >10%. The hypothesis was to be rejected, and the study was considered to have met its primary objective, if the lower bound of the 2-sided 95% Clopper Pearson CI for the primary efficacy endpoint was >10%. If H_{01} was rejected, a second hypothesis testing of the primary efficacy endpoint was to be performed based on the Pooled Cohorts 2 and 4 data, null hypothesis (H_{02}) of an ORR ≤10% versus alternative hypothesis (H_{a2}) of an ORR >10%. Analyses were performed on Cohort 2 and Pooled Cohorts 2 and 4 because the patient populations were aligned with each other and the intended indication. Cohort 2 and Cohort 4 subjects met the same primary eligibility criteria, had the same study assessments, and had received the same regimen and lifileucel that was produced using the same cryopreserved TIL manufacturing

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process (Gen 2) and product formulation. The pooled data facilitated a safety assessment in a larger pool of patients, provided greater confidence around the point estimate of the ORR, and provided a longer duration of follow-up for the DOR.

For time-to-event endpoints such as DOR, PFS, and OS, the Kaplan Meier product limit method was used to estimate the survivorship function. The censoring rules and the definition of progression date for PFS and DOR followed FDA's guidance. For subjects with PD or death after a single missing tumor assessment visit, the PFS or DOR were considered as having an event at date of progression assessment or death. For subjects with PD or death after 2 or more consecutive missing tumor assessment visits, the PFS or DOR were censored at the last adequate tumor assessment prior to the missing tumor assessments. The missing response assessments were ignored if the subsequent assessment showed no progression. For subjects who received new anticancer therapies, DOR or PFS was censored at the date of the last tumor response assessment prior to the start of new anticancer therapies.

No interim analysis was performed.

Additional analyses of time to response and number of subjects with deepened response over time were performed using descriptive statistics.

Subgroup analyses of ORR and disease control rate (DCR) as assessed by the IRC were performed on prespecified demographic and baseline disease characteristics.

Separate SAPs were also prepared to provide additional analyses to support the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS). An Efficacy Analysis Set was added in the SCE and was defined as subjects in the FAS who received lifileucel manufactured at (b) (4) (b) (4) A Safety Population was added in the SCS and was defined as subjects who received any component of the TIL regimen (i.e., cyclophosphamide, fludarabine, TIL, or IL-2).

The FDA's Assessment

FDA concurs with the Applicant's overall analysis plan. FDA assesses the magnitude of the observed ORR, the 95% CI around the point estimate, the durability of the observed ORR, and available therapies for the study population at the time of reviewing this BLA. For single arm trials, FDA also assesses whether study subjects are significantly heterogenous with respect to baseline characteristics, and whether the observed ORRs appear to be driven by one or more subgroups of the study subjects. Finally, in order for FDA to take regulatory action, the clinical meaningfulness of the observed ORR must outweigh the risks among subjects treated with the lifileucel regimen.

As stated by FDA at the pre-BLA meeting with the Applicant on 7/29/2022, FDA assesses the safety of the entire lifileucel regimen, which includes a lymphodepleting pre-conditioning chemotherapy with cyclophosphamide and fludarabine, followed by one dose of lifileucel and

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up to six doses of IL-2. For severe, life-threatening, and fatal AEs, FDA assesses the safety of the entire lifileucel regimen as one entity, given its multi-component nature.

8.1.1.5. Protocol Amendments

The Applicant's Description

The original protocol was Version 1 dated 12/30/2014. The final version (i.e., Version 9) was dated 10/22/2019. The major changes between versions of the protocol are summarized below. The Applicant does not believe that any of the amendments impacted the integrity of the study or the interpretation of the results.

Table 9. Applicant – Protocol Amendments

Version No.	Date	Key Change(s)
1	12/19/2014	Initial IND/Initial Protocol Version
2	NA	Not submitted to IND/No patients treated
3	7/16/2015	Inclusion/Exclusion Criteria: Included patients >18 years of age Safety Procedures: • DSMB added • Updated text of "The final cell product" and added information on product administration • Corrected IL-2 administration route and management of IL-2 toxicity
4	7/18/2016	Inclusion/Exclusion Criteria • Clarified criteria for patients >65 years of age • Excluded patients with melanoma of uveal/ocular origin • No lower limit of number of TIL infused Secondary Efficacy Endpoints: Added CR rate, PFS, DOR, and OS
5	2/4/2017	Study Design • Added 2 cohorts to evaluate treatment with cryopreserved lifileucel product (Cohorts 2 and 3) • Total patients changed from 20 to 40 (20 Cohort 1+20 Cohort 2; Cohort 3 = retreatment cohort)
6	5/13/2017	Study Design: Increased total planned pts, from 40 to 60 (30 Cohort 1 [closed] +30 Cohort 2) Study Objectives: Primary objective changed from "characterize safety profile" to "evaluate efficacy using the ORR." Safety profile characterization changed to secondary objective. Inclusion Criteria • Patients must have unresectable metastatic melanoma (Stage IIIc or Stage IV) and must have progressed following ≥1 line of prior systemic therapy, including immune checkpoint inhibitor (e.g., anti-PD-1), and if BRAF mutation-positive, after BRAF inhibitor systemic therapy • Added patients must have an "estimated life expectancy of >3 months" • Specified that patients >70 years of age must have had Medical Monitor's consent to be enrolled

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Version No.	Date	Key Change(s)
7	3/23/2018	Study Design: Total patients (i.e., Cohort 1 [closed] + Cohort 2) increased from 60 to 85 (minimum of 60 in Cohort 2) Study Objectives • Primary objective pertaining to efficacy evaluation using ORR and the secondary objective using DOR, DCR, and PFS were clarified by adding "as assessed by the Investigator per RECIST 1.1" • A secondary objective was added for ORR, DOR, DCR, and PFS as assessed by the IRC per RECIST 1.1 Study Drug Administration: Required premedication prior to the infusion of lifileucel for prophylaxis
8	12/20/2018	Study Design • Added Cohort 4, ~75 patients • Primary endpoint of ORR per RECIST v1.1 was to be assessed by the IRC, not Investigator. • Statistical and analysis plans updated to include the following analysis populations: TH Set (Enrolled Set) and FAS Study Procedures • IRC was implemented to review Cohort 4 efficacy data • Updated lifileucel Toxicity Prevention and Management to provide clearer, more comprehensive AE management guidance.
9	10/22/2019	Study Design • Established an IDMC • Updated the role of the DSMB Study Drug Administration • Replaced prior guidance allowing stopping fludarabine dosing after 2 doses, based solely upon ALC levels being below a specified threshold (i.e., 100/mm3). Clarified that the full 5-dose fludarabine course was to be given with dose hold or discontinuation allowed only in the case of toxicity described in its prescribing information or per institutional standards. • Clarified range of cell numbers per lifileucel dose: 1 x 10^9 to 150 x 10^9 cells. Clarified patients would receive the full dose of product manufactured and released. • High-resolution CT with PO/IV contrast or contrast-enhanced MRI was the preferred imaging modality for assessing radiographic tumor response. All references to an interim analysis of data for Cohort 4 were deleted.

Abbreviations: AE = adverse event; ALC = absolute lymphocyte count; BRAF = proto-oncogene B-Raf; CR = complete response; CT = computerized tomography; DCR = disease control rate; DOR = duration of response; DSMB = Data and Safety Monitoring Board; FAS = Full Analysis Set; IDMC = Independent Data Monitoring Committee; IL-2 = interleukin-2; IND = Investigational New Drug; IRC = Independent Review Committee; IV = intravenous; MRI = magnetic resonance imaging; NA = not applicable; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death protein 1; PFS = progression-free survival; PO = per os; RECIST = Response Evaluation Criteria in Solid Tumors; TH = Tumor Harvested; TIL = tumor-infiltrating lymphocytes

The FDA's Assessment

FDA concurs with the Applicant regarding main protocol amendments made to Study C-144-01. Key amendments included: 1) adding Cohort 4 to provide primary efficacy evidence intended to support a marketing application; 2) implementing an IRC to assess and adjudicate lesion status

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at the baseline and follow-ups per RECIST v 1.1; 3) ORR and DOR results based on tumor responses assessed by IRC are the basis of efficacy evidence intended to support a marketing application; 4) removing interim analysis of the primary endpoint; and 5) establishing an Independent Data Monitoring Committee (IDMC) for Study C-144-01.

Also refer to FDA comments in Section 3 "Regulatory Background."

8.1.2. Study Results

8.1.2.1. Compliance With Good Clinical Practices

Data

The study was designed in accordance with the ethical principles of the Declaration of Helsinki to ensure that the Sponsor, its authorized representative(s), and Investigators abided by Good Clinical Practice (GCP). It was conducted and evaluated in conformance with GCP, as described in the International Council for Harmonisation (ICH) guideline, E6, as well as those of the major regulatory authorities including, but not limited to, the rules and regulations of the U.S. government's Office of Human Research Protection.

The Applicant's Position

The study was conducted in accordance with the provisions of the Declaration of Helsinki (Oct 2008) and all revisions thereof, and in accordance with FDA regulations (21 Code of Federal Regulations [CFR] Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

The FDA's Assessment

Overall, Study C-144-01 was conducted in compliance with GCP described in ICH E6. However, FDA form 483 was issued to one of the three inspected sites (Site 19). The FDA inspector identified some discrepancies between source documents and records captured by electronic data capture (EDC) at Site 19. In response to the FDA form 483, the site principal investigator concluded that the root cause of the errors was a lack of quality control with the study site.

Because the errors occurred at Site 19, they were closely relevant to two study subjects who contributed to key clinical efficacy or safety outcomes. The FDA clinical reviewer requested additional information regarding these two study subjects. The following summarizes the data errors that occurred in these two subjects:

- Subject (b) (6) Study site inadvertently missed capturing positive baseline brain imaging result of this subject in the electronic case report form (eCRF). Therefore, the brain magnetic resonance imaging (MRI) results were not provided to IRC. Per Applicant's account, brain MRI at follow-up visits were performed for this subject and

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results were provided to IRC. The subject achieved PR in Study C-144-01 and maintained a durable response as of Day 588 post lifileucel infusion.

- Subject (b) (6) The investigator assessed the subject to have a brain lesion at the baseline. However, the IRC did not identify a brain lesion at the baseline but identified a new brain lesion at Day 84 visit. The FDA inspector believed that the baseline brain imaging was not provided to the IRC. In response to a subsequent clinical information request (IR), the Applicant stated that the baseline brain imaging was provided to the IRC. Because tumor assessments were completely independent between the investigators and IRC, the Applicant was unable to determine the cause of the discrepancy between investigators and IRC.

In addition to Subject (b) (6), FDA identified six additional study subjects (b) (6) (b) (6) who had brain lesions at the baseline that were assessed by investigators, but not by IRC. FDA queried the Applicant regarding their brain imaging review history by the IRC. The Applicant confirmed that IRC reviewed baseline brain imaging for all FDA-queried study subjects.

The Applicant further clarified that for subjects with baseline brain metastasis identified and assessed by the IRC but not the investigators, the majority (13/15 subjects) had follow-up brain scans provided to IRC. Follow-up brain MRIs were not available for two subjects because the investigators had determined there was no baseline brain metastasis; follow-up was not indicated in these subjects and was not required per study protocol.

Based on clarifications provided by the Applicant, FDA concluded that the errors occurring during the study operation at Site 19 have not changed the primary clinical efficacy and safety outcomes of Study C-144-01.

Also refer to bioresearch monitoring (BIMO) reviewer's memo.

8.1.2.2. Financial Disclosure

Data

All of the 669 principal investigators and sub-investigators participating in Study C-144-01 (Cohort 4 and Cohort 2) were assessed for financial disclosures as defined in 21 CFR Part 54, and 2 investigators had disclosable financial interests. Further details of financial disclosure are provided in Section 21.2.

The Applicant's Position

The Applicant has adequately assessed clinical investigators for any financial interest/arrangements. A Form FDA 3455 is included in the BLA submission for each

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investigator disclosing significant payments of other sorts and includes steps taken to minimize potential bias. Further details are provided in Section 21.2.

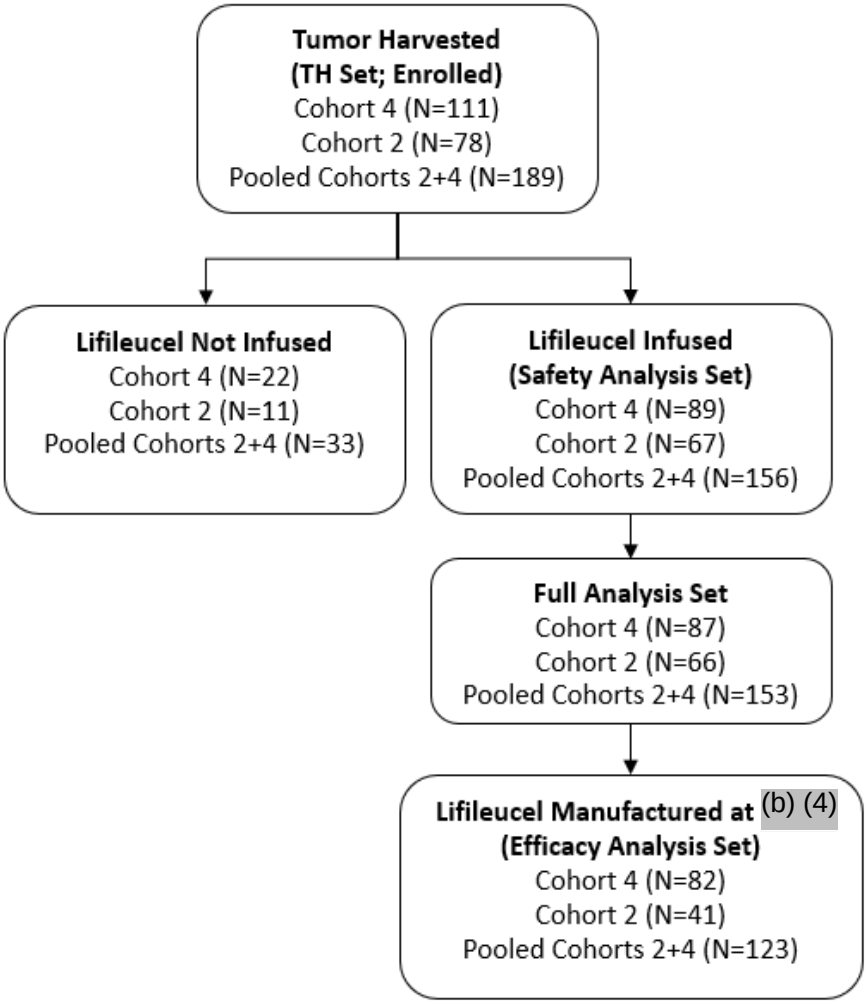
The FDA's Assessment

FDA inspectors verified information submitted to the BLA for each of the inspected clinical study sites and did not find violations of financial disclosures per 21 CFR Part 54.

8.1.2.3. Patient Disposition

Data

Figure 5. Applicant – Patient Disposition Flow Chart



Source: Data: ADSL

Of the subjects who underwent tumor harvest (i.e., TH Set):

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- In Cohort 4, 16 subjects did not receive lifileucel due to subject-related reasons (disease progression, start of new anticancer therapy, AEs, death, withdrawal of consent, or other). Ten of these subjects did not receive lifileucel because of disease progression, start of new anticancer therapy, or death, which was consistent with the advanced disease of the enrolled patient population. Lifileucel was not available for six subjects.
- In Cohort 2, nine subjects did not receive lifileucel for subject-related reasons (disease progression, AEs, death, withdrawal of consent, or other), while lifileucel was not available for two subjects.

Of the subjects who were infused with lifileucel (i.e., Safety Analysis Set):

- In Cohort 4, two subjects were excluded from the FAS because they were infused with lifileucel that did not meet the manufacturing product specification.
- In Cohort 2, one subject was excluded from the FAS because the subject was infused with <1 x 10^9 viable cells (i.e., the minimum dose per product release criteria, as specified in the last version of the protocol [Version 9]).

As of the 9/15/2021 data cutoff date for Study C-144-01, 11.5% of the subjects in the FAS of Cohort 4 continue to be followed in the Assessment Period and 29.9% are continuing in the study. 16.7% of the subjects in the FAS of Cohort 2 continue to be followed in the Assessment Period and 28.8% are continuing in the study.

The Applicant's Position

The primary analysis was performed on data that were reported up to 9/15/2021. These data provide median study follow-up of 23.5 months for Cohort 4 (N=87 based on the FAS, i.e., subjects who had received lifileucel that met the manufacturing product specification). All Cohort 4 confirmed responders in the FAS had been followed for a minimum of 17 months starting from their initial response, unless discontinued. Data from Cohort 2 (N=66 based on the FAS), which completed dosing prior to the addition of Cohort 4 to Study C-144-01, had a longer median study follow-up of 36.6 months and are provided separately and pooled with Cohort 4 as supportive for efficacy.

Data from Cohort 2 have also been pooled with Cohort 4 data to facilitate a safety assessment in a larger patient population, which is particularly relevant for the characterization of events that occurred at a low incidence and the analysis of TEAEs by subgroup.

The FDA's Assessment

FDA concurs with the Applicant regarding the timeline for final study analysis.

Refer to FDA Figure 4 in Section 8.1.1.1 for the number of study subjects included in the enrollment set (i.e., TH set, N=189), full efficacy analysis set (N=153), primary efficacy analysis

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set (N=82), Cohort 4 full efficacy analysis set (N=87), Cohort 2 full efficacy analysis set (N=66), and Applicant's primary safety analysis set (N=156), as well as the reasons for exclusion.

FDA verified that in Study C-144-01, 33 (33/189=17.5%) enrolled subjects who underwent TH did not receive lifileucel. Based on a review of patient narratives and disposition data submitted in the BLA, FDA characterized the reasons for these 33 subjects not receiving lifileucel in FDA Table 10.

As shown in the FDA Table 10, eight subjects did not have lifileucel generated or meeting the release criteria; five subjects died within 40 days from TH and never initiated NMA-LD. FDA agrees that for these five (5/189=2.6%) subjects who died within 40 days from TH, the reason for not receiving the lifileucel regimen was most likely due to rapid disease progression during the time of awaiting lifileucel manufacturing.

Except for these five subjects who died within 40 days after TH and three additional subjects who had brain metastases which met the protocol exclusion criteria, FDA did not find evidence to suggest that additional subjects who underwent TH experienced rapid disease progression or died during the time of awaiting lifileucel manufacturing. FDA reviewed detailed information of nine study subjects whose reason for not receiving lifileucel was assessed as disease progression or disease progression with brain metastases by the Applicant. FDA found that the timing of the deaths of these study subjects were 70 to 400 days from TH with a median and mean time of their death of 157 and 176 days, respectively, with no indication of rapid progression or death that prevented the subjects from receiving the lifileucel regimen.

Given the manufacturing process (22 days for lifileucel manufacturing, a median of 26 days from TH to the initiation of NMA-LD, and a median of 33 days from TH to lifileucel infusion; refer to Section 8.1.2.6) and non-bridging therapy permitted by the Study C-144-01 protocol, some subjects were discontinued from proceeding to the lifileucel treatment regimen at the discretion of the investigators or study subjects.

FDA also notes that four study subjects were discontinued from receiving lifileucel after the initiation of NMA-LD. These four subjects had lifileucel ready at the study site for infusion. The reason for these four subjects not receiving lifileucel was either death from NMA-LD related toxicity (n=2) or withdrawal from the study after experiencing toxicities during NMA-LD period (n=2).

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Table 10. FDA – Reasons for Not Receiving Lifileucel After Tumor Harvest

Reason	Number of Subjects (N=33)
Inability to manufacture lifileucel	8
Disease progression	6
Met exclusion criteria including 3 subjects with brain metastasis	5
Death due to progressive disease (died within 40 days from TH)	5
Started new anti-cancer or consent withdrawal	4
Died from NMA-LD related toxicities	2
Discontinued for further treatment due to NMA-LD related toxicities and overall health condition	2
Negative for melanoma, positive for lymphoma	1

Source: Patient Narratives, Datasets: ADDS ADSL
Abbreviations: NMA-LD = nonmyeloablative lymphodepletion; TH = tumor harvest.

Study Follow-Up Time

The Applicant mentioned in this memo that the median study follow-up time was 23.5 months for Cohort 4 (N=87, Section 8.1.2.3) and 27.6 months for pooled Cohort 2 and 4 (N=153, Sections 8.2.2.3 and 8.2.4.1). These follow-up times were potential follow-up times estimated by reversed Kaplan-Meier (KM) method (Schemper and Smith 1996), had the subject survived to the final study data cutoff date (9/21/2021). FDA notes that these median potential follow-up times were much longer than the actual median follow-up times based on study visits information from Study C-144-01 (see below).

In study C-144-01, only 16% (14/87) of Cohort 4 subjects were followed for more than 23 months for survival; and 17% (26/153) of pooled Cohort 2 and 4 subjects were followed for more than 27 months for survival. In fact, 66.7% (102/153) of Study C-144-01 subjects died by the study data cutoff of 9/15/2021. The median overall survival estimated by KM analysis for Cohort 4 (N=87) and pooled Cohort 2 and 4 (N=153) was 12.7 (95% CI: 8.3 to 17.8) months and 13.9 (95% CI: 10.6 to 17.8) months, respectively.

Therefore, the actual median follow-up times should not be longer than the median survival time.

Per FDA's request, the Applicant provided actual median study follow-up times based on the last study visit. The median actual follow-up time for Cohort 4 full efficacy set (N=87), Cohort 4 primary efficacy analysis set (N=82), and pooled Cohort 2 and 4 full efficacy analysis set (N=153) was 8.4 (range: 0.4 to 27.6) months, 8.2 (range: 0.4 to 27.6) months, and 9.5 (range: 0.2 to 46.4) months, respectively.

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8.1.2.4. Protocol Violations/Deviations

Data

In the FAS of Pooled Cohorts 2 and 4 (N=153), 3 (2.0%) subjects had 1 or more important protocol deviations (Data: ADSL and ADDV). The important deviations pertained to eligibility criteria, informed consent, and administration of the investigational product, reported in 1 subject each. There were no additional subjects in the Safety Analysis Set who experienced an important protocol deviation.

The Applicant's Position

The three important protocol deviations identified during Study C-144-01 did not lead to exclusion of data from the analyses nor impacted the interpretation of the results.

The FDA's Assessment

FDA inspectors inspected three study sites (Site 3, 4, and 19). The FDA inspector did not identify significant non-adherences at Sites 3 and 4 with respect to the report of protocol deviations and violations.

The FDA inspector for Site 19 identified protocol deviations and non-adherences which were not reported by the study site. For example, IL-2 dosage should have been based on study subjects' body weight recorded on Day 0 which was the day lifileucel and IL-2 were administered per protocol; however, the actual IL-2 dosages at Site 19 were based on body weight on Day -7.

After reviewing FDA inspector's Establishment Inspection Report for Site 19, the FDA clinical reviewer requested additional information from the Applicant pertinent to the safety and efficacy of the study report. The FDA clinical reviewer concluded that protocol deviations and non-adherences did not impact the interpretation of the primary study results.

Refer to FDA assessment under "Compliance with Good Clinical Practices" earlier in Section 8.1.2.1 regarding discrepancies between source documents and data entered to EDC system.

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8.1.2.5. Table of Demographic Characteristics

Data

Table 11. Applicant – Demographic Characteristics of the Primary Efficacy Analysis (Full Analysis Set)

Demographic Characteristic	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled Cohorts 2 and 4 (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)			
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 (%)			
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)
Other	1 (1.1)	0	1 (0.7)
Region, n (%)			
U.S.	54 (62.1)	55 (83.3)	109 (71.2)
Europe	33 (37.9)	11 (16.7)	44 (28.8)

Source: C-144-01, Program: t14-1-5-2-1-demo-c2c4-fas.sas, Data: ADSL, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Abbreviations: max = maximum; min = minimum; SD = standard deviation; US = United States

The Applicant's Position

A majority of subjects in Study C-144-01 were treated at sites in the U.S. with the remainder treated at sites in Europe (Table 11). The subjects were representative of the melanoma patient population in the U.S., where melanoma is most commonly diagnosed in white patients and is associated with risk that increases with age, especially in males (average age at diagnosis is 60 years, (American Cancer Society 2022)).

The FDA's Assessment

FDA notes that FDA's primary efficacy analysis was not based on either the pooled full efficacy analysis set (N=153) or the full Cohort 4 efficacy set (N=87) as described in the Applicant's Table 11. Refer to Section 8.1.2.8 for discussion regarding FDA's primary efficacy analysis set (N=82).

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Overall, the demographics of the study subjects are reasonably representative of the melanoma patient population in the U.S. Of note, among 156 study subjects who received lifileucel in Study C-144-01, 111 were enrolled in the study sites in the U.S., 19 in Germany, 13 in Spain, 7 in United Kingdom, 3 in France, 2 in Hungary, and 1 in Switzerland.

The median age and sex distributions of study subjects enrolled in Study C-144-01 were slightly different from the general U.S. patient population. The median age of the melanoma patient population in the U.S. is 66 years old versus 56 years old in Study C-144-01. The incidence of melanoma is 1.6 times higher in males than in females in the U.S. versus about a 1:1 ratio in Study C-144-01 (NCI-SEER 2023).

8.1.2.6. Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Data

Table 12. Applicant – Baseline Disease Characteristics (Full Analysis Set)

Disease Characteristic	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled Cohorts 2 and 4 (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)
Subjects with baseline liver and/or brain lesions by IRC, n (%)	44 (50.6)	28 (42.4)	72 (47.1)
Subjects with at least one baseline lesion(s) in the liver, brain, or lung by IRC, n (%)	71 (81.6)	44 (66.7)	115 (75.2)
Screening ECOG score, n (%)	-	-	-
0	62 (71.3)	42 (63.6)	104 (68.0)
1	25 (28.7)	24 (36.4)	49 (32.0)
Resected tumor site, n (%)	-	-	-
Lymph node	23 (26.4)	20 (30.3)	43 (28.1)
Other	12 (13.8)	26 (39.4)	38 (24.8)
Skin/subcutaneous	20 (23.0)	8 (12.1)	28 (18.3)
Liver	7 (8.0)	5 (7.6)	12 (7.8)
Lung	11 (12.6)	1 (1.5)	12 (7.8)
Other visceral	4 (4.6)	3 (4.5)	7 (4.6)
Peritoneal/retroperitoneal	5 (5.7)	2 (3.0)	7 (4.6)
Breast	3 (3.4)	1 (1.5)	4 (2.6)
Musculoskeletal	2 (2.3)	0	2 (1.3)
% PD-L1 TPS per central laboratory, n (%)	-	-	-
PD-L1 positive (TPS ≥5%)	20 (23.0)	23 (34.8)	43 (28.1)
PD-L1 negative (TPS <5%)	39 (44.8)	26 (39.4)	65 (42.5)
Missing	28 (32.2)	17 (25.8)	45 (29.4)
BRAF status, n (%)	-	-	-
Mutated (V600E or V600K)	24 (27.6)	17 (25.8)	41 (26.8)
Wild type	58 (66.7)	45 (68.2)	103 (67.3)
Other	5 (5.7)	1 (1.5)	6 (3.9)
Unknown	0	3 (4.5)	3 (2.0)

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Disease Characteristic	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled Cohorts 2 and 4 (N=153)
Baseline LDH (U/L), n (%)	-	-	-
≤ULN	31 (35.6)	39 (59.1)	70 (45.8)
>1 - ≤2 x ULN	35 (40.2)	19 (28.8)	54 (35.3)
>2 x ULN	21 (24.1)	8 (12.1)	29 (19.0)
Target lesion SoD assessed by IRC (mm)	-	-	-
n	86	63	149
Mean (SD)	126.59 (95.693)	108.00 (65.861)	118.73 (84.624)
Median	99.45	95.80	97.80
Min, Max	15.7, 552.9	13.5, 271.3	13.5, 552.9
Number of involved organs/sites of baseline lesions by IRC, n (%)	-	-	-
<3	22 (25.3)	21 (31.8)	43 (28.1)
≥3	65 (74.7)	44 (66.7)	109 (71.2)

Source: C-144-01, Program: t2-7-3-2-3-bldis-c2c4-fas.sas, Data: ADSL, ADBL, ADCM and ADPR, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Abbreviations: BRAF = proto-oncogene B-Raf; ECOG = Eastern Cooperative Oncology Group; IRC = Independent Review Committee; LDH = lactate dehydrogenase; max = maximum; min = minimum; PD-L1 = programmed death-ligand 1; SD = standard deviation; SoD = sum of diameters; TPS = tumor proportion score; ULN = upper limit of the normal range

Table 13. Applicant – Prior Anticancer Therapies (Full Analysis Set)

Type of Anticancer Therapy	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled Cohorts 2 and 4 (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	-	-	-
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
Prior Anti-PD-1/L1 treatment setting, n (%)	-	-	-
Adjuvant/Neoadjuvant Only	8 (9.2)	5 (7.6)	13 (8.5)
Metastatic only	70 (80.5)	59 (89.4)	129 (84.3)
Both adjuvant/neoadjuvant and metastatic	9 (10.3)	2 (3.0)	11 (7.2)
Number of lines containing Anti-PD-1/L1	-	-	-
Mean (SD)	1.8 (0.85)	1.7 (0.75)	1.8 (0.81)
Median	2.0	2.0	2.0
Min, Max	1, 5	1, 4	1, 5
Primary refractory to prior Anti-PD-1/PD-L1 therapy, n (%) [2]	41 (47.1)	42 (63.6)	83 (54.2)

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Type of Anticancer Therapy	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled Cohorts 2 and 4 (N=153)
Resistance to prior Anti-PD-1/L1 as per SITC definition, n (%)	-	-	-
All resistant	84 (96.6)	66 (100)	150 (98.0)
Primary resistance to prior Anti-PD-1/L1 [3]	57 (65.5)	52 (78.8)	109 (71.2)
Secondary resistance to prior Anti-PD-1/L1 [4]	27 (31.0)	14 (21.2)	41 (26.8)
Late progressor	2 (2.3)	0	2 (1.3)
Not evaluable	1 (1.1)	0	1 (0.7)
Time from tumor harvest to infusion (Days)	-	-	-
Mean (SD)	37.4 (11.61)	33.7 (7.91)	35.8 (10.32)
Median	34.0	31.0	33.0
Min, Max	26, 99	25, 61	25, 99

Source: C-144-01, Program: t2-7-3-2-3-bldis-c2c4-fas.sas, Data: ADSL, ADBL, ADCM and ADPR, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
[1] Includes patients who are BRAF V600E or V600K mutated and received BRAF Inhibitor ± MEK Inhibitor.
[2] Primary refractory to anti-PD-1/PD-L1 is defined as patients who had best response of PD to prior anti-PD-1/anti-PD-L1; the first anti-PD-1/anti-PD-L1 with documented response was considered if multiple anti-PD-1/anti-PD-L1 blocking therapies were received.
[3] Includes primary resistance to prior anti-PD-1/L1 therapy in the metastatic setting and primary resistance/early relapse to prior anti-PD-1/L1 in the adjuvant setting
[4] Includes secondary resistance to prior anti-PD-1/L1 therapy in metastatic setting and late relapse in adjuvant setting.
Abbreviations: BRAF = proto-oncogene B-Raf; CTLA-4 = cytotoxic T lymphocyte antigen-4; IL-2 = interleukin-2; max = maximum; MEK = mitogen-activated extracellular signal-regulated kinase; min = minimum; PD = progressive disease; PD-1 = programmed cell death protein-1; PD-L1 = programmed death-ligand 1; SD = standard deviation; SITC = Society for Immunotherapy of Cancer

The Applicant's Position

The subjects in Study C-144-01 had baseline disease characteristics that were consistent with late-stage disease (Table 12):

- In Cohort 4, 98.9% of the subjects had Stage IV melanoma at study entry and 81.6% had liver, brain, and/or lung lesions. At screening, all Cohort 4 subjects had an ECOG performance score of 0 (71.3%) or 1 (28.7%).
- In Cohort 2, 86.4% of the subjects had Stage IV melanoma at study entry and 66.7% had liver, brain, and/or lung lesions. At screening, all Cohort 2 subjects had an ECOG performance score of 0 (63.6%) or 1 (36.4%).

There was a high tumor burden at baseline as evidenced by the baseline lactate dehydrogenase (LDH) and target lesion SoD parameters.

- More than half of the subjects in Cohort 4 had elevated baseline LDH levels (64.4% above upper limit of normal range [ULN]), of which 24.1% were >2 × ULN. The median target lesion SoD as assessed by the IRC per RECIST v1.1 was 99.5 mm (min, max: 15.7, 552.9).
- In Cohort 2, 40.9% of the subjects had elevated baseline LDH levels (12.1% >2 × ULN) and the median target lesion SoD as assessed by the IRC per RECIST v1.1 was 95.8 mm (min, max: 13.5, 271.3).

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The Cohort 4 subjects were heavily pretreated, with a median of 3.0 (min, max: 1, 8) prior systemic therapies (Table 13). All subjects, as required for inclusion in the study, received prior anti-PD-(L)1 therapy. Additionally, 82.8% received prior anti-CTLA-4 therapy and 55.2% received prior anti-PD-1/CTLA-4 combination therapy. 47.1% of the subjects were primary refractory to anti-PD-(L)1 therapy (i.e., subjects who had best response of PD to prior anti-PD-[L]1 agent) and 65.5% had primary resistance as per the Society for Immunotherapy of Cancer (SITC) definition (Kluger et al. 2020). All subjects who had BRAF V600 mutation-positive melanoma received prior BRAF ± MEK inhibitor therapy.

The prior melanoma therapies for Cohort 2 were similar to those for Cohort 4. In Cohort 2, 63.6% of the subjects were primary refractory to anti-PD-(L)1 therapy and 78.8% had primary resistance as per the SITC definition.

The FDA's Assessment

FDA concurs that the baseline characteristics of subjects enrolled in Study C-144-01 were consistent with late-stage melanoma which had been treated with multiple lines of systemic therapies, including at least one line of anti-PD1-based therapy, before being enrolled to Study C-144-01.

FDA verified baseline characteristics pertinent to the study eligibility. All study subjects included in the Cohort 4 full efficacy analysis set (N=87, refer to Table 12 and Table 13) met protocol-defined eligibility criteria.

FDA notes that, as indicated in Applicant Table 13, approximately 9% of subjects (9.2% for Cohort 4 and 8.5% for pooled Cohort 2 and 4 full efficacy analysis set) only received prior anti-PD1 treatment in neoadjuvant and/or adjuvant settings, but not in the metastatic setting. As Study C-144-01 was a single arm trial, it remains uncertain whether or not these subjects would still benefit from another anti-PD1 therapy as monotherapy or in combination with another ICI in the metastatic setting. Refer to Applicant Table 1 and FDA assessments of current subsequent lines of therapies for metastatic melanoma after the first line anti-PD1-based ICIs in Section 2.2.

FDA identified two study subjects from Cohort 2 full efficacy analysis set (N=66) who had BRAF V600 mutation but were not treated with a BRAF inhibitor with or without MEK inhibitor before study enrollment: Subject (b) (6) achieved a complete response and Subject (b) (6) achieved a partial response. In response to an FDA IR, the Applicant stated that these two subjects (b) (6) met the eligibility criteria of the active Study C-144-01 protocol at the time of their enrollment. The inclusion criteria regarding treatment for BRAF V600 mutation were required at a later version of the Study C-144-01 protocol. Nevertheless, FDA did not pursue sensitivity analyses given that the previously untreated BRAF V600E/K in subjects from Cohort 2 does not affect the primary efficacy analysis which was based on Cohort 4 data.

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Additional Baseline Characteristics Assessed by FDA

Number of Prior Lines of Anti-PD1 Therapies and Longest Treatment Duration on a Single Line

To assess whether study subjects enrolled to Study C-144-01 had been adequately treated with at least one line of FDA-approved anti-PD1 therapy and would be unlikely to respond to another anti-PD1 therapy, FDA queried information regarding durations and doses of prior anti-PD1 therapies for study subjects included in the full efficacy analysis set (N=153). Per Applicant's response to FDA, information on the number of anti-PD1 doses on a single anti-PD1 was not collected.

FDA Table 14 below shows that prior anti-PD1 treatment duration varies. With additional data provided by the Applicant, FDA identified nine subjects (four from Cohort 4, five from Cohort 2) whose longest one line of prior anti-PD1 therapy was less than 8 weeks. Specifically, the longest one line of anti-PD1 therapy was 2.9 weeks (discontinued due to toxicity) for one subject (b) (6) (b) (6) Cohort 4), 6.0 to 6.7 weeks for six subjects, and 7.4 to 7.6 weeks for two subjects. The short treatment duration with prior anti-PD1 raises the question of the adequacy of the prior treatment with anti-PD1 in some study subjects, as "pseudo-progression" can occur in approximately 5% to 10% of patients receiving anti-PD1 therapy (Beaver et al. 2018; Kluger et al. 2020).

FDA notes that prior treatment and response information in Study C-144-01 were collected from medical records. Some subjects had the most recent anti-PD1 more than 2 years before participating in Study C-144-01. Therefore, the accuracy of this prior treatment and response information remains uncertain.

Based on information submitted to the BLA, FDA concludes that it remains uncertain whether all subjects in Study C-144-01 were unlikely to respond to another anti-PD1 therapy. Due to these uncertainties, FDA advises against defining the Study C-144-01 study population as anti-PD1 refractory or resistant population. FDA concurs with the Applicant that the study population of Study C-144-01 were patients who were previously treated with at least one line of anti-PD1 agent (also refer to FDA assessment under "Eligibility Criteria" in Section 8.1.1.2).

Table 14. FDA – Treatment Duration and Doses of Prior Anti-PD(L)1 Therapy (FDA)

Parameter	Median (min-max)
**Number of adjudicated prior lines of anti-PD1 therapy	2 (1-5)
Longest duration (weeks) on a single line of prior anti-PD1 therapy (N=153)	23.0 (2.9-270.3)
Duration (months) of the first prior anti-PD1 therapy (N=153)	3.7 (0.03-56.4)
Cumulative duration (months) of combined prior anti-PD1 therapies (N=153)	7.0 (0.66-75.8)

Source: Dataset ADBL, L1
**: FDA did not adjudicate prior lines of anti-PD1 therapy for each study subject. However, FDA did find one (Subject (b) (6) who appeared to only have one prior line of anti-PD1 therapy as assessed by FDA, but the Applicant assessed it as two lines of prior anti-PD1.
Abbreviations: PD(L)1 = programmed death-ligand 1

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Number of Anatomic Sites with Lesions, Number of Lesions, and Target Lesions at the Baseline per IRC

In the pooled full efficacy analysis set (N=153), 152 subjects had information on the number of anatomic sites with lesions (mean and median =4, min =1, max =12) and total number of lesions (mean =6, median =5, min =1, max =16) at the baseline assessed by IRC. Among the 153 subjects, 149 subjects had information on the number of target lesions at the baseline, per IRC (mean and median =3, min =1, max =5).

FDA identified that, as assessed by IRC, one subject from Cohort 2 (b) (6) did not have a baseline lesion, and one subject from Cohort 4 (b) (6) and three subjects from Cohort 2 (b) (6) did not have any target lesions at the baseline. In FDA's opinion, these study subjects should not have been enrolled to the study. Per the Applicant's response to FDA IR, these study subjects were enrolled because study eligibility criteria were assessed by investigators, not IRC. In response to FDA's clinical IR, the Applicant clarified that IRC review of imaging and lesions at the screening was not required for eligibility evaluation.

FDA did not pursue sensitivity analysis of the primary outcome given that the lack of baseline target lesions only affected one subject (b) (6) from the Cohort 4 primary efficacy analysis set and this subject had unequivocal progression of the non-target lesions (n=2) at the Day 42 visit, per IRC. Therefore, the primary endpoint of ORR was not overestimated due to the lack of baseline target lesion in Subject (b) (6)

Number of Anatomic Sites for TH

Among all subjects in the full analysis set (N=153), 145 (94.8%) subjects had 1 anatomic site, 7 (4.6%) subjects had 2 anatomic sites, and 1 (0.7%) subject had 3 anatomic sites that were used for TH.

For the Cohort 4 full efficacy analysis set (N=87), 79 (90.8%) subjects had 1 anatomic site, 7 (8.1%) subjects had 2 anatomic sites, and 1 (1.2%) subject had 3 anatomic sites that were used for TH.

Anatomic Sites Being Used for TH

Among all subjects in the full analysis set (N=153), 38 (24.8%) subjects underwent TH in visceral lesions (liver, lung, peritoneal, or other visceral locations), 43 (28.1%) in lymph nodes, 28 (18.3%) in skin or subcutaneous sites, and the remaining 44 (28.8%) in breast, musculoskeletal, or other anatomic sites.

For the Cohort 4 full efficacy analysis set (N=87), 27 (31.0%) subjects underwent TH in visceral lesions (liver, lung, peritoneal, or other visceral locations), 23 (26.4%) in lymph nodes, 20 (23.0%) in skin or subcutaneous sites, and the remaining 17 (19.5%) in breast, musculoskeletal, or other anatomic sites.

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Days From TH to NMA-LD

Median days from TH to NMA-LD was 26 days (range: 18 to 92) for subjects in the pooled full efficacy analysis set (N=153) and 27 days (range: 19 to 92) for subjects in the Cohort 4 full efficacy analysis set (N=87).

FDA found that time from TH to NMA-LD was >50 days in six subjects (five from Cohort 4, one from Cohort 2). FDA notes that Study C-144-01 did not allow for bridging therapy while study subjects were waiting for lifileucel manufacturing. For patients with ongoing progressive disease, more than 50 days of waiting to initiate lifileucel regimen may not be feasible or practical.

8.1.2.7. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data

The NMA-LD preparative regimen, lifileucel, and IL-2 were administered at the clinical sites by qualified healthcare professionals.

Concomitant medications are defined as medications that were either initiated before and continued after the first dose of NMA-LD or initiated after the first dose of NMA-LD through 30 days post lifileucel infusion, not including the study regimen. The protocol required additional concomitant medications such as infectious disease prophylactic medications, hydration, premedications, and supportive therapy. In Cohort 4, the use of steroids, at any dose (oral or IV), from 21 days prior (i.e., Day -28) to the initiation of lymphodepletion (i.e., Day -7) through 60 days post-lifileucel infusion was prohibited but allowed if used to treat immediately life-threatening conditions. In Cohort 2, the use of systemic steroids was not prohibited.

Among the subjects in the safety analysis set (N=156), the most common concomitant medications included study mandated/recommended supportive medications such as mesna (98.7%), antibiotics (e.g., sulfamethoxazole; trimethoprim, 66.0%), antifungals (i.e., fluconazole, 89.1%), and filgrastim (78.2%), as well as supportive blood products (e.g., red blood cells [35.9%] and platelets [62.2%], Data: ADSL and ADCM). The most common non-study mandated concomitant medications included diuretics (i.e., furosemide, 75.0%), electrolyte supplements (e.g., potassium [44.2% to 50.0%] and magnesium [40.4%]), and lorazepam (52.6%).

The Applicant's Position

The concomitant medications reported were expected and appropriate based on the protocol-required medications, patient population including the underlying disease, and AEs that are expected with the administration of NMA-LD and IL-2.

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The FDA's Assessment

Lifileucel regimen, including NMA-LD preparative regimen, lifileucel, and IL-2, were administered at the study sites by qualified healthcare professionals. FDA did not identify treatment non-compliance issues.

FDA concurs that the concomitant medications and rescue medications used in the trial were adequate.

Based on additional data submitted by the Applicant, FDA confirmed that most study subjects in the safety analysis set (N=156) received antibiotics (85.3%), antifungals (89.1%; e.g., fluconazole), pneumocystis jirovecii pneumonia (PJP, 74.4%; e.g., sulfamethoxazole and trimethoprim), or antivirals (72.4%; e.g., acyclovir or valacyclovir) including herpes simplex virus (HSV, 71.8%) prophylaxis, as recommended by the study protocol.

The study protocol's general guidance was to begin fungal prophylaxis (e.g., fluconazole) on Day 1, PJP prophylaxis (e.g., trimethoprim-sulfamethoxazole double strength, pentamidine) on Day 14, and HSV prophylaxis on Day 14 or as the investigator deemed appropriate. Per study protocol, acyclovir or valacyclovir was recommended as HSV prophylaxis for subjects with positive HSV immunoglobulin M or PCR results.

FDA confirmed that 100% subjects in the safety set (N=156) received mesna along with cyclophosphamide as a hemorrhage cystitis prophylaxis, per study protocol requirement.

In response to FDA's clinical IR, the Applicant confirmed that some form of granulocyte colony stimulating factor (G-CSF, including filgrastim) was administered beginning on Day 1 and was continued each day until absolute neutrophil count was >1000/mm^3 for 3 consecutive days or followed institutional standards, per study protocol schedule. Among the study subjects in the safety analysis set (N=156), 93.6% of subjects received G-CSF. The mean and median number of doses were 9.9 and 9.0, respectively; the mean and median duration of G-CSF use were 10.5 and 8.0 days, respectively.

8.1.2.8. Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data

The study met its primary objective, with an ORR, as assessed by IRC per RECIST v1.1, in the FAS of Cohort 4 of 28.7% (95% CI: 19.5, 39.4, Table 15).

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Table 15. Applicant – Objective Response Rate by IRC per RECIST v1.1 (Full Analysis Set)

Statistic	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled Cohorts 2 and 4 (N=153)
Objective response rate, n (%)	25 (28.7)	23 (34.8)	48 (31.4)
(95% CI)	(19.5, 39.4)	(23.5, 47.6)	(24.1, 39.4)

Source: C-144-01, Program: t14-2-1-1-2-1-rsp-irc-c2c4-fas.sas, Data: ADSL and ADRS, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Objective response refers to subjects with best overall response of CR and PR.
The 95% CI was calculated using the Clopper-Pearson Exact test.
Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors

In the efficacy analysis set, the ORR in Cohort 4, as assessed by IRC per RECIST v1.1, was similar to the FAS (Table 16) at 28.0% (95% CI: 18.7, 39.1).

Table 16. Applicant – Objective Response Rate by IRC per RECIST v1.1 (Efficacy Analysis Set)

Statistic	Cohort 4 (N=82)	Cohort 2 (N=41)	Pooled Cohorts 2 and 4 (N=123)
Objective response rate, n (%)	23 (28.0)	16 (39.0)	39 (31.7)
(95% CI)	(18.7, 39.1)	(24.2, 55.5)	(23.6, 40.7)

Source: C-144-01, Program: t2-7-3-4-2-rsp-irc-c2c4-eff2.sas, Data: ADBL and ADRS, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Objective response refers to subjects with best overall response of CR and PR.
The 95% CI was calculated using the Clopper-Pearson Exact test.
Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors

The Applicant's Position

The study met its primary objective. The lower bound of the 95% CI exceeded the prespecified null hypothesis threshold of 10%, a value that was based on the ORR observed with standard-of-care chemotherapy established in an earlier-line patient population that had not received prior anti-PD1 therapy (Weber et al. 2015a; Hamid et al. 2017a). The robustness of the ORR in Cohort 4 in both the FAS and efficacy analysis set is supported by the ORRs for Cohort 2 and Pooled Cohorts 2 and 4.

The FDA's Assessment

FDA agrees that Study C-144-01 met its primary objective. However, FDA's assessment of the primary evidence was not based on a lower bound threshold of 10% for the 95% CI of ORR. Instead, FDA assessed the totality of evidence from this single arm trial accounting for treatment options for the intended patient population at the time of reviewing this BLA. Also refer to Section 8.1.1.4 and Section 8.1.2.10 regarding FDA assessment of the primary efficacy evidence.

Due to unresolved product comparability issues among lifileucel manufacturing facilities, FDA's assessment of the primary efficacy results was based on 82 study subjects from Cohort 4 who received lifileucel manufactured at (b) (4) facility (refer to Cohort 4 primary efficacy analysis set in Table 16 and FDA Table 17).

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In summary, Study C-144-01 achieved an ORR of 28.0% (95% CI: 18.7% to 39.1%, N=82; refer to Applicant Table 16). Among 82 subjects included in the primary efficacy analysis, 23 subjects achieved a PR (n=20) or CR (n=3).

FDA notes that DOR results based on Cohort 4 efficacy analysis set (N=82) are assessed as primary evidence to support the BLA submission, although the Applicant assessed DOR as a secondary endpoint. Refer to FDA assessment in "Efficacy Results – Secondary and other relevant endpoints" in Section 8.1.2.10.

FDA also notes that the median DOR follow-up time of 18.6 months (95% CI: 12.5 to 22.2) shown in Table 17 was potential follow-up time, estimated by reverse KM method (Schemper and Smith 1996). The actual median follow-up time for DOR based on the last imaging scan of the responders (n=23) was 8.3 (range: 1.4 to 26.3) months, per additional information requested by FDA.

Table 17. FDA – Primary Efficacy and Key Secondary Efficacy Results From C-144-01

Endpoint	Lifileucel (Cohort 4, N=82)
Best overall response by IRC per RECIST v1.1	-
Objective response rate, n (%) [95% CI]	23 (28.0) [18.7, 39.1]
Complete response rate, n (%)	3 (3.7)
Partial Response rate, n (%)	20 (24.4)
Duration of response (DOR)	-
Median in months (95% CI)	NR (4.1, NR)
Range in months	1.4+, 26.3+
% with duration ≥6 months	56.5%
% with duration ≥9 months	47.8%
% with duration ≥12 months	43.5%
Follow-up time for response in months	-
Median (95% CI)	18.6 (12.5, 22.2)
Min, max	1.4, 26.3

Source: Datasets: ADSL ADRS ADTTE
Abbreviations: CI = confidence interval; IRC = Independent Review Committee; NR = not reached; RECIST = Response Evaluation Criteria in Solid Tumors

Based on data submitted by the Applicant, FDA found that for the partial responders (n=20), the median reduction of the target lesion size (based on SoD, %) from the baseline was 58.7% (range: 33.4% to 86.3%), and the best change of non-target lesion was NON-CR/NON-PD for 90% of the partial responders and CR for 10% of partial responders.

The following FDA Table 18 further characterizes age and baseline characteristics of the responders.

In summary, the median age of the responders was 58, median prior lines of systemic therapy was 3 (range: 1 to 9), median prior lines of anti-PD1 containing therapy was 2 (range: 1 to 4), median longest consecutive weeks on a prior line anti-PD1 was 32.7 weeks (range: 7.4 to 227.3 weeks), median number of target lesions at the baseline was 2 (range: 1 to 5), median SoD of

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target lesions at the baseline was 70.8 mm (range: 23.9 to 552.9), median time from TH to baseline tumor scan was 21 days (range: 7 to 39 days), and median time from TH to NMA-LD was 29 days (range: 19 to 45 days). Of note, most responders (n=19, 82.6%) had only one anatomic site used for TH.

FDA notes that all responders from the Cohort 4 primary efficacy analysis set (N=23) had target lesions at the baseline. All but two responders had non-target lesions at the baseline (see below for details).

FDA found that the baseline tumor burden for the complete responders (n=3) was lower than the overall responders. Specifically, two complete responders (b) (6) had two target lesions but no non-target lesion; the other complete responder (b) (6) had one target lesion and one non-target lesion at the baseline. The baseline SoD of target lesions among these 3 complete responders was between 38.4 and 40.6 mm, smaller than that of overall responders shown in FDA Table 18.

Table 18. FDA – Baseline Characteristics of Responders in Cohort 4 Primary Efficacy Analysis Set (N=23)

Baseline Characteristics	N	Median (Min, Max)	Mean
Age	23	58.0 (25.0, 74.0)	55.3
Number of targe lesion	23	2.0 (1.0, 5.0)	2.7
Number of non-target lesion	21	2.0 (1.0, 6.0)	2.6
Baseline target lesion SoD per IRC (mm)	23	70.8 (23.9, 552.9)	103.7
Number of prior lines of anti-PD1	23	2.0 (1.0, 4.0)	2
Longest weeks on a single anti-PD1 therapy	23	32.7 (7.4, 227.3)	48.2
Days from TH to baseline scan	23	21.0 (7.0, 39.0)	20.8
Days from TH to NMA-LD	23	29.0 (19.0, 45.0)	30.9

Source: Datasets: ADSL L1
Abbreviations: SoD = sum of diameters; IRC = Independent Review Committee; NMA-LD = nonmyeloablative lymphodepletion; PD(L)1 = programmed death-ligand 1; TH = tumor harvest

FDA confirms that the primary efficacy results from Cohort 4 primary efficacy set were consistent with results from several other analyses based on data from Cohort 2 and pooled Cohort 2 and 4 full efficacy analysis sets. Refer to ORR results shown in Table 15 and Table 16 provided by the Applicant).

8.1.2.9. Data Quality and Integrity

Data and The Applicant's Position

The study was conducted in accordance with GCP regulations.

The impact of the coronavirus disease 2019 (COVID-19) pandemic on Study C-144-01 was investigated. All subjects in Cohorts 2 and 4 had received their lifileucel infusion no later than 1/15/2020, before the declaration of the pandemic by the World Health Organization on 3/11/2020. The impact of the pandemic upon premature discontinuation from the response

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assessment period and the study were assessed. In addition, the frequency of assessments at an alternative imaging facility and/or having missed response assessments due to the pandemic were evaluated. Overall, the pandemic did not prevent Study C-144-01 from meeting its objectives and had minimal impact on the study data.

The FDA's Assessment

FDA concurs with the Applicant's assessment. The FDA site inspectors did not find evidence that the COVID-19 pandemic affected the frequency of imaging scans and tumor response assessments.

8.1.2.10. Efficacy Results – Secondary and Other Relevant Endpoints

Data

In Cohort 4, there were 3 CR and 22 PR (Table 19). The DCR, which, by definition, included CR, PR, SD, and non-CR/non-PD, was 82.8%.

Table 19. Applicant – Disease Control Rate and Best Overall Response by IRC per RECIST v1.1 (Full Analysis Set)

Statistic	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled Cohorts 2 and 4 (N=153)
Disease control rate, n (%)	72 (82.8)	48 (72.7)	120 (78.4)
(95% CI)	(73.2, 90.0)	(60.4, 83.0)	(71.1, 84.7)
Best overall response, n (%)	-	-	-
CR	3 (3.4)	5 (7.6)	8 (5.2)
PR	22 (25.3)	18 (27.3)	40 (26.1)
SD	47 (54.0)	24 (36.4)	71 (46.4)
NN	0	1 (1.5)	1 (0.7)
PD	12 (13.8)	15 (22.7)	27 (17.6)
NE	3 (3.4)	3 (4.5)	6 (3.9)

Source: C-144-01, Program: t14-2-1-1-2-1-rsp-irc-c2c4-fas.sas, Data: ADSL and ADRS, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Notes: Non-CR/non-PD is for subjects who did not have acceptable target lesions by IRC assessment.
Disease control refers to subjects with BOR of CR, PR, SD, and NN.
95% CI was calculated using the Clopper-Pearson Exact test.
Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; IRC = Independent Review Committee; NE = not evaluable; NN = non-CR/non-PD; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

81.5% of subjects in Cohort 4 experienced tumor size reductions per the best percent change in target lesion SoD from baseline, as assessed by the IRC per RECIST v1.1 (Figure 6).

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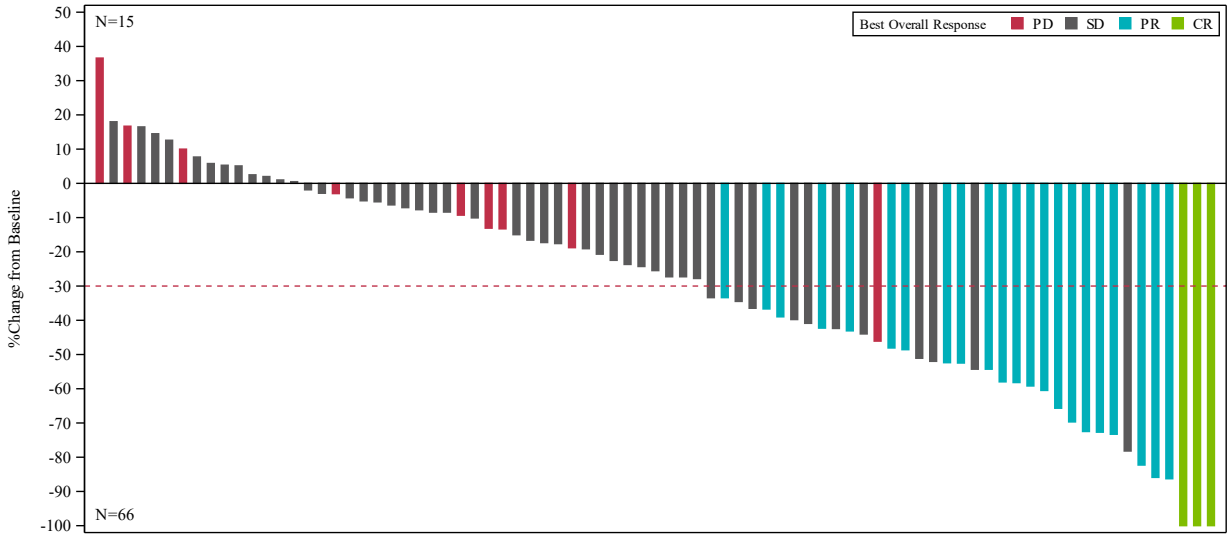
Figure 6. Applicant – Best Percent Change From Baseline for Target Lesion SoD by IRC per RECIST v1.1 for Cohort 4 (Full Analysis Set)



Source: C-144-01, Program: f14-2-1-1-1-waterfall-irc-c4-fas.sas, Data: ADTR and ADRS, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Note: Subjects in the FAS but not included in the figure: 3 NE subjects had no post-TIL target lesion SoD measurements due to early death; 3 PD subjects (1 subject had no acceptable target lesions by IRC; 2 subjects had no post-TIL target lesion SoD measurements on or before their PD date).
Abbreviations: CR = complete response; FAS = Full Analysis Set; IRC = Independent Review Committee; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SoD = sum of diameters; TIL = tumor-infiltrating lymphocytes

At the data cutoff date, all Cohort 4 confirmed responders in the FAS and efficacy analysis set had been followed for a minimum of 17 months starting from their initial response, unless discontinued.

In the FAS (Table 20), of the 25 responders, 56.0% had a DOR of ≥6 months, 48.0% ≥9 months, 44.0% ≥12 months, and 36.0% had an ongoing response. The median DOR was 10.4 months (min, max: 1.4+, 26.3+). Similarly in the efficacy analysis set (Table 21), of the 23 responders, 56.5% had a DOR of ≥6 months, 47.8% ≥9 months, 43.5% ≥12 months, and 39.1% had an ongoing response. The median DOR has not been reached (min, max: 1.4+, 26.3+).

The efficacy results in Cohort 4 in both analysis sets are supported by those in Cohort 2 and in the pooled data from Cohorts 2 and 4.

Table 20. Applicant – Duration of Response by IRC per RECIST v1.1 in Confirmed Responders (Full Analysis Set)

Statistic	Cohort 4 (N=25)	Cohort 2 (N=23)	Pooled Cohorts 2 and 4 (N=48)
Events, n (%)	13 (52.0)	4 (17.4)	17 (35.4)
Progressive disease	13	4	17
Death	0	0	0

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Statistic	Cohort 4 (N=25)	Cohort 2 (N=23)	Pooled Cohorts 2 and 4 (N=48)
Censored, n (%)	12 (48.0)	19 (82.6)	31 (64.6)
Primary reason for censoring	-	-	-
Death or PD after 2 or more missed visits	2 (8.0)	0	2 (4.2)
Start of a new anticancer therapy	1 (4.0)	8 (34.8)	9 (18.8)
Discontinued assessment without PD or death	0	1 (4.3)	1 (2.1)
Ongoing without PD or death	9 (36.0)	10 (43.5)	19 (39.6)
DOR [1], months	-	-	-
Median (95% CI)	10.4 (4.1, NR)	NR (NR, NR)	NR (8.3, NR)
Min, Max	1.4+, 26.3+	1.4+, 45.0+	1.4+, 45.0+
DOR ≥6 Months, n (%)	14 (56.0)	16 (69.6)	30 (62.5)
DOR ≥9 Months, n (%)	12 (48.0)	15 (65.2)	27 (56.3)
DOR ≥12 Months, n (%)	11 (44.0)	15 (65.2)	26 (54.2)
DOR ≥15 Months, n (%)	9 (36.0)	15 (65.2)	24 (50.0)
DOR ≥18 Months, n (%) [3]	7 (28.0)	13 (56.5)	20 (41.7)
DOR ≥24 Months, n (%) [3]	1 (4.0)	11 (47.8)	12 (25.0)
Follow-up time for Response [2], months	-	-	-
Median (95% CI)	18.6 (12.5, 22.2)	31.0 (16.6, 34.2)	21.5 (18.2, 31.0)

Source: C-144-01, Program: t14-2-1-3-2-1-dor-irc-c2c4-fas.sas, Data: ADTTE, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
[1] Based on Kaplan-Meier estimates.
[2] Based on the reverse Kaplan-Meier method.
[3] In Cohort 4, the percentage of subjects with a DOR ≥18 or 24 months is immature and underestimated since it includes ongoing responders who have not reached 18 months and 24 months of follow-up.
Abbreviations: CI = confidence interval; DOR = duration of response; IRC = Independent Review Committee; NR = not reached; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors

Table 21. Applicant – Duration of Response by IRC per RECIST v1.1 in Confirmed Responders (Efficacy Analysis Set)

Statistic	Cohort 4 (N=23)	Cohort 2 (N=16)	Pooled Cohorts 2 and 4 (N=39)
Events, n (%)	11 (47.8)	3 (18.8)	14 (35.9)
Progressive disease	11	3	14
Death	0	0	0
Censored, n (%)	12 (52.2)	13 (81.3)	25 (64.1)
Primary reason for censoring	-	-	-
Death or PD after 2 or more missed visits	2 (8.7)	0	2 (4.2)
Start of a new anticancer therapy	1 (4.3)	5 (31.3)	9 (18.8)
Ongoing without PD or death	9 (39.1)	8 (50.0)	17 (43.6)
DOR [1], months	-	-	-
Median (95% CI)	NR (4.1, NR)	NR (2.9, NR)	NR (4.8, NR)
Min, Max	1.4+, 26.3+	1.6+, 40.0+	1.4+, 40.0+

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Statistic	Cohort 4 (N=23)	Cohort 2 (N=16)	Pooled Cohorts 2 and 4 (N=39)
DOR ≥6 Months, n (%)	13 (56.5)	11 (68.8)	24 (61.5)
DOR ≥9 Months, n (%)	11 (47.8)	10 (62.5)	21 (53.8)
DOR ≥12 Months, n (%)	10 (43.5)	10 (62.5)	20 (51.3)
DOR ≥18 Months, n (%) [3]	7 (30.4)	10 (62.5)	17 (43.6)
DOR ≥24 Months, n (%) [3]	1 (4.3)	9 (56.3)	10 (25.6)
Follow-up time for response [2], months	-	-	-
Median (95% CI)	18.6 (12.5, 22.2)	31.7 (6.4, 34.2)	22.2 (18.2, 31.0)

Source: C-144-01, Program: t2-7-3-5-2-dor-irc-c2c4-eff2.sas, Data: ADBL and ADTTE, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
[1] Based on Kaplan-Meier estimates.
[2] Based on the reverse Kaplan-Meier method.
[3] In Cohort 4, the percentage of subjects with a DOR >=18 or 24 months is immature and underestimated since it includes ongoing responders who have not reached 18 months and 24 months of follow-up.
Abbreviations: CI = confidence interval; DOR = duration of response; IRC = Independent Review Committee; NR = not reached; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors

The Applicant's Position

After treatment with lifileucel, durable responses were observed in a heavily pretreated patient population with unresectable or metastatic melanoma with a high baseline tumor burden that had progressed on multiple standard therapies, including ICIs (i.e., anti-PD-(L)1±anti-CTLA-4 therapies) and targeted therapies such as BRAF with or without MEK inhibitors. This represents a difficult-to-treat patient population with a high unmet clinical need and limited effective treatment options.

The results observed in Cohort 2 were similar to those observed for Cohort 4.

The FDA's Assessment

Although the Applicant assessed DCR as a secondary efficacy endpoint for Study C-144-01, FDA is unable to interpret DCR results from a single arm trial because SD may simply reflect the natural disease history instead of evidence of a therapeutic effect. SD and DCR should be assessed in a randomized controlled trial setting through PFS or TTP analysis. For this reason, FDA did not assess DCR as direct evidence of clinical efficacy.

In contrast to DCR, FDA assessed the DOR results based on Cohort 4 efficacy analysis set (N=82) as primary evidence to support this BLA application.

FDA confirms that among the 23 responders from the primary efficacy analysis set, 13 (56.5%), 11 (47.8%), and 11 (43.5%) responders maintained durable responses at 6, 9, and 12 months from the initial responses, respectively (refer to Applicant Table 21 and FDA Table 17).

The following FDA Table 22 summarizes DOR results of the responders (n=23) as part of the basis of primary efficacy evidence.

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Table 22. FDA – DOR Among Responders in Cohort 4 (N=23) Primary Efficacy Assessment

Number of Responders	DOR (Months)	FDA Comments
9	16.3-26.3	Responses continued without PD till final data cutoff (9/11/2021)
1	12.5	The subject (b) (6) started a new anti-cancer therapy at 12.5 months (Day 381 by IRC) and was censored.
1	9.6	The subject (b) (6) was censored at 9.6 months post the initial response after missing at least 2 tumor assessments before PD (this subject was re-enrolled to Cohort 3 for retreatment and received LN-144 on Day 419, but disease progressed on Day 461)
11	2.6-8.3	Subject experienced PD
1	1.4	The subject was censored at 1.4 months post the initial response after missing at least two tumor assessments due to the COVID-19 pandemic and subsequent PD on Day 258 and death on Day 268

Source: Dataset: ADTTE
Abbreviations: COVID-19 = coronavirus disease 2019; DOR, = duration of response; IRC, Independent Review Committee; PD = progressive disease

Based on the KM analysis of DOR, the median DOR was NR among the 23 responders. FDA cautions interpreting "NR" for DOR. Several factors might have contributed to the "NR" median DOR: 1) although less than 50% of responders (n=11, 11/23=47.8%) had PD, less than 50% of responders (n=10, 10/23=43.5%) maintained durable responses beyond 12 months; and 2) as indicated in FDA Table 22 above, several responders were censored early and contributed limited information to the KM analysis.

FDA notes that DOR follow-up times for responders shown the Applicant's Table 20 and Table 21 were potential DOR follow-up times estimated by reverse KM method (Schemper and Smith 1996). The actual DOR follow-up time based on the last imaging scans of study subjects (per additional data provided by the Applicant) was 8.3 months (range: 1.4 to 26.3, N=25), 8.3 months (range: 1.4 to 26.3, N=23), 21.5 months (range: 1.4 to 45.0, N=23), and 13.8 months (range: 1.4 to 45.0, N=48) for responders in Cohort 4 full efficacy analysis set, Cohort 4 primary analysis set, Cohort 2 full efficacy set, and pooled Cohort 2 and 4 full efficacy set, respectively.

FDA Conclusion Based on the Primary Efficacy Evidence from Study C-144-01

Study subjects from Study C-144-01 were patients with unresectable or metastatic melanoma who had a median of three prior lines of systemic treatment including median of two lines containing an anti-PD1 agent. The prognosis for such patients is poor with no FDA-approved therapy. An ORR of 28.1% observed in Study C-144-01, along with durable response rates of 56.5% and 43.5% among responders at 6 and 12 months, respectively, indicate clinically meaningful benefits to these patients with a high unmet medical need. Therefore, FDA agrees that Study C-144-01 met its primary objectives.

However, FDA cautiously interprets the ORR results from this single arm trial. First, as ORR is an early clinical outcome, whether the observed 28.0% ORR will translate to an improvement in PFS and OS needs to be verified by a randomized well-controlled confirmatory trial. Second, as

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the primary efficacy evidence from Study C-144-01 was based on a relatively small sample size (N=82) and consequently a relatively wide 95% CI (18.7% to 39.1%) around the point estimate, it remains uncertain at this time whether the observed ORR may be replicated in another clinical trial and in the real-world clinical setting.

FDA advised the Applicant at the pre-BLA meeting on 7/29/2022 that the clinical benefit observed in Study C-144-01 requires verification in a well-controlled randomized confirmatory trial.

Following FDA's recommendations at the Phase 3 trial design meeting on 9/29/2022, the Applicant proposed a new Phase 3 RCT (IOV-MEL-301) in subjects with newly diagnosed unresectable or metastatic melanoma which is now open for enrollment. This trial serves as the confirmatory for Study C-144-01, intended to compare lifileucel regimen plus pembrolizumab versus pembrolizumab alone in the first line systemic treatment setting. Refer to the regulatory history of Study C-144-01 in Section 3.2 of this memo for the most recent update of the confirmatory trial.

8.1.2.10.1. ORR and DOR Results from Cohort 2 as Supporting Evidence

FDA concurs with the Applicant that ORR and DOR results from Cohort 2 (N=66) and pooled Cohort 2 and 4 (N=153) were consistent with the results from Cohort 4 primary efficacy analysis set (N=82).

FDA emphasizes that efficacy results from Cohort 2 are only assessed as supporting evidence. This was the agreement between the Applicant and FDA for multiple historical reasons (refer to Section 3.2 for regulatory history). The following issues with Cohort 2 explain some of these reasons:

a. Approximately 38% of study subjects in Cohort 2 received lifileucel manufactured at non-(b) (4) facilities (16.7% at (b) (4) and 21.2% at (b) (4)). Due to product comparability issues between (b) (4) and other facilities, FDA considers (b) (4) as the primary manufacturing facility to support this BLA application.
b. The vast majority of Cohort 2 subjects were enrolled before the implementation of IRC in Study C-144-01 in December of 2018 (refer to Applicant Table 2 and FDA Table 3 in Section 3.2). Therefore, IRC review of Cohort 2 tumor response data was not pre-defined in the protocol.
c. Cohort 2 was an earlier cohort before the Applicant decided to use Study C-144-01 as a pivotal trial intended to support a marketing application. Some eligibility changes to the protocol at later time points did not apply to Cohort 2. FDA identified two subjects in Cohort 2 who had BRAF mutation but were not treated with a BRAF inhibitor before study enrollment.
d. FDA identified three subjects from Cohort 2 (b) (6) versus one subject from Cohort 4 (b) (6) who did not have baseline target lesions per IRC.

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e. Baseline sum of diameter (SoD) of target lesions among Cohort 2 responders were overall smaller than that of Cohort 4 responders (median and mean baseline SoD for Cohort 2 responders were 59 mm and 62 mm, respectively, versus 71 mm and 103 mm for Cohort 4 responders, respectively), which may have played a role in the slightly higher point estimate of ORR observed in Cohort 2 than in Cohort 4.
f. FDA found that one subject (b) (6) from Cohort 2 had not received an FDA-approved first line anti-PD1 therapy before enrollment. The subject had received atezolizumab in combination with cobimetinib (MEK inhibitor) which was approved by FDA for patients with BRAF V600E/K mutations. However, per the Applicant's data, this subject had wild-type BRAF. The subject maintained SD in Study C-144-01 until PD on Day 127 and death on Day 190. Therefore, the apparent non-adequate prior anti-PD1 therapy in Subject (b) (6) did not overestimate the overall ORR observed in the pooled full efficacy analysis.

8.1.2.10.2. Disagreement on Tumor Assessments at Subject Level Between IRC and Investigators

The Applicant's submitted data suggest that the concordance rates between IRC- and investigator-assessed ORRs were approximately 90% (92.0% for Cohort 4 full efficacy analysis set, 89.4% for Cohort 2 full efficacy analysis set, and 90.8% for pooled Cohort 2 and 4 full efficacy set).

The following FDA Table 23 below also suggests that ORR and DOR rates at 6, 9, and 12 months following initial responses were similar between the assessments by IRC and the investigators.

Table 23. FDA – ORR and DOR Results by IRC and INV

Tumor Assessment Type	Cohort 4 Primary Analysis Set (N=82)	Pooled Cohort 2+4 Full Efficacy Analysis Set (N=153)
ORR by IRC	28.0% (95% CI: 18.7%-39.1%)	31.4% (95% CI: 24.1%-39.4%)
ORR by INV	25.6% (95% CI: 16.6%-36.4%)	31.4% (95% CI: 24.1%-39.4%)
DOR by IRC	n=23 (responders)	n=48 (responders)
DOR ≥6 Months, n (%)	13 (56.5)	30 (62.5)
DOR ≥9 Months, n (%)	11 (47.8)	27 (56.3)
DOR ≥12 Months, n (%)	10 (43.5)	26 (54.2)
DOR by INV	n=21 (responders)	n=48 (responders)
DOR ≥6 Months, n (%)	12 (57.1)	34 (70.8)
DOR ≥9 Months, n (%)	12 (57.1)	30 (62.5)
DOR ≥12 Months, n (%)	9(42.9)	26 (54.2)

Source: Dataset ADTTE ADSL
Abbreviations: CI = confidence interval; DOR = duration of response; INV = Investigator; IRC = Independent Review Committee; ORR = objective response rate

However, FDA suggests caution in interpreting these concordance rates. FDA found that concordance rates between investigators and IRC at the subject level were lower than at the summary level. See below for details.

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Disagreements on BOR Assessment Between IRC and Investigators

For the Cohort 4 primary efficacy analysis set (N=82), FDA found that IRC and investigators disagreed on tumor responses of 20 (25%) subjects (refer to FDA Table 24 and Table 25 below).

FDA Table 24 below shows that among 3 complete responders assessed by IRC, 1 (33.3%) was disagreed on by the investigators, and among 20 partial responders assessed by the IRC, 5 (25%) were disagreed on by the investigators. Similarly, FDA Table 24 below shows that among 3 complete responders assessed by the investigators, 1 (33.3%) was disagreed on by the IRC, and among 18 partial responders assessed by the investigators, 3 (16.7%) were disagreed on by the IRC.

Table 24. FDA – IRC-Assessed Tumor Responses in Primary Efficacy Set (N=82) Disagreed by INV

Tumor Response by IRC	Number of Subjects	Number of Subjects Disagreed by INV
CR	3	1
PR	20	5
NE	3	0
PD	11	3
SD	45	11

Source: Datasets: ADRS ADSL ADBL
Abbreviations: CR = complete response; INV = investigator; IRC = Independent Review Committee; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Table 25. FDA – INV-Assessed Tumor Responses in Primary Efficacy Set (N=82) Disagreed by IRC

Tumor Response by INV	Number of Subjects	Number of Subjects Disagreed by IRC
CR	3	1
PR	18	3
NE	3	0
PD	17	9
SD	41	7

Source: Datasets: ADRS ADSL ADBL
Abbreviations: CR = complete response; INV = investigator; IRC = Independent Review Committee; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

For the overall pooled Cohort 2 and 4 full efficacy analysis set (N=153), IRC and investigators disagreed on tumor responses of 42 (27.5%) subjects.

FDA notes that although both IRC and investigators identified 48 responders with CR or PR, due to disagreement on responders, a total of 55 subjects were identified as responders either by IRC or investigators. FDA Table 26 below shows that among 8 complete responders assessed by IRC, 3 (3/8=37.5%) were disagreed on by the investigators, and among 40 partial responders assessed by the IRC, 8 (8/40=20%) were disagreed on by the investigators. Similarly, FDA Table 27 below shows that among 6 complete responders assessed by the investigators, 1 (16.7%) was disagreed on by the IRC, and among 42 partial responders assessed by the investigators, 10 (23.8%) were disagreed on by the IRC.

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Table 26. FDA – IRC-Assessed Tumor Responses in Pooled Full Efficacy Set (N=153) Disagreed by INV

Tumor Response by IRC	Number of Subjects	Number of Subjects Disagreed by INV
CR	8	3
PR	40	8
NE	6	0
NON-CR/NON-PD	1	1
PD	27	12
SD	71	18

Source: Datasets: ADRS ADSL ADBL
Abbreviations: CR = complete response; INV = investigator; IRC = Independent Review Committee; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Table 27. FDA – INV-Assessed Tumor Response in Pooled Full Efficacy Set (N=153) Disagreed by IRC

Tumor Response by INV	Number of Subjects	Number of Subjects Disagreed by IRC
CR	6	1
PR	42	10
NE	6	0
PD	27	12
SD	72	19

Source: Datasets: ADRS ADSL ADBL
Abbreviations: CR = complete response; INV = investigator; IRC = Independent Review Committee; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Disagreement on DOR Assessment Between IRC and Investigators

Among 23 responders in the Cohort 4 primary efficacy analysis set (N=82) determined by the IRC, 14 (14/23=60.9%) had a DOR different from the DOR determined by the investigators. Among 21 responders determined by investigators, 12 (12/21=57.1%) had a DOR different from the DOR determined by IRC.

As noted above, in pooled Cohort 2 and 4 full efficacy analysis set, 55 subjects were identified as responders either by IRC or investigators. IRC and investigators disagreed with the result of DOR in 34 (34/55=61.8%) responders. Specifically, among 48 responders identified by IRC, 27 (27/48=56.3%) had a DOR different from the DOR determined by investigators. Among 48 responders identified by the investigators, 27 (27/48=56.3%) had a DOR different from the DOR determined by IRC.

Disagreement on Censor and Event Determination Between IRC and INV for DOR Analysis Among Responders

For the Cohort 4 primary efficacy analysis set (N=82), among 25 identified as responders by either IRC or investigators, IRC and investigators disagreed on 8 (8/25=32%) subjects in terms of assignment of censor and event for the DOR analysis.

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FDA Table 28 below shows that among 11 events assessed by IRC, 3 (27.3%) were disagreed on by the investigators, and among 12 censors assessed by IRC, 3 (25%) were disagreed on by the investigators.

Table 28. FDA – IRC-Assessed Event and Censor in Responders (N=23) of Primary Efficacy Set Disagreed by INV

Event/Censor by IRC	Number of Subjects	Number of Subjects Disagreed by INV
Event	11	3
Censor	12	3

Source: Datasets: ADTTE ADRS ADBL
Abbreviations: INV = investigator; IRC = Independent Review Committee

FDA Table 29 below shows that among 12 events assessed by the investigators, 4 (33.3%) were disagreed on by the IRC. However, all 9 censors assessed by the investigators were agreed on by the IRC (0% disagreement).

Table 29. FDA –INV-Assessed Event and Censor in Responders (N=21) of Primary Efficacy Set Disagreed by IRC

Event/Censor by INV	Number of Subjects	Number of Subjects Disagreed by IRC
Event	12	4
Censor	9	0

Source: Datasets: ADTTE ADRS ADBL
Abbreviations: INV = investigator; IRC = Independent Review Committee

For the pooled Cohort 2 and 4 full efficacy analysis set, among the 55 subjects identified as responders either by IRC or investigators, IRC and investigators disagreed on the assignment of censor/event in 21 (21/55=38.2%) responders.

FDA Table 30 below shows that among 17 events assessed by IRC, 4 (23.5%) were disagreed on by the investigators, and among 31 censors assessed by IRC, 10 (32.3%) were disagreed on by the investigators.

Table 30. FDA –IRC-Assessed Event and Censor in Responders (N=48) of Pooled Cohort 2+4 Efficacy Set Disagreed by INV

Event/Censor by IRC	Number of Subjects	Number of Subjects Disagreed by INV
Event	17	4
Censor	31	10

Source: Datasets: ADTTE ADRS ADBL
Abbreviations: INV = investigator; IRC = Independent Review Committee

FDA Table 31 below shows that among 25 events assessed by the investigators, 12 were disagreed on by IRC, and among 23 censors assessed by the investigators, 2 were disagreed on by IRC.

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Table 31. FDA – INV-Assessed Event and Censor in Responders (N=48) of Pooled Cohort 2+4 Efficacy Set Disagreed by IRC

Event/Censor by INV	Number of Subjects	Number of Subjects Disagreed by IRC
Event	25	12
Censor	23	2

Source: Datasets: ADTTE ADRS ADBL
Abbreviations: INV = investigator; IRC = Independent Review Committee

In summary, the disagreements between IRC and investigators at subject level underscore the importance of implementing a central IRC for tumor response-based assessments. From a regulatory point of view, the establishment of a central IRC is especially important in the context of single arm trials to reduce biases and discrepancies across site investigators.

8.1.2.10.3. Dose/Dose Response

Data

See Section 6.3.2.2.

The Applicant's Position

Disease control, tumor burden reductions, and tumor responses were achieved across the entire range of doses administered in Cohort 4.

The FDA's Assessment

The lifileucel dosing range selected by the Applicant for the lifileucel trials was 1 x 10^9 to 150 x 10^9 viable cells. The higher dosing limit was based on published literature (Dudley et al. 2005; Radvanyi et al. 2012), and the lower limit was based on data collected in the initial study subjects enrolled to Cohort 1 of Study C-144-01. Study subjects were expected to receive all manufactured viable cells that met release criteria.

Although FDA concurs that disease control, tumor burden reductions, and tumor responses were achieved across a wide range of lifileucel doses and as FDA noted in Section 8.1.2.10 "Efficacy Results – Secondary and other relevant endpoints," it is difficult to draw conclusions on treatment effect based on DCR results or SD results from the single arm Study C-144-01.

In FDA's view, the recommended lifileucel dosing range should be mainly based on dose-objective response relationship (Refer to FDA assessment in Section 6.3.2.2) and the mechanism of action accounting for the complexity of lifileucel as an autologous T cells which are derived from individual patients' tumor tissues and are expected to be heterogenous from patient to patient (refer to FDA comments on FDA recommended dose range in Section 12 "Labeling Recommendations").

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Efficacy data submitted by the Applicant suggest that responders (n=48) from the pooled Cohort 2 and 4 full efficacy analysis set assessed by IRC received lifileucel ranging from 6.2 x 10^9 to 72 x 10^9 viable cells with a mean of 31.1 x 10^9 and a median of 30.0 x 10^9 viable cells. For responders (PR or CR) from the Cohort 4 primary efficacy analysis set, the infused viable cells ranged from 7.56 x 10^9 to 72 x 10^9 with a mean of 30.3 x 10^9 and a median of 26.8 x 10^9 (n=23). FDA inquired of the Applicant regarding one subject who achieved a PR after receiving 1.2 x 10^9 viable cells, per the investigator. However, per the Applicant's response, this responder was enrolled to Cohort 1 and received non-cryopreserved Gen 1 lifileucel, not the same as the cryopreserved Gen 2 lifileucel administered to Cohort 2 and 4 subjects.

8.1.2.10.4. Durability of Response

Data

In most cases, initial responses were observed shortly after the lifileucel infusion in Cohort 4, generally by the time of the first or second assessment (Day 42/Week 6 or Week 12, Figure 7 [FAS] and Figure 8 [Efficacy Analysis Set]).

In the FAS, 76% of the 25 responders achieved a response at the first scheduled assessment on Day 42. The data demonstrated deepening of response over time. Of the subjects with a response, 28.0% converted from an initial assessment of SD to a PR at a subsequent time point, and 12.0% converted from a PR to a CR. Similarly in the efficacy analysis set, 74% of the 23 responders achieved a response at the first scheduled assessment on Day 42. The data demonstrated deepening of response over time. Of the subjects with a response, 30.4% converted from an initial assessment of SD to a PR at a subsequent time point, and 13.0% converted from a PR to a CR.

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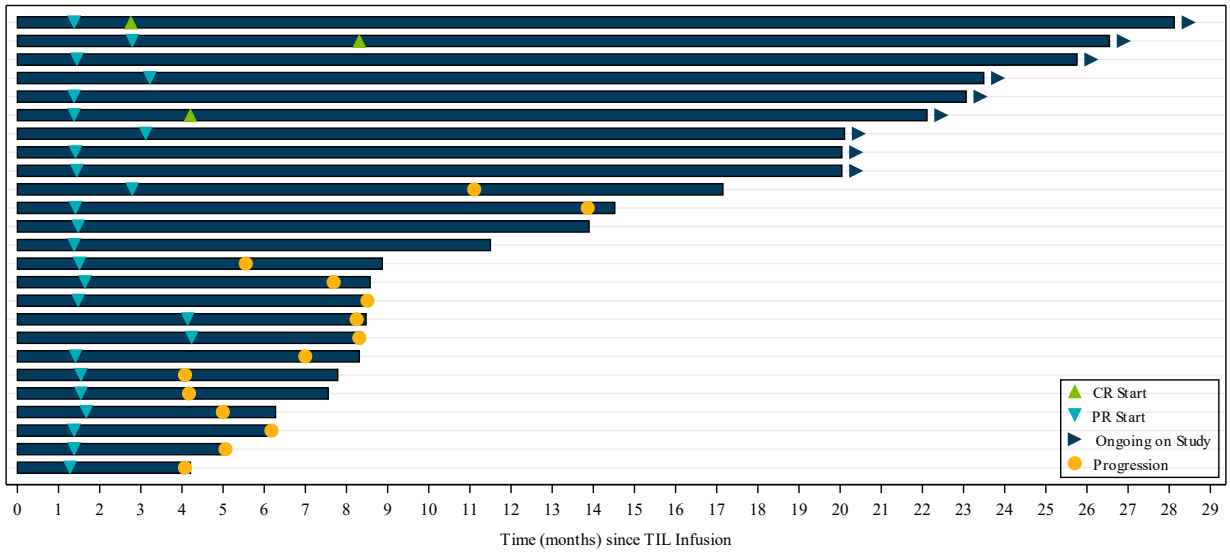
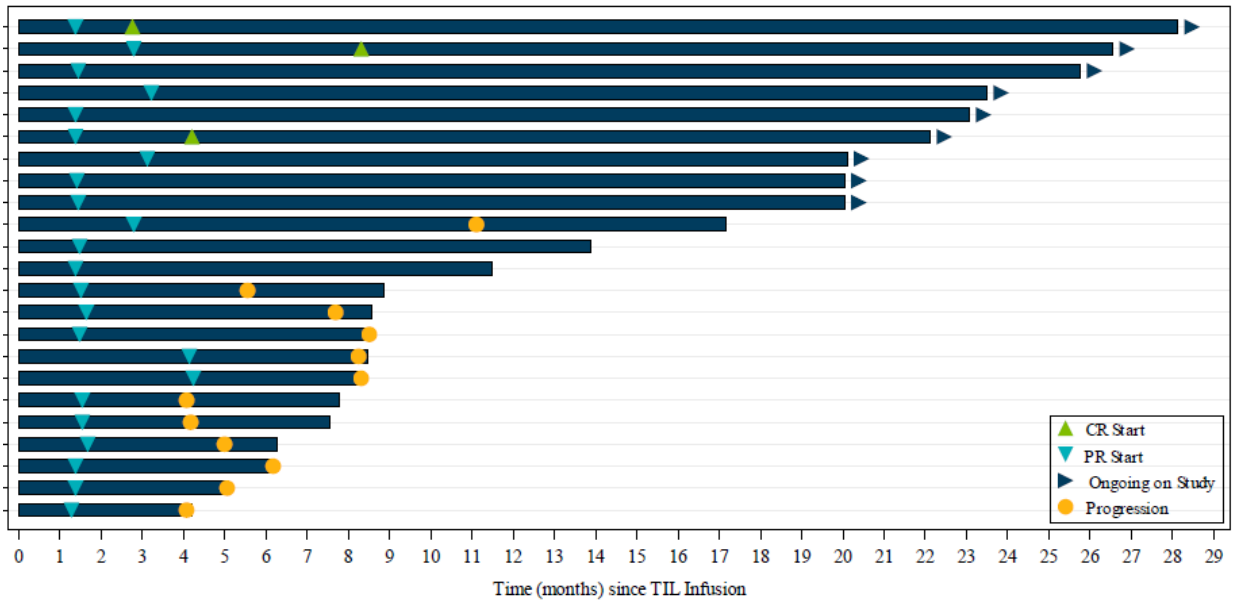
Figure 7. Applicant – Time to First Response, Duration of Response, and Time on Efficacy Assessment for Responders as Assessed by the IRC per RECIST v1.1 in Cohort 4 (Full Analysis Set)



Source: C-144-01, Program: f14-2-1-4-1-swimmer-resp-irc-c4-fas.sas, Data: ADRS and ADINTDT, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Note: A bar is presented for each subject starting from the date of lifileucel infusion up to the date of new anticancer therapy, end of assessment, death, or data cutoff date, whichever occurred earlier.
Abbreviations: CR = complete response; IRC = Independent Review Committee; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Figure 8. Applicant – Time to First Response, Duration of Response, and Time on Efficacy Assessment for Responders as Assessed by the IRC per RECIST v1.1 in Cohort 4 (Efficacy Analysis Set)



Source: C-144-01, Program: f2-7-3-2-2-1-swimmer-resp-irc-c4-eff2.sas, Data: ADBL, ADRS and ADTTE, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Note: A bar is presented for each subject starting from the date of lifileucel infusion up to the date of new anticancer therapy, end of assessment, death, or data cutoff date, whichever occurred earlier.
Abbreviations: CR = complete response; IRC = Independent Review Committee; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors

The Applicant's Position

The responses occurred early and deepened over time. The efficacy results in Cohort 4 are supported by those in Cohort 2 and in the pooled data from Cohorts 2 and 4.

The FDA's Assessment

FDA verified the DOR of all responders in Study C-144-01 and concurs with the Applicant regarding the durability of objective responses among responders in Study C-144-01. As shown in Figure 7 and Figure 8, most of the responders showed initial tumor responses at the Day 42 visit (median of 1.5 months ranging from 1.3 to 4.2 months). These responses were confirmed at the Day 84 visit. Among the three responders in Cohort 4 who achieved CR, two initially achieved PR. The timing of tumor responses was consistent across Cohort 2 and 4.

8.1.2.10.5. Persistence of Effect

Data

See both Section 6.2.1 and Figure 7.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The Applicant's Position

The durability and deepening of responses over time (Figure 7) taken together with the observation of in vivo persistence of lifileucel at all post-infusion time points analyzed (i.e., 6 weeks, 6 months, and 12 months; Section 6.2.1) are supportive of the sustained antitumor activity of the tumor-specific TIL clones that comprise lifileucel.

The FDA's Assessment

FDA verified the durability and deepening of responses shown in Figure 7. FDA concurs that the objective responses were generally durable considering the late-stage disease and multiple lines of prior systemic therapies among those subjects enrolled to Study C-144-01.

Refer to FDA comments in Section 6.2.1 regarding antitumor activity of the tumor-specific tumor-derived T cell clones that comprise lifileucel.

8.1.2.11. Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Data

Patient-reported outcomes for health-related quality of life (HRQoL) were assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30) during Study C-144-01. Among the subjects for whom both Baseline and Week 12 data were available (N=104), the baseline (i.e., prior to NMA-LD) and Week 12 global health status/HRQoL scores were similar (mean [standard deviation]: 69.15 [20.54] and 70.11 [21.18], respectively; Data: ADSL and ADQS).

The Applicant's Position

Based on the EORTC QLQ-C30 global health status scores between baseline and Week 12, there was no worsening in the quality of life despite the administration of NMA-LD and IL-2 as well as the late-stage disease. This supports the benefit from the one-time administration of lifileucel.

The FDA's Assessment

FDA concurs with the Applicant's assessment of HRQoL.

However, FDA does not use HRQoL outcomes to support this BLA application.

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8.1.2.12. Additional Analyses Conducted on the Individual Trial

Data

Subgroup analyses of ORR and DCR, as assessed by IRC per RECIST v1.1, were performed across various demographic and baseline disease characteristics and prior melanoma therapy categories. The results from these analyses were similar for Cohort 4 and Cohort 2. The ORRs across the various subgroups were generally consistent with that of the overall population. Similar findings were observed for the subgroup analyses of DCR.

Of note, responses were demonstrated in ORR for Cohort 4 (Data: ADSL, ADBL, and ADRS):

- In subjects who had study-defined primary refractory disease to prior PD-(L)1 blocking therapy (i.e., subjects who had best response of PD to prior anti-PD-[L]1 blocking therapy): 29.3% (95% CI: 16.1, 45.5)
- In subjects who had SITC consensus criteria-defined primary resistance to prior anti-PD-(L)1 blocking therapy (i.e., primary resistance to prior anti-PD-(L)1 blocking therapy in the metastatic setting and primary resistance/early relapse to anti-PD-(L)1 blocking therapy in the adjuvant setting): 29.8% (95% CI: 18.4, 43.4)
- In subjects with a high tumor burden including:
  - >3 baseline target and non-target lesions: 24.7% (95% CI: 15.3, 36.1)
  - Baseline target lesion SoD as assessed by the IRC per RECIST v1.1≥median SoD: 20.9% (95% CI: 10.0. 36.0)
  - Elevated LDH levels > ULN: 25.0% (95% CI: 14.4, 38.4)
- In subjects with brain and/or liver metastases: 27.3% (95% CI: 15.0, 42.8)

The Applicant's Position

Responses across pre-specified patient subgroups were generally consistent with that of the overall population. Additionally, efficacy of the lifileucel regimen was similar in the overall patient population and the patient subgroup that was primary refractory and/or primary resistant to PD-(L)1 blocking therapy, demonstrating that lifileucel treatment is capable of inducing responses through mechanisms that are distinct from checkpoint blockade.

The FDA's Assessment

FDA agrees with the Applicant's overall assessment of efficacies of subgroups.

Due to small sample sizes in the subgroups (e.g., refer to FDA Table 32), it is difficult for FDA to make meaningful conclusions based on subgroup analyses except for describing some trends, as follows. All subgroup analyses are exploratory in nature and are not used for the approval of lifileucel.

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8.1.2.12.1. Differences in ORR by Baseline Characteristics

One way to assess relationships between baseline characteristics and tumor responses is to assess ORR by baseline characteristics, as presented below.

Based on submitted data, FDA found that subgroups with less baseline tumor burden (e.g., LDH, size and number of target lesions), high PD-L1 expression levels in the tumor, and that received more than the median viable cells achieved higher ORR than their counterparts. Study subjects who had not received anti-PD1 or anti-CTLA-4 combination therapy, or who had achieved a CR or PR to the first line anti-PD1 or a more recent last anti-PD1 therapy, also had slightly higher ORR than their counterparts. In contrast, the number of prior lines of systemic therapies, number of prior anti-PD1 containing therapies, and whether the subject had primary resistance to prior anti-PD1 therapy did not appear to affect ORR. However, FDA notes that some of these subgroups had very small sample sizes. Results from these subgroup analyses should not be used for providing treatment indications for future melanoma patients. Refer to the following FDA Table 32.

Table 32. FDA – Differences in ORR by Baseline Characteristic in Pooled Full Efficacy Set (N=153)

Category Subgroup	ORR (95% CI)
PD-L1 status (TPS ≥5% vs. <5%)	-
TPS ≥5% (n=43)	49% (33%-65%)
TPS <5% (n=65)	28% (17%-40%)
Baseline lactate dehydrogenase (LDH)	-
≤2 x ULN (n=124)	36% (28%-45%)
>2 x ULN (n=29)	10% (2-27%)
BL target lesions	-
≤3 (n=87)	43% (32%-54%)
>3 (n=66)	17% (9%-28%)
Baseline SoD of target lesions	-
<72 mm (n=59)	47% (34%-61%)
≥72 mm (n=94)	21% (14%-31%)
Infused lifileucel viable cells	-
> Median (21.1 x 10^9, n=76)	45% (33%-57%)
≤ Median (21.1 x 10^9, n=77)	18% (10%-29%)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Category Subgroup	ORR (95% CI)
Anti-PD1 and CTLA4 combination therapy	-
No (n=71)	37% (26%-49%)
Yes (n=82)	27% (18%-38%)
Achieved CR or PR to the first anti-PD1	-
Yes (n=16)	44% (20%-70%)
No (n=105)	30% (21%-39%)
Time from the last anti-PD1 to lifileucel infusion (Months)	-
≤ Median (4.6 months, n=80)	35% (25%-46%)
> Median (4.6 months, n=73)	27% (18%-39%)
Number of prior lines of systemic therapy	-
<3 lines (n=53)	30% (18%-44%)
≥3 lines (n=100)	32% (23%-42%)
Number of prior lines of anti-PD1 therapy	-
<3 lines (n=128)	30% (23%-39%)
≥3 lines (n=25)	36% (18%-57%)
Primary refractory to anti-PD1	-
Yes (n=83)	31% (22%-42%)
No (n=70)	31% (21%-44%)

Source: Datasets: ADSL ADBL L1
Abbreviations: BL = baseline; CI = confidence interval; CR = complete response; ORR = Objective response rate; PDL1 = programmed death-ligand 1; PR = partial response; SoD = summary of diameter; TPS = tumor proportion score; ULN = upper limit of normal

8.1.2.12.2. Differences in Baseline Characteristics Between Responders and Non-Responders

Another way to assess relationships between baseline characteristics and tumor responses is to characterize baseline characteristics between responders and non-responders, as presented below.

Number of Anatomic Sites with Lesions at the Baseline Assessed by IRC

FDA Table 33 below shows that the number of anatomic sites with lesions was slightly lower in responders than in non-responders (both median and mean were 3 in responders versus 4 in non-responders). Results were consistent across Cohort 4 primary efficacy analysis set to pooled Cohort 2 and 4 full efficacy analysis set.

Table 33. FDA – Number of Anatomic Sites With Lesions at Baseline, Assessed by IRC

Analysis Set Objective Response Status	Median (Min, Max)	Mean
Primary Analysis Set (N=82)	-	-
Responder (n=23)	3 (1, 9)	3
Non-responder (n=59)	4 (1, 12)	4
Pooled Cohort 2 and 4 (N=153)	-	-
Responder (n=48)	3 (1, 9)	3
Non-responder (n=105)	4 (0, 12)	4

Source: Datasets: ADBL ADSL
Abbreviations: IRC = Independent Review Committee

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Target Lesions at the Baseline Assessed by IRC

FDA Table 34 below shows that the median number of target lesions was numerically lower in responders (median =2) than in non-responders (median =4). Results were consistent across Cohort 4 primary efficacy analysis set to pooled Cohort 2 and 4 full efficacy analysis set.

Table 34. FDA – Number of Target Lesions at Baseline, Assessed by IRC

Analysis Set Objective Response Status	Median (Min, Max)	Mean
Primary Analysis Set (N=82)	-	-
Responder (n=23)	2 (1, 5)	3
Non-responder (n=58)	4 (0, 5)	3
Pooled Cohort 2+4 (N=153)	-	-
Responder (n=48)	2 (1, 5)	2
Non-responder (n=105)	4 (0, 5)	3

Source: Datasets: ADBL ADSL
Abbreviations: IRC = Independent Review Committee

SoD of Target Lesions at the Baseline by IRC

FDA Table 35 below suggests that overall SoD of target lesions was numerically lower in responders than in non-responders. Results were consistent across Cohort 4 primary efficacy analysis set to pooled Cohort 2 and 4 full efficacy analysis set.

Table 35. FDA – Target Lesion SoD at Baseline, Assessed by IRC

Analysis Set Objective Response Status	Median (Min, Max)	Mean
Primary Analysis Set (N=82)	-	-
Responder (n=23)	70.8 (23.9, 552.9)	103.7
Non-responder (n=59)	115.5 (0.0, 385.2)	134.3
Pooled Cohort 2+4 (N=153)	-	-
Responder (n=48)	68.8 (13.5, 552.9)	83.6
Non-responder (n=105)	119.6 (0.0, 385.2)	130.3

Source: Datasets: ADBL ADSL
Abbreviations: IRC = Independent Review Committee; SoD = summary of diameter

Prior Lines of Therapies Including an Anti-PD1 Agent

FDA Table 36 suggests that both the median and mean prior lines of anti-PD1-based systemic therapies were approximately 2 lines in both responders and non-responders.

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Table 36. FDA – Median and Mean Prior Lines Containing Anti-PD(L)1

Objective Response Status	Primary Efficacy Analysis Set (N=82) Median/Mean	Pooled Cohort 2+4 (N=153) Median/Mean
Responders	2/2	2/1.8
Non-Responders	2/1.8	2/1.7

Source: Datasets: ADBL ADSL
Abbreviations: PD(L)1 = programmed death-ligand 1

Responses to Prior Lines of Anti-PD1 Therapies Among Responders and Non-Responders

Data presented in FDA Table 37 and Table 38 suggest that both responders and non-responders to lifileucel in Study C-144-01 were mainly non-responders during their prior lines of anti-PD1 therapies. As a large proportion of study subjects did not have information regarding their response to the third line of anti-PD1 therapy, FDA did not include these results in Table 37 and Table 38. FDA notes that the prior treatment and response information in Study C-144-01 appeared to be extracted from medical records. FDA did not examine the quality of these data.

Table 37. FDA – Response to Prior Lines of Anti-PD(L) 1 Among Responders and Non-Responders From Primary Efficacy Analysis Set (N=82)

Prior Line of Anti-PD1 Therapy Objective Response Status in C-144-01	PD or SD to prior anti-PD1	PR or CR to prior anti-PD1
First line anti-PD1[a]	-	-
Responder to lifileucel (n=19)	14 (74%)	5 (26%)
Non-responder to lifileucel (n=44)	40 (91%)	4 (9%)
Second line anti-PD1[b]	-	-
Responder to lifileucel (n=9)	6 (67%)	3 (33%)
Non-responder to lifileucel (n=27)	26 (96%)	1 (4%)

Source: Datasets: ADRS ADBL ADSL
a. 19 subjects without information of response to prior anti-PD1 excluded
b. 46 subjects without information of response to prior anti-PD1 excluded
Abbreviations: CR = complete response; PD(L)1 = programmed death-ligand 1; PD = progressive disease; PR = partial response; SD = stable disease

Table 38. FDA – Response to Prior Lines of Anti-PD(L)1 Among Responders and Non-Responders from Pooled Cohort 2 and 4 Full Efficacy Analysis Set (N=153)

Prior Line of Anti-PD1 Therapy Objective Response Status in C-144-01	PD or SD to Prior Anti-PD1	PR or CR to Prior Anti-PD1
First line anti-PD1[a]	-	-
Responder to lifileucel (n=38)	31 (82%)	7 (18%)
Non-responder to lifileucel (n=83)	74 (89%)	9 (11%)
Second line anti-PD1[b]	-	-
Responder to lifileucel (n=20)	16 (80%)	4 (20%)
Non-responder to lifileucel (n=48)	44 (92%)	4 (8%)

Source: Datasets: ADRS ADBL ADSL
a. 32 subjects without information of response to prior anti-PD1 excluded
b. 85 subjects without information of response to prior anti-PD1 excluded
Abbreviations: CR = complete response; PD1 = programmed death1; PD = progressive disease; PR = partial response; SD = stable disease

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Time to PD From the First Anti-PD1 Agent

Data presented in FDA Table 39 below suggest that responders and non-responders did not appear to have significant differences in the median time to PD from prior first-line anti-PD1 therapy.

Table 39. FDA – Time (Months) to PD From First Anti-PD1 Therapy

Analysis Set Response Status to lifileucel	Median	Mean
Cohort 4 primary efficacy analysis set (N=80)	-	-
Responder (n=23)	4.7 (0.9, 53.0)	11.3
Non-responder[a]	5.7 (1.4, 57.4)	9.0
Pooled Cohort 2+4 full efficacy analysis set (N=147)	-	-
Responder (n=47 with 1 subject excluded due to missing time to PD)	4.2 (0.7, 53.0)	8.5
Non-responder[b]	4.7 (1.4, 57.4)	7.7

Source: Datasets: ADRS ADBL ADSL
a. n=57 with 2 subjects without information of time to PD excluded
b. n=100 with 5 subjects without information of time to PD excluded
Abbreviations: PD(L)1 = programmed death-ligand 1; PD = progressive disease

Anatomic Sites Used for TH

FDA found no evidence that the number of anatomic sites used for TH between responders and non-responders were significantly different. In fact, for the vast majority of study subjects, only one anatomic site was used for TH, as suggested by the results below:

- Among all subjects in the full efficacy analysis set (N=153), 94.8% (145/153) had only 1 anatomic site used for TH, 4.6% (7/153) had 2 anatomic sites used for TH, and 0.7% (1/153) had 3 anatomic sites used for TH.
- For subjects in the full efficacy analysis set (N=153), 89.6% (43/48) of responders and 97.1% (102/105) of non-responders had 1 anatomic site used for TH.
- For subjects in the Cohort 4 primary efficacy analysis set (N=82), 82.6% (19/23) of responders and 94.9% (56/59) of non-responders had only 1 anatomic site used for TH.

Visceral Anatomic Sites (Liver, Lung, Peritoneal, or Other Visceral Locations) Used for TH

FDA found no evidence that the number of visceral sites used for TH were different between responders and non-responders, as shown by the results below:

- Among all subjects from the full efficacy analysis set (N=153), 24.8% (38/153) underwent TH in visceral lesions. The proportion was consistent across responders (12/48=25.0%) and non-responders (26/105=24.8%).
- For subjects in the primary efficacy analysis set (N=82), 30.4% (7/23) of responders and 32.2% (19/59) of non-responders underwent TH in visceral lesions, respectively.

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Lung Lesions in Responders and Non-Responders

FDA Table 40 below suggests that at the baseline, proportionally fewer responders had lung lesions than non-responders.

Table 40. FDA – Lung Lesions in Responders vs. Non-Responders by Analysis Set

Analysis Set Responder Status	Without Lung Lesion	With Lung Lesion(s)
Cohort 4 primary efficacy analysis set (N=82)	-	-
Responders (n=23)	15 (65.2%)	8 (34.8%)
Non-responders (n=59)	18 (30.5%)	41 (69.5%)
Pooled Cohort 2+4 full analysis set (N=153)	-	-
Responders (n=48)	27 (56.3%)	21 (43.8%)
Non-responders (n=105)	39 (37.1%)	66 (62.9%)

Source: Datasets: ADBL ADSL L1

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment

FDA's review of efficacy evidence was primarily based on ORR and DOR results from multi-cohort Study C-144-01 with Cohort 4 to provide primary efficacy evidence (N=82) and Cohort 2 and pooled Cohort 2 and 4 to provide supportive efficacy evidence. Refer to FDA assessments in Section 8.1.2.

8.1.4. Assessment of Efficacy Across Trials

Not applicable.

8.1.5. Integrated Assessment of Effectiveness

Data

Refer to the efficacy results presented in Section 8.1.2.

The Applicant's Position

Lifileucel, a one-time cellular therapy, demonstrated efficacy with durable benefit in heavily pretreated patients with unresectable or metastatic melanoma after progression on standard therapies, including anti-PD-(L)1 therapies and BRAF ± MEK inhibitors if BRAF V600-mutated.

The efficacy results observed in Cohort 2 were similar to those observed for Cohort 4, thereby increasing the confidence in lifileucel treatment effects. The consistency of treatment effects was also observed for the time to onset of response and response observed across patient subgroups.

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The FDA's Assessment

FDA agrees with the Applicant in terms of overall efficacy of lifileucel and durability of tumor responses in subjects previously treated with at least one line of anti-PD1-based therapy and BRAF ± MEK inhibitor(s) if positive for BRAF V600 mutation. The efficacy results were generally consistent across Cohort 2 and 4 (refer to "FDA Conclusion Based on the Primary Efficacy Evidence from Study C-144-01" and "ORR and DOR Results from Cohort 2 as Supporting Evidence" in Section 8.1.2.10.)

However, FDA notes that Study C-144-01 was a single arm trial with a heterogeneous population. Subjects enrolled to the trial received lifileucel at a wide dosing range. Some subgroups such as subjects with less baseline tumor burden (e.g., lower LDH level, smaller size and number of target lesions, without lung lesion), shorter time from the last anti-PD1 to lifileucel infusion, high PD-L1 expression levels in the tumor, or that were receiving more than median viable cells achieved numerically higher ORR than their counterparts (refer to FDA assessments of subgroups under "Differences in ORR by Baseline Characteristics" in Section 8.1.2.12.1 and "Differences in Baseline Characteristics between Responders and Non-Responders" in Section 8.1.2.12.2). The tumor response differences in subgroups and underlying heterogenicity among the study population confound the interpretation of clinical benefit observed in Study C-144-01. Therefore, it is important to verify the efficacy of lifileucel for the treatment of advanced or metastatic melanoma in a large confirmatory RCT setting, which is ongoing. Refer to the update of Phase 3 RCT (IOV-MEL-301) under "Summary of Pre-submission/Submission Regulatory Activity" in Section 3.2 of this memo.

8.2. Review of Safety

8.2.1. Safety Review Approach

Data

Safety data from Study C-144-01 Cohort 2 (N=67 based on the safety analysis set, data cutoff date: 9/15/2021) have been pooled with Cohort 4 data (N=89) to facilitate a safety assessment in a larger patient population (N=156), which is particularly relevant for the characterization of events that occurred at a low incidence and the analysis of TEAEs by subgroup.

Additional supportive safety data are presented from the monotherapy cohorts from the Iovance studies of Gen 2 TIL (Section 8.2.12).

All AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) v24.0, and AE severity was graded by the study investigators using the NCI's Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

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The following hematologic Preferred Terms (PTs; i.e., cytopenias) were pooled to facilitate a comprehensive analysis of medically similar/equivalent AEs and are presented on the summary tables under the MedDRA System Organ Class of Blood and Lymphatic Disorders:

- Thrombocytopenia: thrombocytopenia and platelet count decreased
- Neutropenia: neutropenia and neutrophil count decreased
- Leukopenia: leukopenia and white blood cell count decreased
- Lymphopenia: lymphopenia and lymphocyte count decreased

The Applicant's Position

The safety data supporting this BLA submission for lifileucel come primarily from the 156 subjects who received lifileucel in Cohorts 2 and 4 in Study C-144-01. These are supported by data from 344 subjects who received any component of the TIL regimen across the studies of Gen 2 TIL monotherapy in melanoma, cervical cancer, NSCLC, and HNSCC. These data are sufficient to allow for the adequate characterization of the lifileucel treatment regimen safety profile and provide appropriate guidance to both the physician and patient on what to expect from this treatment.

The FDA's Assessment

The administration of lifileucel was preceded by tumor harvest followed by a preparative NMA-LD regimen of cyclophosphamide with mesna followed by fludarabine. Following lifileucel infusion on Day 0, subjects received IL-2. NMA-LD and IL-2 were included in the treatment regimen to support the engraftment, expansion, and activation of lifileucel.

Subjects may have received other concomitant medications, leading to difficulty to definitively establish the causality of adverse events occurring after lifileucel administration. During this safety review, TEAE was defined as an adverse event occurring within the first 30 days after the start of lifileucel infusion.

The FDA clinical safety review was based on Study C-144-01 pooled Cohorts 2 and 4 with a data cutoff date of 9/15/2021 and comprised 189 subjects who were enrolled and underwent tumor harvest (TH). Among these 189 enrolled subjects, 160 initiated the lifileucel regimen by receiving at least one dose of NMA-LD, and 156 subjects received lifileucel and were included in the primary safety analysis set.

The Applicant provided safety summaries of other lifileucel trials among patients with cervical cancer, NSCLC, or HNSCC, and who received lifileucel regimen as monotherapy. Patients in these trials treated with lifileucel in combination with an ICI were excluded from the safety summary.

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FDA reviewed all safety data including summaries, listings, and narratives in the BLA submission. FDA's assessment included safety data in four time periods: 1) TH related severe adverse events post TH (N=189) before NMA-LD; 2) severe adverse events and deaths during the NMA-LD period (N=160); 3) high grade TEAEs and resolutions among subjects who received lifileucel (N=156); and 4) unresolved high grade TEAEs and deaths during the post TEAE period among subjects who received lifileucel.

FDA also assessed severe adverse events in other ongoing or completed lifileucel trials.

8.2.2. Review of the Safety Database

8.2.2.1. Overall Exposure

Data

The lifileucel regimen in Study C-144-01 included a preparative regimen of NMA-LD (2 days of cyclophosphamide 60 mg/kg with mesna followed by 5 days of fludarabine 25 mg/m^2), followed by the infusion of lifileucel, and post-infusion administration of IL-2 (600,000 IU/kg every 8 to 12 hours for up to a maximum of 6 infusions over a period of up to 4 days following the lifileucel infusion, see Table 5).

Subjects in Study C-144-01 Cohorts 2 and 4 (N=156) received a median of 2 doses of cyclophosphamide (min, max: 1, 2) with a median relative dose intensity of 100.00% (min, max: 50.0%, 108.4%, Data: ADSL, ADES, and ADEX). The subjects received a median of 5.0 doses of fludarabine (min, max: 2, 5), with a median relative dose intensity of 99.03% (min, max: 31.0%, 107.3%). The median dose of lifileucel was 20.87 x 10^9 viable cells (min, max: 0.4 x 10^9, 99.5 x 10^9). All but 11 subjects (92.9%) received the entire planned infusion, with a median relative infusion of 100.00% (min, max: 3.5%, 100%). All but 3 (98.1%) of the subjects were administered IL-2, with a median of 6 (min, max: 0, 6) doses and a median relative dose intensity of 100.00% (min, max: 0, 108.6%).

The median dose of Gen 2 TIL across the monotherapy studies, including Study C-144-01, of 20.64 x 10^9 infused cells was similar to that observed in Study C-144-01 alone.

The Applicant's Position

A total of 156 subjects from Study C-144-01 Cohorts 2 and 4 and an additional 157 subjects from the other Gen 2 TIL monotherapy studies received TIL for a total of 313 subjects. The majority of subjects received the lifileucel regimen at the intended doses.

The FDA's Assessment

FDA concurs that the size of the safety database supporting this BLA is adequate for the assessment of the safety of the lifileucel regimen.

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FDA notes that following the 90-day safety update of the 4 other lifileucel trials, the total number of subjects who received Gen 2 lifileucel as monotherapy in these 4 trials was increased from 157 to 173, thus the total number of subjects who received Gen 2 lifileucel as monotherapy was increased from 313 (156+157) to 329 (156+173). Refer to FDA Table 6 in Section 7.1.

As the Applicant noted above, 11 subjects did not receive the manufactured full dose of lifileucel. Based on information contained in the BLA submission and additional information from the Applicant per FDA IR, reasons included a damaged infusion bag (n=9) and anaphylactic reaction to lifileucel (n=2) leading to early termination of the lifileucel infusion. All 9 subjects who had a damaged infusion bag received at least 6.16 x 10^9 viable cells. The 2 subjects with an anaphylactic reaction (1 Grade 4 and 1 Grade 3) received 4.27 x 10^8 and 5.56 x 10^9 viable cells, respectively.

8.2.2.2. Relevant Characteristics of the Safety Population:

Data

Table 41. Applicant – Demographic Characteristics of the Safety Population (Safety Analysis Set)

Demographic Characteristic	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Gender, n (%)	-	-	-
Female	44 (49.4)	28 (41.8)	72 (46.2)
Male	45 (50.6)	39 (58.2)	84 (53.8)
Age, (years)	-	-	-
Mean (SD)	55.4 (11.93)	54.3 (11.40)	54.9 (11.68)
Median	58.0	55.0	56.0
Min, Max	25, 74	20, 79	20, 79
Age, n (%)	-	-	-
<40	9 (10.1)	7 (10.4)	16 (10.3)
≥40 - <65	57 (64.0)	46 (68.7)	103 (66.0)
≥65	23 (25.8)	14 (20.9)	37 (23.7)
Race, n (%)	-	-	-
American Indian or Alaska Native	0	0	0
Asian	1 (1.1)	2 (3.0)	3 (1.9)
Black or African American	2 (2.2)	1 (1.5)	3 (1.9)
White	85 (95.5)	64 (95.5)	149 (95.5)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (1.1)	0	1 (0.6)

Source: C-144-01, Program: t14-1-5-2-2-demo-c2c4-saf, Data: ADSL, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Abbreviations: max = maximum; min = minimum; SD = standard deviation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table 42. Applicant – Baseline Disease Characteristics (Safety Analysis Set)

Disease Characteristic	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Stage at study entry, n (%)	-	-	-
IIIC	1 (1.1)	9 (13.4)	10 (6.4)
IV	88 (98.9)	58 (86.6)	146 (93.6)
Subjects with baseline liver and/or brain lesions by IRC, n (%)	46 (51.7)	28 (41.8)	74 (47.4)
Screening ECOG score, n (%)	-	-	-
0	64 (71.9)	43 (64.2)	107 (68.6)
1	25 (28.1)	24 (35.8)	49 (31.4)
≥2	0	0	0
Baseline LDH (U/L), n (%)	-	-	-
≤ULN	31 (34.8)	39 (58.2)	70 (44.9)
1-2 x ULN	36 (40.4)	19 (28.4)	55 (35.3)
>2 x ULN	22 (24.7)	9 (13.4)	31 (19.9)
Target lesion SoD assessed by IRC (mm)	-	-	-
n	88	63	151
Mean (SD)	126.28 (94.609)	108.00 (65.861)	118.65 (84.061)
Median	103.00	95.80	101.10
Min, Max	15.7, 552.9	13.5, 271.3	13.5, 552.9

Source: C-144-01, Program: t14-1-6-2-2-bldis-c2c4-saf, Data: ADSL, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Abbreviations: ECOG = Eastern Cooperative Oncology Group; IRC = Independent Review Committee; LDH = lactate dehydrogenase; max = maximum; min = minimum; SD = standard deviation; SoD = sum of diameters; ULN = upper limit of the normal range

Table 43. Applicant – Prior Anticancer Therapies (Safety Analysis Set)

Prior Therapy Category, n (%)	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Anti-CTLA-4	73 (82.0)	54 (80.6)	127 (81.4)
Anti-PD-1/PD-L1	89 (100)	67 (100)	156 (100)
Anti-PD-1/CTLA-4 Combo	49 (55.1)	35 (52.2)	84 (53.8)
BRAF/MEK Inhibitor [1]	24 (27.0)	15 (22.4)	39 (25.0)
IL-2	6 (6.7)	7 (10.4)	13 (8.3)
Radiotherapy	44 (49.4)	35 (52.2)	79 (50.6)
Surgery	88 (98.9)	66 (98.5)	154 (98.7)

Source: C-144-01, Program: t14-1-6-2-2-bldis-c2c4-saf, Data: ADSL, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
[1] Includes subjects who were BRAF V600E or V600K-mutated and received BRAF inhibitor ± MEK inhibitor.
Abbreviations: BRAF = proto-oncogene B-Raf; CTLA-4 = cytotoxic T lymphocyte-associated antigen-4; IL-2 = interleukin-2; MEK = mitogen-activated extracellular signal-regulated kinase; PD-1 = programmed cell death protein-1; PD-L1 = programmed death-ligand 1

The Applicant's Position

The demographic (Table 41), baseline disease characteristics (Table 42), and prior anticancer therapies (Table 43) of the safety analysis set of Cohorts 2 and 4 from Study C-144-01 were similar to those presented for the FAS in Table 11, Table 12, and Table 13, respectively.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The FDA's Assessment

FDA concurs that the demographics and baseline characteristics of subjects included in the primary safety analysis set (N=156) were similar to those in the pooled full efficacy analysis set (N=153). Refer to FDA comments on demographics and baseline characteristics in Section 8.1.2.5 and 8.1.2.6.

FDA notes that the primary safety analysis set (N=156) of Study C-144-01 included three additional subjects who were excluded from the pooled full efficacy analysis set (N=153). Among these three subjects, two subjects from Cohort 4 (b) (6) received lifileucel that was out of specification and one subject from Cohort 2 (b) (6) received less than 10^9 viable cells (4.27 x 10^8) due to a life-threatening anaphylactic reaction.

FDA notes that Subject (b) (6) died on Day 27 following receiving lifileucel. The Applicant assessed this death as related to PD whereas FDA assessed the death as at least possibly related to the study treatment. Refer to FDA Table 45 in Section 8.2.4.1 of this memo.

8.2.2.3. Adequacy of the Safety Database

Data and Applicant's Position

The subjects treated in Study C-144-01 are representative of the unresectable or metastatic melanoma patient population.

Safety data from the safety analysis set of 156 subjects with melanoma in Study C-144-01 and from 344 subjects in the safety population across the studies of Gen 2 TIL monotherapy in melanoma, cervical cancer, NSCLC, and HNSCC are adequate to identify the most common AEs and support the benefit-risk assessment.

The lifileucel treatment regimen was administered in Study C-144-01 as a one-time treatment over a period of up to 12 days (7 days of NMA-LD followed by a single infusion of lifileucel and then up to 4 days of IL-2). At the time of the cutoff for Study C-144-01, the median study follow-up was 27.6 months for Cohorts 2 and 4 (FAS, N=153, Data: ADSL and ADTTE). This is considered adequate follow-up to assess the safety of lifileucel in patients with unresectable or metastatic melanoma.

The FDA's Assessment

The safety data from Study C-144-01 adequately represent the target population and allow for an informed assessment of the safety profile of lifileucel and evaluation of the benefit-risk in adult patients with unresectable or metastatic melanoma previously treated with at least one systemic therapy, including a PD-1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

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FDA's assessment of safety information for non-melanoma lifileucel trials are based on safety summaries and listing tables provided by the Applicant without subject-level database. For this reason, FDA did not conduct independent analysis of the safety data from these non-melanoma lifileucel trials.

Refer to FDA safety review approach under Section 8.2.1.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

8.2.3.1. Issues Regarding Data Integrity and Submission Quality

Data

Study C-144-01 was conducted in accordance with the provisions of the Declaration of Helsinki (Oct 2008) and all revisions thereof, and in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

Steps taken by the Applicant to assure the accuracy and reliability of data included: the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by the Applicant/designee. The eCRFs were reviewed for accuracy and completeness by Clinical Research Associates during on-site monitoring visits and any discrepancies are resolved with the Investigator or designees, as appropriate. Data were verified for accuracy. Representatives of the Sponsor's Clinical Quality Assurance department conducted GCP compliance audits of clinical investigator sites according to company procedures.

An IDMC provided oversight of the study to ensure quality and consistency of study conduct as well as data collection and analyses across international sites (i.e., the U.S. and Europe).

All subjects were enrolled and received lifileucel on or before 1/15/2020 and the last date for TEAE reporting was 2/14/2020; these dates are considered to be before the COVID-19 pandemic onset or during the initial phase of the pandemic. Therefore, the patient enrollment, study population characteristics, study treatment, and TEAEs are not considered to be substantially impacted by the pandemic.

The Applicant's Position

No issues related to data integrity or quality of the overall submission were identified by the Applicant.

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The FDA's Assessment

FDA found some data errors (e.g., AE was not resolved, but had an AE end date) in the safety database which appeared to be related to quality control and data cleaning, but there was no evidence of data integrity issues.

FDA did not find specific examples of data reporting issues during the pandemic and therefore agrees with the Applicant that TEAE reporting was not substantially impacted by the COVID-19 pandemic.

Refer to FDA BIMO review memo for details regarding data integrity and quality in the inspected study sites (Site 3, 4 and 19).

8.2.3.2. Categorization of Adverse Events

Data

In Study C-144-01, AEs were collected during the screening, enrollment, and treatment periods. Treatment-emergent AEs were defined as those that began starting from the lifileucel infusion to 30 days post lifileucel infusion. All medically significant AEs considered related to lifileucel by either the Investigator or the Applicant were reported and followed until resolved or resolved with sequelae.

Clinically significant findings from a physical examination, vital sign measurements, or electrocardiograms (ECGs) were recorded on the AE eCRF.

Safety events were recorded as AEs in the subject's source documents and on the AE eCRF. AEs were graded for severity by the Investigators using the NCI's CTCAE v4.03. AEs were coded by the Applicant using MedDRA v24.0.

Adverse reactions were defined as AEs that were reported as at least possibly related to any component of the lifileucel regimen (i.e., cyclophosphamide, fludarabine, lifileucel, or IL-2).

The Applicant's Position

The recording, classification, and coding of AEs is considered by the Applicant to be appropriate.

The FDA's Assessment

Adverse events from Study C-144-01 were coded using MedDRA version 24.0, which is appropriate for coding PTs used for the safety analyses.

AE severity was graded using CTCAE version 4.03. Although the Applicant did not use the newer version of CTCAE (v5.0) published in November 2017 for grading the severity of adverse events

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because the enrollment of Study C-144-01 was initiated in 2016, the use of CTCAE version 4.03 did not have an impact on the safety analyses of the lifileucel trial.

8.2.3.3. Routine Clinical Tests

Data

All subjects were assessed for safety with specimen sampling at the visits specified in Table 7, and at unscheduled visits, if necessary, including serum chemistry, hematology, urinalysis, and/or a thyroid panel. All clinical laboratory safety testing was performed at local clinical laboratories.

The Applicant's Position

The clinical laboratory tests in Study C-144-01 are established standard safety measures.

The FDA's Assessment

FDA concurs with the Applicant's selection of clinical laboratory tests and schedules.

8.2.4. Safety Results

8.2.4.1. Deaths

Data

Of the 189 subjects who had tumor harvested in Study C-144-01, 23 subjects (12.2%) died during the period from tumor harvest to lifileucel infusion. In the majority of those 23 subjects (18/23), the primary cause of death was progressive disease. Deaths that occurred after the lifileucel infusion are presented in Table 44.

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Table 44. Applicant – Deaths That Occurred After the Lifileucel Infusion (Safety Analysis Set)

Death Details	Cohort 4 (N=89) n (%)	Cohort 2 (N=67) n (%)	Pooled Cohorts 2 and 4 (N=156) n (%)
Number of deaths that occur after lifileucel infusion	59 (66.3)	46 (68.7)	105 (67.3)
Number of deaths that occur after lifileucel infusion to 30 days post lifileucel infusion	4 (4.5)	2 (3.0)	6 (3.8)
Primary cause of death	-	-	-
Adverse event	2 (2.2)	2 (3.0)	4 (2.6)
Progressive disease	2 (2.2)	0	2 (1.3)
Number of deaths that occur after 30 days post lifileucel infusion	55 (61.8)	44 (65.7)	99 (63.5)
Primary cause of death	-	-	-
Adverse event	4 (4.5)	4 (6.0)	8 (5.1)
Progressive disease	47 (52.8)	36 (53.7)	83 (53.2)
Other	4 (4.5)	4 (6.0)	8 (5.1)

Source: C-144-01, Program: t14-3-2-13-2-1-death-c2c4-saf.sas, Data: ADSL, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021

The Applicant's Position

With a study follow-up of 27.6 months, 67.3% (105/156) of subjects died following the lifileucel infusion (Table 44). Of these, six deaths occurred within 30 days following the lifileucel infusion with two deaths primarily attributed to PD and four deaths due to an AE (pneumonia, arrhythmia, intra-abdominal haemorrhage, acute respiratory failure). At the time of death, 16.0% (25/156) of subjects had at least 1 Grade 3 or 4 unresolved TEAE.

Of the 99 deaths that occurred >30 days following the lifileucel infusion, the majority were primarily attributed to PD (83/99). Eight of the deaths were primarily attributed to an AE, 5 of the 8 occurred between >30 days and up to 180 days, and 3 occurred >180 days following the lifileucel infusion. The cause of the remaining 8 deaths was "other." Amongst the 8 cases with "other" as the cause of death, the descriptions for the primary cause of death, as provided by the Investigators, were as follows:

- Four were due to an unknown cause and occurred 94 to 508 days (median 350 days) following the lifileucel infusion.
- Three were due to disease progression or metastatic melanoma and occurred 559, 707, and 1050 days following the lifileucel infusion.
- One described a subject who died in his sleep 185 days following the lifileucel infusion.

The FDA's Assessment

In the BLA submission and Table 44 shown above, the Applicant did not provide direct assessment of the relationship between study treatment and deaths. For this reason, FDA conducted an independent review of the narratives of all deaths and requested additional

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information from the Applicant regarding the clinical course of some of the deaths possibly related to the study treatment.

After reviewing all information provided by the Applicant, FDA did not identify any TH related deaths during the post TH period. FDA identified two deaths during the NMA-LD period resulting from NMA-LD related toxicity. FDA also identified 10 deaths post lifileucel infusion period at least possibly related to the study treatment regimen, including NMA-LD, lifileucel, and/or IL2. Refer to FDA Table 45 below for the list of these 12 deaths and relevant AEs.

The following are FDA assessments of deaths during four time periods as defined by FDA under "Safety Review Approach" in Section 8.2.1.

Deaths During Post TH Period (Before NMA-LD)

Based on the submitted data, 19.6% of subjects experienced at least one Grade 3 or 4 adverse event during the post TH period. FDA did not identify any deaths related to TH.

In the BLA submission, the Applicant states, "Of the 189 patients who had tumor harvested in Study C-144-01, 23 patients (12.2%) died during the period from tumor harvest to lifileucel infusion." FDA further clarifies this statement as it implies that 23 of the 189 subjects did not receive lifileucel due to death, which was incorrect. Based on FDA's assessment (refer to Table 10), there were 5 (5/189=2.6%) subjects who died from disease progression within 40 days after TH (lifileucel manufacturing time was 22 days). These 5 deaths were probably related to PD and were the reason for not receiving lifileucel.

Other than the above 5 deaths, the remaining 18 deaths did not occur during the lifileucel manufacturing waiting period, and some of the deaths occurred a long time after TH. Therefore, these deaths were not likely to be the reason for these subjects not receiving lifileucel.

Refer to FDA Table 10 "Reasons for Not Receiving Lifileucel after Tumor Harvest" in Section 8.1.2.3

Study Treatment-Related Deaths During the NMA-LD Period

The Applicant's submitted data suggest that two subjects died after initiating NMA-LD and prior to receiving lifileucel. One of these two subjects experienced septic shock and one experienced acute kidney failure during NMA-LD period. These two subjects had lifileucel ready for infusion but were unable to receive lifileucel infusion due to death. Refer to FDA Table 45 below.

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Study Treatment-Related Deaths Post Lifileucel Infusion (Including Both TEAE and Post TEAE Periods)

FDA verified that six subjects died within 30 days following lifileucel infusion as suggested in Applicant's Table 44 above. In addition, one subject died on Day 38 following lifileucel infusion, and four subjects died between 46 and 60 days following lifileucel infusion.

Among the six subjects who died within 30 days following lifileucel infusion, the Applicant assessed that four of the deaths were due to adverse events and two were due to disease progression (Table 44). However, based on FDA's assessment, all six deaths (Subject (b) (6) died on Day 6, Subject (b) (6) died on Day 12, Subject (b) (6) died on Day 14, Subject (b) (6) (b) (6) died on Day 17, Subject (b) (6) died on Day 24, and Subject (b) (6) died on Day 27) were at least possibly related to the study treatment (refer to FDA Table 45 below).

To assess the attribution of study treatment to deaths occurring post 30 days after lifileucel infusion, FDA reviewed the following safety information of each deceased subject: 1) narratives of each subject who died (N=105, 59 enrolled to Cohort 4 and 46 enrolled to Cohort 2); 2) Grade 3 or higher AEs prior to the death and relationships to the study treatment assessed by the investigator or Applicant, temporal relationship between the safety events and the death; and 3) relationship between the death and Grade 3 or 4 TEAE which was not resolved at the time of death.

After assessing the above information submitted in the BLA and additional information provided by the Applicant, FDA identified 10 deaths post lifileucel infusion at least possibly related to the study treatment. Among these 10 deaths, 6 occurred within 30 days post lifileucel infusion and 4 occurred on Day 38, 58, 73, and 150 post lifileucel infusion (refer to FDA Table 45 below).

FDA did not assess deaths in relation to study treatment if the death occurred 6 months after lifileucel infusion because the causes of the deaths were more likely multi-factorial including disease condition, unresolved toxicities from the study treatment, as well as subsequent therapies.

Table 45. FDA – Study Treatment-Related Deaths

Subject ID	Adverse Event	Day of Death (Day 0 = Day of lifileucel infusion)	FDA Comment
(b) (6)	Septic shock	3 days into NMA-LD	Death occurred during NMA-LD. Lifileucel was not infused.
(b) (6)	Acute kidney injury	2 days post the last dose of NMA-LD	Death occurred during NMA-LD. Lifileucel was not infused.

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Subject ID	Adverse Event	Day of Death (Day 0 = Day of lifileucel infusion)	FDA Comment
(b) (6)	Acute respiratory failure	Day 6	Death occurred during the TEAE period. Subject also had unresolved Grade 3 encephalopathy, febrile neutropenia, hypotension, pneumonia, and pancytopenia.
(b) (6)	Renal tubular necrosis. Renal failure	Day 12	Death occurred during the TEAE period. Subject had unresolved Grade 4 renal tubular necrosis and urine output decreased (complete anuric); unresolved Grade 3 hypoxia and cytopenia; and unresolved Grade 2 pleural effusion and anemia. Applicant had initially assessed death as due to PD.
(b) (6)	Abdominal hemorrhage, Sepsis	Day 14	Death during the TEAE period
(b) (6)	Pneumonia	Day 17	Death during TEAE period. Subject also had ongoing Grade 3 anemia, thrombocytopenia at the time of death.
(b) (6)	Arrhythmia	Day 24	Death during the TEAE period
(b) (6)	Ascites, liver injury, pancytopenia – poor response to platelets, deteriorating overall condition.	Day 27	Death during the TEAE period. Applicant assessed the death as due to PD. The subject developed extensive ascites within 2 weeks of receiving lifileucel and IL-2 infusions. No ascites mentioned in the medical history. Subject received 6 doses of IL-2. Subject also had pancytopenia with poor response to platelets. Without autopsy evidence and an imaging confirmation of disease progression, there was reasonable possibility that the results shown on the imaging done on Day 18 post lifileucel was pseudo-progression due to inflammatory effect of adoptive immune cells (lifileucel) and IL-2.
(b) (6)	Sepsis and septic shock.	Day 38	Subject also had unresolved Grade 2 vasogenic cerebral edema, Grade 4 liver injury and Grade 3 renal injury. Applicant had initially assessed the death as due to PD.
(b) (6)	Intracranial hemorrhage	Day 58	Applicant had initially assessed the event of intracranial hemorrhage as unrelated to any study treatment. However, FDA found that the subject experienced worsened thrombocytopenia (Grade 4) shortly prior to the fatal event of intracranial hemorrhage.

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Subject ID	Adverse Event	Day of Death (Day 0 = Day of lifileucel infusion)	FDA Comment
(b) (6)	Encephalitis	Day 73	The subject achieved SD, had ongoing Grade 3 thrombocytopenia and encephalitis at the time of death. The Applicant had initially assessed the death as due to PD. However, the submitted data suggest that the subject achieved a SD. The Applicant had initially assessed the encephalitis as not related to any study drug, but the event was resolved on the date of death. Given that the onset of the event of encephalitis was on Day 17 following lifileucel infusion and was assessed as related to HHV-6 reactivation by the Applicant, FDA assessed the encephalitis event and death as related to the lifileucel treatment regimen.
(b) (6)	Bone marrow failure	Day 150	Subject had Grade 4 cytopenia and Grade 2 CMV infection unresolved at the time of death. The Applicant assessed this fatal event as lifileucel treatment regimen-related. FDA agreed with the Applicant's assessment.

Source: Study C-144-01-14 Patient Narratives; Datasets: ADAE ADSL
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV = cytomegalovirus; CT = computerized tomography; HHV-6 = human herpesvirus 6; IL-2 = interleukin-2; IR = information request; NMA-LD = nonmyeloablative lymphodepletion; PD = progressive disease; SD = stable disease; TEAE = treatment-emergent adverse event

FDA notes that among these 12 study treatment-related deaths, only 2 adverse events (abdominal hemorrhage in Subject (b) (6) and bone marrow failure in Subject (b) (6) were assessed by the Applicant as related to lifileucel in addition to NMA-LD and IL-2. However, due to the multi-component nature of the lifileucel regimen, FDA assessed the contribution of the lifileucel treatment regimen as one entity. Refer to Table 45.

In summary, FDA assessed the adverse events listed in Table 45 as the most serious adverse reactions related to 12 deaths in Study C-144-01 including acute respiratory failure (n=1), renal failure (n=2), cardiac arrhythmia (n=1), severe infections (n=4) including sepsis and septic shock, pneumonia, and encephalitis, internal organ hemorrhage (n=2), ascites and liver injury (n=1) and bone marrow failure (n=1).

Unresolved Grade 3 or 4 TEAEs at Time of Death

FDA identified a total of 79 important unresolved Grade 3 or 4 TEAEs (not resolved to Grade 2 or lower) occurring in 25% (39/156) of subjects who received lifileucel (refer to FDA Figure 9 below for these unresolved TEAEs), which is higher than 16% (25/156) identified by the Applicant (refer to the Applicant's position above in this Section).

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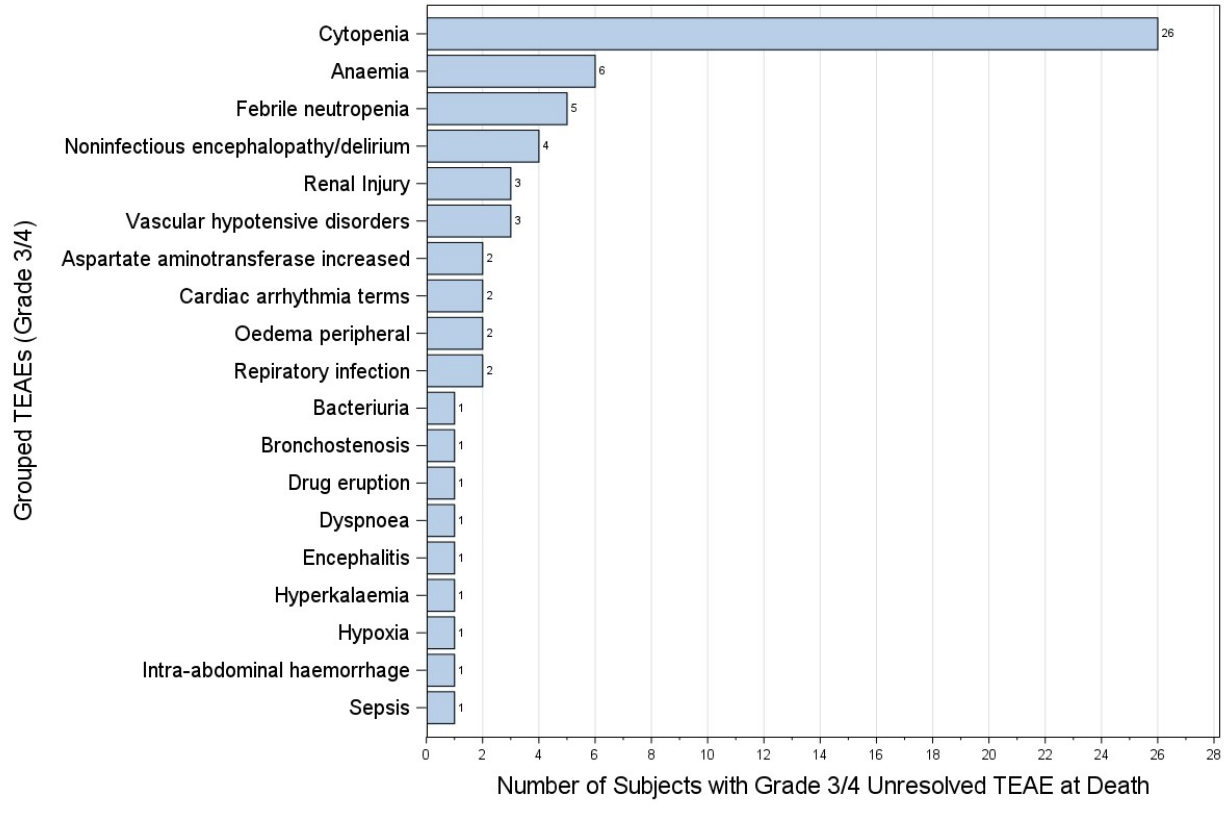
The most common high grade unresolved event was cytopenia. Some subjects had multiple unresolved high-grade adverse events.

Through reviewing unresolved high-grade TEAEs, FDA identified five deaths (Subject (b) (6) (b) (6) at least possibly related to study treatment (refer to FDA Table 45). For four of these five deaths, the Applicant assessed the primary cause of death as PD, and for the fifth death (Subject (b) (6) the Applicant assessed the primary cause of death as the fatal event of intracranial hemorrhage but assessed this fatal intracranial hemorrhage as unrelated to the study treatment.

Most of the 12 study subjects whose deaths were related to the lifileucel treatment regimen, as assessed by either Applicant or FDA, had Grade 3 or 4 TEAEs that were not resolved at the time of death. Refer to FDA comments in Section 8.2.5.3 and FDA Table 45 in Section 8.2.4.1.

Figure 9. FDA – Selected Unresolved Grade 3 or 4 TEAEs at Time of Death (Cohort 2+4)



Source: Datasets: ADAE ADSL
Abbreviations: TEAE, treatment-emergent adverse event

Admitted to ICU for Adverse Events Management or Post-Infusion Stabilization

Based on additional data submitted by the Applicant, FDA found that, among 89 subjects who received lifileucel in Cohort 4, 23.6% (21/89) were transferred to ICU for non-infusion related

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events such as managing serious adverse events, stabilizing, and monitoring of study subjects. Except for one ICU admission which started during the NMA-LD period to manage acute respiratory failure in one study subject (b) (6) all other ICU admissions (n=20) occurred 3 or more days post lifileucel infusion. The median and mean of such ICU stays were 12 and 16 days, respectively. Of note, these ICU stays did not include planned infusions in the ICU setting per institutional standards.

These results suggest that, to enhance safety management, immediate access to ICU should be available to patients who will receive the lifileucel regimen in the future (refer to USPI for Lifileucel).

8.2.4.2. Serious Adverse Events

Data

See Table 46.

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Table 46. Applicant – Treatment-emergent SAEs Reported in ≥2 Subjects in Pooled Cohorts 2 and 4 by Preferred Term (Safety Analysis Set)

	Cohort 4 (N=89)			Cohort 2 (N=67)			Pooled Cohorts 2 and 4 (N=156)		
Preferred Term	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Febrile neutropenia	2 (2.2)	2 (2.2)	0	6 (9.0)	6 (9.0)	0	8 (5.1)	8 (5.1)	0
Thrombocytopenia [1]	3 (3.4)	3 (3.4)	0	4 (6.0)	4 (6.0)	0	7 (4.5)	7 (4.5)	0
Acute kidney injury	2 (2.2)	0	0	2 (3.0)	1 (1.5)	0	4 (2.6)	1 (0.6)	0
Pneumonia	2 (2.2)	1 (1.1)	1 (1.1)	2 (3.0)	2 (3.0)	0	4 (2.6)	3 (1.9)	1 (0.6)
Acute respiratory failure	1 (1.1)	1 (1.1)	0	2 (3.0)	1 (1.5)	1 (1.5)	3 (1.9)	2 (1.3)	1 (0.6)
Hypotension	2 (2.2)	2 (2.2)	0	1 (1.5)	1 (1.5)	0	3 (1.9)	3 (1.9)	0
Hypoxia	3 (3.4)	3 (3.4)	0	0	0	0	3 (1.9)	3 (1.9)	0
Neutropenia [2]	2 (2.2)	2 (2.2)	0	1 (1.5)	1 (1.5)	0	3 (1.9)	3 (1.9)	0
Pulmonary oedema	3 (3.4)	3 (3.4)	0	0	0	0	3 (1.9)	3 (1.9)	0
Pyrexia	1 (1.1)	1 (1.1)	0	2 (3.0)	1 (1.5)	0	3 (1.9)	2 (1.3)	0
Anaphylactic reaction	0	0	0	2 (3.0)	2 (3.0)	0	2 (1.3)	2 (1.3)	0
Aspartate aminotransferase increased	1 (1.1)	1 (1.1)	0	1 (1.5)	0	0	2 (1.3)	1 (0.6)	0
Capillary leak syndrome	2 (2.2)	1 (1.1)	0	0	0	0	2 (1.3)	1 (0.6)	0
Delirium	2 (2.2)	1 (1.1)	0	0	0	0	2 (1.3)	1 (0.6)	0
Dyspnoea	1 (1.1)	1 (1.1)	0	1 (1.5)	1 (1.5)	0	2 (1.3)	2 (1.3)	0
Encephalopathy	0	0	0	2 (3.0)	2 (3.0)	0	2 (1.3)	2 (1.3)	0
Pleural effusion	2 (2.2)	2 (2.2)	0	0	0	0	2 (1.3)	2 (1.3)	0
Sepsis	1 (1.1)	1 (1.1)	0	1 (1.5)	1 (1.5)	0	2 (1.3)	2 (1.3)	0
Tumour pain	0	0	0	2 (3.0)	2 (3.0)	0	2 (1.3)	2 (1.3)	0

Source: C-144-01, Program: t14-3-2-1-2-2-2-teae-sae-2pt-c2c4-saf.sas, Data: ADSL and ADAE, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Notes: SAEs were coded based on MedDRA v24.0. Grades were based on CTCAE v4.03.
Subjects with multiple events for a given PT were counted only once using the maximum grade under each PT.
SAEs are sorted by decreasing frequency of PT per any grade in the Pooled Cohorts 2 and 4 group.
TE SAEs include all AEs that began starting from the lifileucel infusion to 30 days post lifileucel infusion.
[1] AE grouped terms of platelet count decreased and thrombocytopenia.
[2] AE grouped terms of neutrophil count decreased and neutropenia.
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SAE = serious adverse event; TE SAE = treatment-emergent serious adverse event

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The Applicant's Position

Of the 156 subjects, 4 (2.6%) experienced a TE SAE that resulted in death (pneumonia and arrhythmia in Cohort 4 and acute respiratory failure and intra-abdominal haemorrhage in Cohort 2). Twenty-five subjects (16.0%) experienced a Grade 4 TE SAE, of which the grouped term of thrombocytopenia (4.5%), the grouped term of neutropenia (1.9%), acute respiratory failure (1.3%), and sepsis (1.3%) were experienced by more than one subject each.

The most common (>2 subjects) TE SAEs were (Table 46):

- Eight subjects (5.1%): febrile neutropenia
- Seven subjects (4.5%): the grouped term of thrombocytopenia, none of which were associated with a bleeding event
- Four subjects (2.6%) each: acute kidney injury and pneumonia
- Three subjects (1.9%) each: acute respiratory failure, hypotension, hypoxia, the grouped term of neutropenia, pulmonary oedema, and pyrexia

Of the TE SAEs reported, two subjects (1.3%) experienced an anaphylactic reaction and one subject (0.6%) experienced uveitis, which are adverse drug reactions/identified risks of lifileucel.

The FDA's Assessment

FDA found that SAEs were likely underreported in Study C-144-01. The following are FDA findings regarding the reporting of SAEs in Study C-144-01:

- Based on additional data submitted by the Applicant, 23.6% (21/89) of study subjects in Cohort 4 had an ICU stay for non-infusion related events such as managing specific adverse events, stabilizing, and monitoring the condition of study subjects. This ICU stay rate is not reflected by the rate of TE SAE (16.0%) reported by the Applicant.
- In the Applicant Table 49 "Adverse Event Summary (Safety Analysis Set)" in Section 8.2.4.8, the Applicant reported that 4 out of 156 subjects who received lifileucel had Grade 5 TEAEs. However, in Applicant Table 46 above, the Applicant only reported two Grade 5 TE SAEs. FDA notes that all Grade 5 TEAEs should have been reported as Grade 5 TE SAEs.
- FDA identified six study treatment-related deaths during the TEAE period (within 30 days post lifileucel infusion). Refer to FDA Table 45 "Study Treatment-Related Deaths." The number of Grade 5 TE SAEs (n=2) during the TEAE period reported in Applicant

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Table 46 conflicts with the FDA-assessed number of deaths during the TEAE period (n=6) related to high-grade AEs that occurred in these subjects.

- Based on submitted data, FDA found that 87.8% (137/156) of subjects experienced at least one Grade 4 TEAE, 95.5% (149/156) experienced at least one Grade 3 TEAE. Evidently, most of these high-grade TEAEs were not assessed as TE SAEs by the Applicant based on results reported in Applicant Table 46.
- Table 46 by Applicant appears to suggest that there were two subjects with Grade 3 or higher acute respiratory failure assessed as serious events. However, FDA identified eight subjects with Grade 3 or higher respiratory failure/acute respiratory failure that occurred within 30 days after initiating the lifileucel regimen, including one Grade 5, five Grade 4, and two Grade 3. One Grade 4 respiratory failure was unresolved at the time of death of a subject who died from septic shock. Among these eight cases, seven were assessed as related and one (in Subject (b) (6)) as unrelated to the study treatment by the Applicant. However, as Subject (b) (6) began to have respiratory failure after NMA-LD, and continued until 16 days post lifileucel infusion, FDA assessed the respiratory failure as possibly related to NMA-LD.
- The reporting of SAEs across study sites were not always consistent. For instance, one Grade 1 (Subject (b) (6) and one Grade 2 (Subject (b) (6) acute kidney injury were reported as SAEs by two respective study sites. In contrast, two Grade 3 acute renal injury events from two other study sites (Subject (b) (6) were reported as non-SAEs.

Due to likely underreporting of SAEs in Study C-144-01, FDA does not rely on TE SAEs presented in Applicant Table 46 to interpret the seriousness of the adverse events from Study C-144-01. Instead, FDA assessed all AEs by severity (i.e., grade) regardless of whether they were assessed as SAE by the Applicant.

FDA notes that Applicant Table 46 only summarized SAEs occurring during the TEAE period. However, FDA assessed AE onset in four time periods (refer to FDA comments under "Safety Review Approach" in Section 8.2.1). For example, in addition to two Grade 3/4 sepsis events assessed as TE SAEs by the Applicant, using the Applicant's data, FDA identified one fatal (Grade 5) sepsis which occurred on Day 35 following lifileucel infusion, one fatal (Grade 5) septic shock which occurred during NMA-LD period before lifileucel infusion, and an additional four Grade 4 serious sepsis events which occurred during the post TEAE period.

Of note, Study C-144-01 protocol states that "If the institutional guidelines mandate a required hospitalization longer than the protocol required hospitalization, this pre-planned hospitalization event will not be considered an AE." To identify reasons for the likely underreporting of SAEs in Study C-144-01, FDA communicated with the Applicant. However, the Applicant does not believe that the above protocol statement had an impact on the assessment of seriousness of AEs.

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8.2.4.3. Most Common Grade 3 or 4 TEAEs:

The Applicant-submitted safety results suggest that 95.5% of subjects had at least one Grade 3 or higher TEAE. Results shown in FDA Table 47 below based on data submitted in the BLA suggest that the most common (≥10%) Grade 3 or 4 TEAEs reported in Study C-144-01 were cytopenias including thrombocytopenia, neutropenia, leukopenia, and lymphopenia. In addition, FDA notes that Grade 3 or 4 febrile neutropenia and infection in the first 30 days post lifileucel infusion were also common (47.4% and 20.5%, respectively). Although the majority of high-grade infections were Grade 3, there were four cases of Grade 4 sepsis. Of note, one case of Grade 5 pneumonia (respiratory syncytial virus [RSV] infection) leading to death was not included in FDA Table 47 below, but is included in FDA Table 45.

Table 47. FDA – Most Common Grade 3 or 4 TEAEs

Most Common (≥10%) Grade 3 or 4 TEAEs	Number (%) of Subjects (N=156)
Thrombocytopenia	124 (79.5%)
Neutropenia	110(70.5%)
Anemia	104 (66.7%)
Febrile neutropenia	74 (47.4%)
Leukopenia	74 (47.4%)
Lymphopenia	68 (43.6%)
Hypophosphatemia	49 (31.4%)
Infection	32 (20.5%)
Hypoxia	21 (13.5%)
Hypotension	19 (12.2%)
Pyrexia	19 (12.2%)

Source: Dataset ADAE
Abbreviations: TEAE = treatment-emergent adverse event

8.2.4.4. Grade 4 and 5 TEAEs

Based on Applicant's data, FDA identified 169 important Grade 4 TEAEs occurring in 137 (87.8%) study subjects who received lifileucel. The most common Grade 4 TEAE was cytopenia (n=132, 132/156=84.6%, including thrombocytopenia, neutropenia, leukopenia, and lymphopenia). Some subjects (n=21) experienced both Grade 4 cytopenia and other Grade 4 TEAEs.

Refer to FDA Figure 10 below for all Grade 4 TEAEs in descending order.

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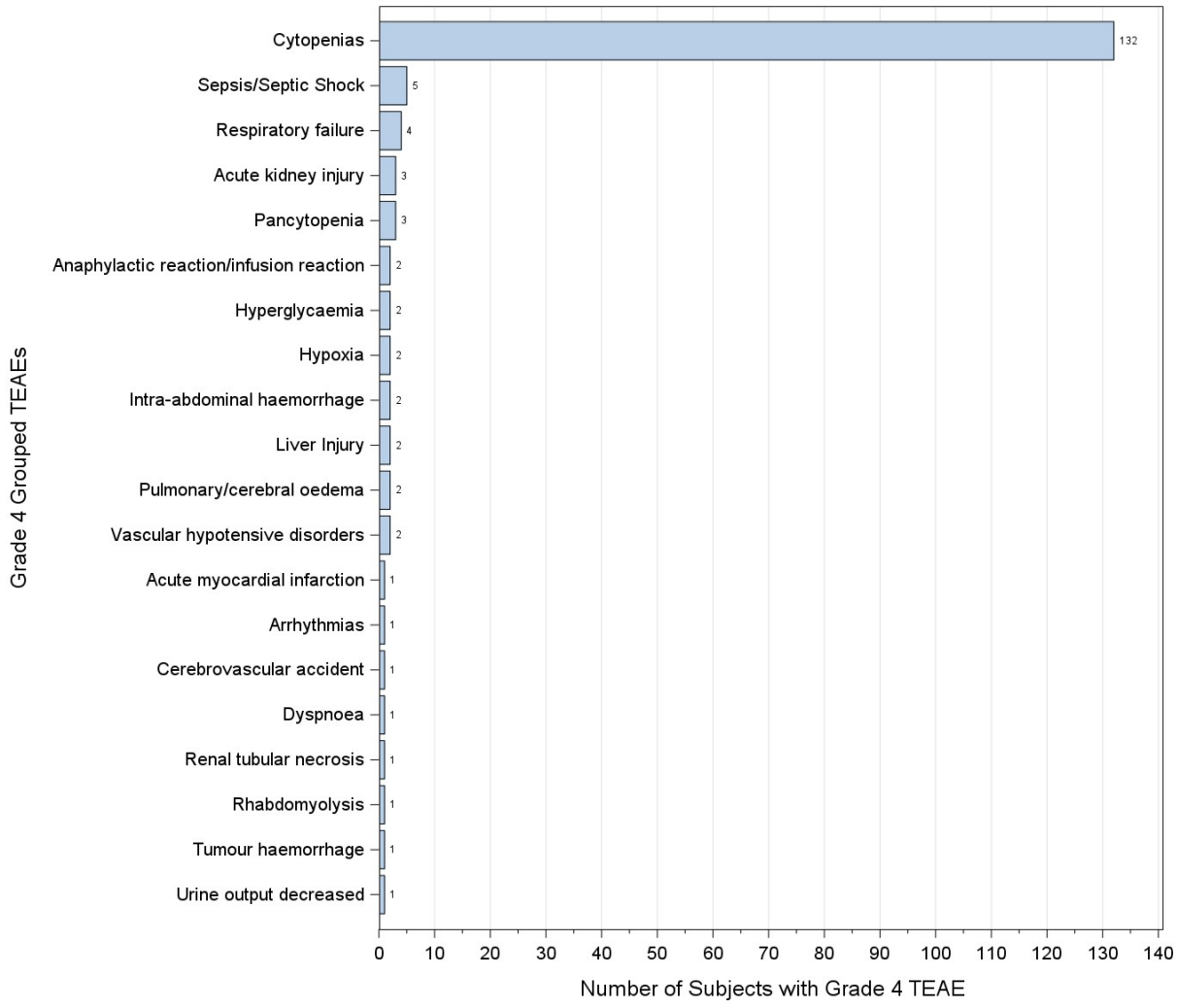
Figure 10. FDA – Number of Subjects in Cohort 2 and 4 With Grade 4 TEAE



Source: Dataset: ADAE
Abbreviations: TEAE, treatment-emergent adverse event

In addition, the Applicant reported four Grade 5 TEAEs (intra-abdominal hemorrhage in Subject (b) (6) pneumonia in Subject (b) (6) acute respiratory failure in Subject (b) (6) and arrhythmia in Subject (b) (6) However, FDA found that eight subjects who died within 30 days after initiating the lifileucel regimen experienced study treatment-related severe/serious adverse events. Refer to Table 45.

Study Treatment-Related Grade 4 or 5 TEAEs Assessed by Applicant

FDA Table 48 below summarizes study treatment-related Grade 4 or 5 TEAEs assessed by Applicant. In total, 128 (82.1%) subjects experienced at least one Grade 4/5 TEAE related to the study treatment, among whom 124 (79.5%) were assessed as related to NMA-LD, 22 (14.1%) as

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related to lifileucel, 66 (42.3%) as related to IL-2, and 16 (10.3%) as related to all components of the lifileucel regimen.

Among the 22 (14.1%) subjects who experienced a lifileucel-related Grade 4 or 5 TEAE assessed by the Applicant, only one TEAE (anaphylactic reaction, Grade 4) was assessed as related to lifileucel alone.

Among the 66 (42.3%) subjects with Grade 4 or 5 TEAEs related to IL-2, 11 (7.1%) experienced events (infusion related reaction, hypotension, tachycardia, thrombocytopenia, hyperglycemia, acute respiratory failure, acute myocardial infarction, hypoxia, cardiogenic shock, hypoxia, pulmonary edema, acute kidney injury, sepsis, and multiple subacute cerebral strokes) which were assessed as related to IL-2 alone by the Applicant.

Among the 124 subjects with Grade 4 or 5 TEAEs related to NMA-LD, 92 (59.0%) had the event related to NMA-LD alone, assessed by the Applicant. Among these 92 subjects, 90 had cytopenia, 1 (Subject (b) (6) had encephalopathy and hypoxia, 1 (Subject (b) (6) had a fatal cardiac arrhythmia, and 1 (Subject (b) (6) had a fatal acute respiratory failure (also refer to FDA Table 45).

Table 48. FDA – Number of Subjects Reporting at Least One Grade 4/5 TEAEs Related to Study Drug as Assessed by Applicant

Analysis Set	NMA-LD or Lifileucel or IL-2 Related	NMA-LD Related	Lifileucel Related	IL-2 Related	NMA-LD and Lifileucel and IL-2 Related
C-144-01 (N=156)	128 (82.1%)	124 (79.5%)	22 (14.1%)	66 (42.3%)	16 (10.3%)

Source: Datasets: ADAE ADSL
Abbreviations: IL-2 = interleukin-2; NMA-LD = nonmyeloablative lymphodepletion.

Safety Profile Across Lifileucel Trials

The Applicant's safety update suggests that occurrence rates of Grade 4 and 5 adverse events were similar across study subjects with advanced melanoma, cervical cancer, NSCLC, and HNSCC except for Grade 4 or higher respiratory disorders.

Overall, occurrence rate of Grade 4 or higher respiratory disorders was higher in the NSCLC cohorts (15.3%) than other indications (6.9% in melanoma cohorts, 5.6% in cervical cancer cohorts, and 0% in the HNSCC cohort). Based on preliminary safety results, approximately 12% of study subjects with NSCLC died from respiratory disorders in the first 30 days after initiating the lifileucel regimen.

In addition, hemophagocytic lymphohistiocytosis (HLH) and HLH-associated complications were related to the deaths of two study subjects with NSCLC (refer to FDA assessment under "Significant Adverse Events" in Section 8.2.4.7).

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8.2.4.5. Dropouts and/or Discontinuations Due to Adverse Effects

Data

Among the subjects who received lifileucel, two (1.3%) had their lifileucel infusion interrupted due to a TEAE (Table 49). Both subjects had an anaphylactic reaction that were considered to be serious.

The Applicant's Position

Hypersensitivity reaction including anaphylactic reaction is an identified risk for lifileucel (see below under "Significant Adverse Events" in Section 8.2.4.7

The FDA's Assessment

FDA concurs that hypersensitivity reaction, including anaphylactic reaction, is an identified risk for lifileucel.

Lifileucel was a single dose administration. The infusion of lifileucel took about 1 to 1.5 hours. Lifileucel study protocols did not allow for lifileucel dose modifications. The infusion of lifileucel was only discontinued in the event of acute adverse events occurring during the infusion. Therefore, dropouts and discontinuation of lifileucel were assessed in the context of a single dose administration.

As Applicant stated, two subjects ((b) (6) and (b) (6) from Cohort 2) had lifileucel infusion terminated early due to anaphylactic reactions.

Additional nine subjects had lifileucel terminated early due to infusion bag damage (refer to "Dose Interruption/Reduction Due to Adverse Effects" in Section 8.2.4.6).

8.2.4.6. Dose Interruption/Reduction Due to Adverse Effects

Data

Dose reductions are not applicable for lifileucel, which was investigated as a single-dose, one-time treatment.

During Study C-144-01, two subjects in Cohort 2 and none in Cohort 4 discontinued the lifileucel infusion in response to an AE (anaphylactic reaction, Data: ADSL and ADAE).

The Applicant's Position

Dose reductions are not applicable to lifileucel. Doses were partially infused in less than 10% of the subjects either in response to an anaphylactic reaction (an identified risk for lifileucel) or due to accidental infusion bag damage.

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The FDA's Assessment

As noted by the Applicant, study subjects were expected to receive all viable lifileucel cells as manufactured. The Applicant's data suggest that, among all subjects who received lifileucel in Study C-144-01 (N=156), 11 subjects did not receive their full dose of lifileucel as manufactured. Of these 11, 2 were due to anaphylactic reactions and 9 due to infusion bag damages, based on information in the BLA submission and additional information from the Applicant.

FDA agrees that dose modification may not apply to lifileucel given that it is a single dose administration. However, criteria for dose modifications, reductions, and terminations of NMA-LD and IL-2 should have been specified in lifileucel protocols. Per communications with the Applicant, the Applicant acknowledges that lifileucel protocols did not set specific criteria for proceeding to NMA-LD, lifileucel, and IL-2 just before the infusions of these treatment components. For example, in response to FDA's clinical IR, the Applicant clarified that although pulmonary function test was required at screening, there were no specific requirements regarding subjects' oxygen saturation level and level of dependence on oxygen prior to proceeding to NMA-LD, lifileucel, and IL-2. FDA notes that screening occurred more than 3 weeks before NMA-LD chemotherapy. In FDA's view, re-assessment of cardiopulmonary, renal, and liver functions within 1 to 2 days prior to NMA-LD and continuous re-assessment of the functions of critical organs are necessary to ensure that the benefit of completing the lifileucel regimen outweighs the risks.

A lack of specific criteria for proceeding to each successive component of the lifileucel regimen may have negatively impacted the overall safety of the lifileucel regimen which includes a 7-day pre-conditioning therapy with cyclophosphamide and fludarabine, followed by one dose of lifileucel and up to six doses of IL-2.

The following are examples identified by the FDA:

- Subject (b) (6) was on IV antibiotics on Day -15 for pyrexia and urine tract infection. Subject had bilateral pleural effusion prior to NMA-LD. The subject did not receive the last dose of fludarabine due to renal tubular necrosis which worsened from Grade 2 to 4. The subject was completely anuric with increased blood creatinine at the time of lifileucel infusion. However, the subject was proceeded to lifileucel infusion. The 3rd bag of lifileucel was interrupted due to an "infusion related reaction." Subject began renal dialysis on Day 0 post lifileucel infusion. IL-2 was withheld. Subject (b) (6) died on Day 12. Renal tubular necrosis was assessed as possibly related to cyclophosphamide. The primary cause of death was assessed by the Applicant as "Progressive Disease." However, FDA assessed the death as related to the study treatment (refer to FDA Table 45).
- Subject (b) (6) from Cohort 4 experienced cardiac ventricular thrombosis and multi-organ dysfunction syndrome 2 days into lymphodepletion, followed by atrial fibrillation (AF), hypotension, cardiomyopathy, and acute respiratory failure 3 days into

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lymphodepletion. The subject only received two out of five doses of planned fludarabine due to these severe adverse reactions. However, the subject was proceeded to lifileucel infusion. IL-2 was not started due to cardiomyopathy. The subject died on Day 24 after another episode of AF.

- Subject (b) (6) with NSCLC enrolled to Protocol IOV-LUN-202 experienced Grade 3 pulmonary embolism/intracardiac thrombus, bacteria pneumonia, and atypical pneumonitis during NMA-LD. The subject was proceeded to lifileucel infusion because of "sufficiently improved respiratory conditions" (subject was on 3 liters/min oxygen) in the Applicant's response to FDA's clinical IR. The subject died from sudden atelectasis on Day 4 post lifileucel infusion.

In FDA's view, criteria for proceeding to lifileucel should be similar to those for the administration of IL-2 given that IL-2 is necessary for the expansion of lifileucel in vivo. The rationale is that if a patient does not meet the criteria for the administration of IL-2, they should not receive lifileucel infusion because lifileucel will not be effective without IL-2, based on years of research of TIL. Additionally, criteria set for NMA-LD should also consider whether the patient will meet the criteria for receiving IL-2.

8.2.4.7. Significant Adverse Events

Data

For the following analyses of significant AEs in Study C-144-01, the treatment-emergent period included AEs that started from the lifileucel infusion to 30 days post lifileucel infusion. The post-treatment-emergent period included AEs that started 30 days post-lifileucel infusion through 6 months after the lifileucel infusion or up to the start of a new anti-cancer therapy, whichever occurred first. The analysis datasets are ADSL and ADAE.

Hypersensitivity Reactions

Across Pooled Cohorts 2 and 4, there have been nine cases (5.8%) of infusion related reaction, two cases (1.3%) of anaphylactic reaction, and one case (0.6%) of hypersensitivity during the treatment-emergent period and none during the post-treatment-emergent period.

- All nine cases of infusion related reaction occurred on the day of or the day after the lifileucel infusion. Most of the events were mild to moderate in intensity (6/9) and resolved on the same day (6/9). One event resolved within 3 days and two events within 4 days of the lifileucel infusion.
- Both cases of anaphylactic reaction (one Grade 3 and one Grade 4) occurred on the day of the lifileucel infusion. Both events were serious and resolved quickly with intervention, which included but was not limited to treatment with oxygen,

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diphenhydramine, IV hydrocortisone, fentanyl, midazolam, and epinephrine, within a day of the infusion.

- One case of hypersensitivity (Grade 3) was reported.

Based on the receipt of some of these cases and the consistency in timing, symptomatology, and clinical relevance of these events, hypersensitivity reaction was considered an identified risk for lifileucel.

Uveitis

Across Pooled Cohorts 2 and 4, there have been 6 cases (3.8%) of uveitis during the treatment-emergent period and 2 cases (1.3%) during the post-treatment-emergent period. Most of the events of uveitis were nonserious (87.5%, 7/8) and moderate to severe in intensity (87.5%, 7/8). The median time to onset following the lifileucel infusion was 16 days (min, max: 5, 119), with most occurring within 3 weeks of the lifileucel infusion (75%, 6/8). There was variability in the duration of the events, with a median duration of 122 days (min, max: 2, 400).

All subjects who experienced uveitis had received prior treatment with ICIs but had discontinued ICI therapy at least 28 days prior to the start of the NMA-LD preparative regimen, per protocol requirements. Given the extended period of time from the start of the last ICI therapy to the onset of uveitis, the temporal relationship between uveitis and the administration of lifileucel, and the biological plausibility based on the MOA of lifileucel in patients with metastatic melanoma, uveitis has been considered an identified risk for lifileucel.

Vitiligo

Across Pooled Cohorts 2 and 4, there have been 9 cases (5.8%) of vitiligo during the treatment-emergent period and 4 cases (2.6%) during the post-treatment-emergent period. Vitiligo was typically reported within 2 weeks to a month of the lifileucel infusion and was Grade 1 or 2 in severity. Ten cases were ongoing as of the data cutoff date. All subjects who experienced vitiligo had received prior treatment with ICIs but had discontinued ICI therapy at least 28 days prior to the start of the NMA-LD preparative regimen, per protocol requirements. Given the extended period of time from the start of the last ICI therapy to the onset of vitiligo, the temporal relationship between vitiligo and the administration of lifileucel, and the biological plausibility based on the MOA of lifileucel in patients with metastatic melanoma, vitiligo has been considered an identified risk for lifileucel.

<u>The Applicant's Position</u>

Hypersensitivity reactions (including infusion-related reactions and anaphylaxis), uveitis, and vitiligo are considered to be identified risks for the infusion of lifileucel. These reactions were infrequent during the treatment-emergent and post-treatment-emergent periods (experienced by <6% of subjects in Pooled Cohorts 2 and 4) and were mostly mild to moderate in intensity.

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The management of hypersensitivity reactions includes administration of hydration per institutional standards within 24 hours prior to lifileucel infusion; premedication with acetaminophen and diphenhydramine, or another H1-histamine antagonist, prior to lifileucel administration; additional supportive therapy with acetaminophen, indomethacin, and ranitidine, meperidine, or other medication per institutional standards if severe chills/rigors develop; and a decreased infusion rate for the first 5 minutes of the lifileucel infusion. Furthermore, continuous supervision of the patient by site medical staff is required until completion of infusion of the first bag of lifileucel to monitor for potential signs and symptoms that may have required immediate medical attention and treatment.

In patients with a history of uveitis, the presence of active uveitis should be ruled out prior to administration of the lifileucel treatment regimen. Patients presenting with symptoms of uveitis following administration of lifileucel can be evaluated and managed according to current treatment guidelines to prevent any potential severe long-term effects.

Patients with vitiligo can also be evaluated and managed according to treatment guidelines balancing benefit of treatment against possible impact of immunosuppressive therapy on the effectiveness of TIL therapy.

The FDA's Assessment

FDA concurs that hypersensitivity reaction, uveitis, and vitiligo were significant adverse events which could be related to lifileucel alone in some cases, as assessed by the Applicant.

Additionally, based on the data submitted in the BLA, FDA found that three uveitis cases (one Grade 3, two Grade 2) were not resolved at the end of the study participation (Subjects (b) (6) (b) (6) FDA recommends that the Applicant continue to monitor the incidence and severity of uveitis in the post-marketing setting (refer to FDA Pharmacovigilance review memo).

In addition to uveitis, FDA found that other low grade (Grade 1 or 2) eye disorders occurred in 7.7% (12/156) of study subjects who received lifileucel, including retinal detachment, retinal hemorrhage, periorbital edema, visual impairment, reduced visual acuity, and blurred vision. These eye disorders were also assessed as related to the lifileucel regimen by the Applicant. FDA recommends that the Applicant continue to assess and report uveitis events via periodic safety reports in the postmarketing setting (refer to FDA Pharmacovigilance plan review memo for this BLA).

However, FDA does not agree that hypersensitivity reaction, uveitis, and vitiligo were the only significant adverse events related to lifileucel.

FDA notes that due to the difficulty to separate the contribution of individual components of the lifileucel treatment regimen (cyclophosphamide, fludarabine, lifileucel, and IL-2), the

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lifileucel treatment regimen should be assessed as one entity in relation to severe and fatal adverse events.

Therefore, FDA considers all events discussed under "Study Treatment-Related Deaths" (Table 45), "Unresolved Grade 3 or 4 TEAEs at Time of Death" (Section 8.2.4.1), "Most Common Grade 3 or 4 TEAEs" (Section 8.2.4.3), "Grade 4 and 5 TEAEs" (Section 8.2.4.4), "Study Treatment-Related Grade 4 or 5 TEAEs Assessed by Applicant" (Section 8.2.4.4), and "Treatment-Emergent Adverse Events and Adverse Reactions" (Section 8.2.4.8) as significant risks related to the lifileucel regimen.

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8.2.4.8. Treatment-Emergent Adverse Events and Adverse Reactions

Data

A high-level summary of AEs and SAEs is presented in Table 49 and a summary of the most common adverse reactions (excluding laboratory-related AEs) is presented in Table 50.

Table 49. Applicant – Adverse Event Summary (Safety Analysis Set)

	Cohort 4 (N=89)			Cohort 2 (N=67)			Pooled Cohorts 2 and 4 (N=156)		
Number of subjects with at least one of the following events	**Any Grade n (%)**	**Grade 3/4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3/4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3/4 n (%)**	**Grade 5 n (%)**
TEAE	89 (100)	83 (93.3)	2 (2.2)	67 (100)	65 (97.0)	2 (3.0)	156 (100)	148 (94.9)	4 (2.6)
TEAE leading to lifileucel discontinuation	0	0	0	2 (3.0)	2 (3.0)	0	2 (1.3)	2 (1.3)	0
Post-Treatment-Emergent AE	44 (49.4)	18 (20.2)	3 (3.4)	53 (79.1)	19 (28.4)	3 (4.5)	97 (62.2)	37 (23.7)	6 (3.8)
Treatment-Emergent SAE	31 (34.8)	29 (32.6)	2 (2.2)	23 (34.3)	22 (32.8)	2 (3.0)	54 (34.6)	51 (32.7)	4 (2.6)
Post-Treatment-Emergent SAE	13 (14.6)	8 (9.0)	3 (3.4)	16 (23.9)	12 (17.9)	3 (4.5)	29 (18.6)	20 (12.8)	6 (3.8)

Source: C-144-01, Program: t14-3-1-2-2-1-ae-sum-c2c4.sas, Data: ADSL and ADAE, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Notes: AEs are coded based on MedDRA v24.0. Grades are based on CTCAE v4.03. Subjects with multiple events are counted only once using the maximum grade.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event

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Table 50. Applicant – Summary of Adverse Reactions Excluding Laboratory-Related Adverse Events Observed in at Least 10% of Subjects Treated with Lifileucel (N=156)

Adverse Reaction	Any Grade n (%)	Grade 3 or Higher n (%)
Blood and lymphatic system disorders	-	-
Febrile neutropenia	73 (46.8)	73 (46.8)
Cardiac disorders	-	-
Tachycardia[a]	74 (47.4)	12 (7.7)
Gastrointestinal disorders	-	-
Nausea	106 (67.9)	4 (2.6)
Diarrhea	73 (46.8)	3 (1.9)
Vomiting	68 (43.6)	2 (1.3)
General disorders and administration site conditions	-	-
Chills	118 (75.6)	8 (5.1)
Pyrexia	95 (60.9)	16 (10.3)
Fatigue[b]	86 (55.1)	8 (5.1)
Edema[c]	64 (41.0)	8 (5.1)
Infections and infestations	-	-
Infection[d]	37 (23.7)	16 (10.3)
Infection with unspecified pathogen[e]	28 (17.9)	15 (9.6)
Investigations	-	-
Weight increased	30 (19.2)	2 (1.3)
Metabolism and nutrition disorders	-	-
Decreased appetite	48 (30.8)	2 (1.3)
Nervous system disorders	-	-
Headache	33 (21.2)	1 (0.6)
Encephalopathy[f]	25 (16.0)	8 (5.1)
Renal and urinary disorders	-	-
Acute kidney injury[g]	31 (19.9)	11 (7.1)
Hematuria	21 (13.5)	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	-	-
Hypoxia[h]	37 (23.7)	19 (12.2)
Dyspnea[i]	33 (21.2)	13 (8.3)
Skin and subcutaneous tissue disorders	-	-
Rash[j]	57 (36.5)	15 (9.6)
Alopecia	44 (28.2)	0
Pruritus	21 (13.5)	0

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Adverse Reaction	Any Grade n (%)	Grade 3 or Higher n (%)
Vascular disorders	-	-
Hypotension[k]	58 (37.2)	17 (10.9)
Capillary leak syndrome	21 (13.5)	7 (4.5)
Hypertension[l]	21 (13.5)	11 (7.1)

Source: C-144-01, Program: t1-r20-ae-react-soc-10pt-c2c4-saf, Data: ADSL and ADAE, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Grades are based on CTCAE v4.03.
Note: Adverse reactions are defined as AEs that were reported as at least possibly related to any component of the lifileucel regimen (i.e., cyclophosphamide, fludarabine, lifileucel, or IL-2) that occurred up to 30 days post lifileucel.
a Tachycardia includes tachycardia, sinus tachycardia, atrial fibrillation, and supraventricular tachycardia.
b Fatigue includes fatigue, asthenia, and malaise.
c Edema includes edema, face edema, generalized edema, localized edema, edema peripheral, peripheral swelling, edema genital, peripheral swelling, edema genital, scrotal edema, brain edema, catheter site edema, conjunctival edema, eyelid edema, laryngeal edema, macular edema, periorbital edema, pulmonary edema, vasogenic cerebral edema, and lymphoedema.
d Infection includes all Preferred Terms within the Infections and Infestations System Organ Class.
e Infection with unspecified pathogen includes cellulitis, conjunctivitis, cystitis, dermatitis infected, device related infection, diarrhea infectious, endocarditis, enterocolitis infectious, infection, meningitis, nasopharyngitis, neutropenic sepsis, pneumonia, pyuria, rash pustular, respiratory tract infection (RTI), rhinitis, sepsis, sinusitis, skin infection, and urinary tract infection (UTI).
f Encephalopathy includes encephalopathy, automatism, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, hypersomnia, lethargy, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, and stupor.
g Acute kidney injury includes acute kidney injury, anuria, azotemia, renal failure, renal tubular dysfunction, renal tubular necrosis, oliguria, and blood creatinine increased.
h Hypoxia includes hypoxia and oxygen saturation decreased.
i Dyspnea includes dyspnea, acute respiratory failure, orthopnea, respiratory distress, respiratory failure, and dyspnea exertional.
j Rash includes rash, rash generalized, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash erythematous, and rash macular.
k Hypotension includes hypotension, blood pressure decreased, blood pressure systolic decreased, blood pressure diastolic decreased, and orthostatic hypotension.
l Hypertension includes hypertension, blood pressure increased, blood pressure systolic increased, and blood pressure diastolic increased.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events

The Applicant's Position

The safety profile was manageable and consistent with the underlying advanced disease and the known toxicities associated with the use of a lymphodepleting preparative regimen and IL-2, with no increase in the frequency or severity.

The FDA's Assessment

Using the Applicant's data, FDA found that Grade 3 or higher adverse reactions (adverse events related to any component of the lifileucel regimen) occurred in 96.9% (155/160) of study subjects who initiated the lifileucel regimen including 93.8% (150/160) of study subjects with Grade 3 or higher non laboratory adverse reactions.

Safety date shown in Table 50 above were revised by the Applicant per FDA's request. FDA verified the occurrence rates of these adverse reactions occurring within 30 days post lifileucel infusion among subjects included in the primary safety analysis set (N=156).

FDA agrees that the majority of high-grade TEAEs were blood and lymphatic disorders expected among patients undergoing NMA-LD and were manageable in most cases. However, in the

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setting of administering lifileucel one day following the completion of NMA-LD and administering IL-2 within 3 to 24 hours following lifileucel infusion, it is difficult for the FDA to exclude lifileucel's contribution to most of the severe and fatal events which were mostly assessed by the Applicant as unrelated to lifileucel. FDA is unable to ascertain if lifileucel may exacerbate the risks known to NMA-LD and IL-2. For this reason, FDA assessed the lifileucel regimen as one entity for severe, life-threatening, and fatal adverse events (refer to FDA comments under "Significant Adverse Events" in Section 8.2.4.7).

FDA notes that a reasonable measurement of serious risks is the death rate possibly related to one or more components of the lifileucel treatment regimen. Refer to FDA memo under "Unresolved Grade 3 or 4 TEAEs at Time of Death" and Table 45 in Section 8.2.4.1.

FDA summarized the adverse reactions occurring within 6 months (182 days) post lifileucel infusion among subjects included in the primary safety analysis set (Table 51 below). The occurrence rates of these adverse reactions occurring within 6 months were similar to those shown in the Applicant revised Table 50, suggesting that the majority of these adverse reactions had an onset within the first 30 days post lifileucel infusion.

Table 51. FDA – Summary of Non-Laboratory Adverse Reactions Observed in at Least 10% of Subjects within 6 months Post Lifileucel Infusion (N=156)

Adverse Reaction	Any Grade n (%)	Grade 3 or Higher n (%)
Blood and lymphatic system disorders	-	-
Febrile neutropenia	73 (46.8)	73 (46.8)
Cardiac disorders	-	-
Tachycardia	74 (47.4)	12 (7.7)
Gastrointestinal disorders	-	-
Diarrhea	73 (46.8)	3 (1.9)
Vomiting	68 (43.6)	2 (1.3)
Nausea	107 (68.6)	4 (2.6)
General disorders and administration site conditions	-	-
Chills	118 (75.6)	8 (5.1)
Pyrexia	95 (60.9)	16 (10.3)
Fatigue	87 (55.8)	8 (5.1)
Edema	66 (42.3)	8 (5.1)
Investigations	-	-
Weight increased	30 (19.2)	2 (1.3)
Infections and infestations*	-	-
Infection with pathogen unspecified	30 (19.2)	17 (10.9)
Infection with pathogen specified	19 (12.2)	6 (3.8)
Metabolism and nutrition disorders	-	-
Decreased appetite	48 (30.8)	2 (1.3)
Nervous system disorders	-	-
Headache	33 (21.2)	1 (0.6)
Encephalopathy	27 (17.3)	9 (5.8)

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Adverse Reaction	Any Grade n (%)	Grade 3 or Higher n (%)
Renal and urinary disorders	-	-
Acute kidney injury	31 (19.9)	11 (7.1)
Hematuria	22 (14.1)	2 (1.3)
Respiratory, thoracic, and mediastinal disorders	-	-
Hypoxia	37 (23.7)	19 (12.2)
Dyspnea	34 (21.8)	13 (8.3)
Skin and subcutaneous tissue disorders	-	-
Rash	58 (37.2)	15 (9.6)
Alopecia	48 (30.8)	0 (0)
Pruritus	21 (13.5)	0 (0)
Vascular disorders	-	-
Hypotension	58 (37.2)	17 (10.9)
Capillary leak syndrome	21 (13.5)	7 (4.5)
Hypertension	21 (13.5)	11 (7.1)

Source: Datasets: ADAE ADSL
*Treatment related infections occurred in 26.9% (42/156) of subjects including 13.5% (21/156) Grade 3 or higher.

8.2.4.9. Laboratory Findings

Data

Table 52. Applicant – Grade 3 or 4 Laboratory Abnormalities Occurring in at Least 10% of Subjects Following Treatment with Lifileucel (N=156)

Laboratory Abnormality	Grade 3 or 4 n (%)
Thrombocytopenia	122 (78.2)
Neutropenia	108 (69.2)
Anemia	90 (57.7)
Leukopenia	72 (46.2)
Lymphopenia	66 (42.3)
Hypophosphatemia	40 (25.6)

Source: C-144-01, Program: t2-r20-ae-lab-pt-c2c4-saf, Data: ADSL and ADAE, Data Extraction Date: 24Feb2022, Data Cut Date: 15Sep2021
Grades are based on CTCAE v4.03.
Adverse reactions are defined as AEs that were reported as at least possibly related to any component of the lifileucel regimen (i.e., cyclophosphamide, fludarabine, lifileucel, or IL-2) that occurred up to 30 days post lifileucel.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events

Of the subjects who experienced Grade 3 or 4 laboratory abnormalities in the hematology parameters (Table 52), most (87.2% to 100%) returned to their baseline status within a median of 13 to 20 days and 95.5% to 100% resolved to Grade 2 or lower within a median of 3 to 17 days. The incidence of Grade 3 or 4 decreases in phosphate or albumin had decreased to 0% and 0.7%, respectively, by Day 28.

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The Applicant's Position

Overall, changes in laboratory parameters were consistent with those expected due to the NMA-LD preparative regimen or IL-2 and resolved quickly.

The FDA's Assessment

Safety date shown in Table 52 above were revised by the Applicant per FDA's request. These laboratory abnormalities occurred within 30 days post lifileucel infusion.

FDA summarized the results occurring within 6 months (182 days) post lifileucel infusion (Table 53 below). The occurrence rates shown in Table 52 and Table 53 were very similar, suggesting that the majority of laboratory abnormalities had an onset within 30 days post lifileucel infusion (TEAE period).

Table 53. FDA – Grade 3 or 4 Study Treatment Related Laboratory Abnormalities Occurring in at Least 10% of Subjects within 6 months Post Lifileucel Infusion (N=156)

Laboratory Abnormality	Grades 3 or 4 (%)
Thrombocytopenia	122 (78.2)
Neutropenia	108 (69.2)
Anemia	91 (58.3)
Leukopenia	73 (46.8)
Lymphopenia	66 (42.3)
Hypophosphatemia	40 (25.6)

Source: Dataset: ADAE ADLB ADSL

FDA notes that some of the laboratory abnormalities were not resolved quickly.

Using the Applicant-submitted data, FDA found that for 45.5% (71/156) of subjects who had ≥ Grade 3 cytopenia, they did not resolve to ≤ Grade 2 or lasted more than 30 days post lifileucel infusion. These cytopenias included thrombocytopenia (30.1%), lymphopenia (19.9%), neutropenia (17.3%), leukopenia (14.7%), and pancytopenia (1.3%).

Additionally, using Applicant's submitted data, FDA identified 39 subjects who had Grade 3 or 4 TEAEs not resolved to Grade 2 or lower at the time of death including unresolved lab abnormalities. For instance, among the subjects with unresolved Grade 3 or 4 TEAEs at the time of death, 26 subjects had cytopenias (thrombocytopenia, lymphopenia, neutropenia, and/or leukopenia), 6 had anemia, 5 had febrile neutropenia, 3 had renal injury, 3 had hypotensive disorders, 2 had increased aspartate aminotransferase, 2 had cardiac arrhythmia, 1 had sepsis, 1 had bacteriuria, etc. (refer to FDA Figure 9).

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8.2.4.10. Vital Signs

Data

Clinically meaningful vital sign findings were to be reported as an AE. There were minimal changes from baseline noted on Day 0 (the day of the lifileucel infusion) for all vital sign parameters in Pooled Cohorts 2 and 4. An analysis of vascular hypotensive disorders is presented below in Section 8.2.5.5.

The Applicant's Position

No clinically meaningful effects on vital signs were observed.

The FDA's Assessment

FDA concurs that, except for hypotension, the lifileucel regimen did not suggest clinically meaningful effects on the vital signs.

8.2.4.11. Electrocardiograms

Data

ECGs were performed during screening and during the baseline period, and then only as clinically indicated. Clinically meaningful ECG findings were to be reported as an AE. An analysis of cardiac arrythmias is presented below in Section 8.2.5.4.

The Applicant's Position

No clinically meaningful effects on ECG were observed.

The FDA's Assessment

Refer to FDA assessment in Section 8.2.5.4.

8.2.4.12. QT

Data

A thorough QT clinical trial was not conducted.

The Applicant's Position

Not applicable.

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The FDA's Assessment

FDA concurs. Refer to FDA assessment in Section 8.2.5.4.

8.2.4.13. Immunogenicity

Data and The Applicant's Position

Not applicable.

The FDA's Assessment

FDA concurs.

8.2.5. Analysis of Submission-Specific Safety Issues

The datasets for the following analyses are ADSL and ADAE.

8.2.5.1. Hypersensitivity Reactions

Data and The Applicant's Position

Hypersensitivity reactions (including infusion related reactions and anaphylaxis) are considered to be identified risks for lifileucel and are discussed in Section 8.2.4 under "Significant Adverse Events."

The FDA's Assessment

FDA concurs that hypersensitivity reactions (including infusion-related reactions and anaphylaxis) are considered identified risks for lifileucel.

Based on Applicant's data, FDA found that 10 (10/156=6.4%) subjects experienced infusion-related reactions and 2 (2/156=1.3%,) subjects experienced anaphylactic reactions (1 Grade 4, 1 Grade 3) among subjects who initiated lifileucel regimen (i.e., at least received 1 dose of NMA-LD, N=160).

Among all 12 cases of hypersensitivity reactions, 8 were related to lifileucel, 3 related to IL-2, and 1 related to NMA-LD as assessed by the Applicant. Among all 12 cases, 2 were Grade 4, 3 were Grade 3, 6 were Grade 2, and 1 was Grade 1.

FDA notes that no infusion-related reaction or anaphylaxis in Study C-144-01 resulted in death.

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8.2.5.2. Cytokine Release Syndrome

Data

Cytokine release syndrome (CRS) is a potentially life-threatening condition that results from overactivation of T cells, leading to hypersecretion of cytokines by T cells and other immune cell types. CRS can be observed in all adoptive cell therapies but is most frequently seen with engineered T cell-engaging immunotherapies such as TCR- or chimeric antigen receptor (CAR-) T cell therapy (Wolf et al. 2019). CRS is clinically characterized by fever, hypoxia, and hypotension. Laboratory markers of systemic inflammation, such as interleukin-6, C-reactive protein, and ferritin are often elevated.

Among the subjects who received lifileucel in Study C-144-01, CRS was reported in 2.6% (4/156) of the subjects. One of the four TEAEs of CRS was Grade 3 and none was fatal. The time to onset following the lifileucel infusion was 1 to 9 days. Two of the 4 events resolved on the same day as they occurred (1 after treatment with IV methylprednisolone, and the other with no treatment) while the other two events resolved within 4 days of onset after treatment with IV dexamethasone and within 7 days of onset with no treatment. Of note, no laboratory markers of systemic inflammation that are normally observed with CRS were reported in association with the four TEAEs of CRS; however, three of the four TEAEs of CRS occurred concurrently with capillary leak syndrome (n=3), respiratory failure (n=1), or pyrexia (n=1). Respiratory failure and pyrexia could represent symptoms of CRS or, alternatively, symptoms of capillary leak syndrome, which is an AE commonly associated with IL-2 therapy.

The Applicant's Position

Reports of CRS were infrequent in Study C-144-01, typically mild to moderate in intensity, and manageable, resolving either spontaneously or after treatment with IV corticosteroids. Given the timing of the CRS and symptoms in the subjects who experienced the event, it is possible that the subjects experienced capillary leak syndrome, which can have a similar presentation as CRS and is a common adverse reaction to IL-2 therapy, rather than CRS.

The FDA's Assessment

FDA agrees that CRS was not a significant risk among subjects enrolled in lifileucel trials. However, FDA recommends that the Applicant continue to assess and report CRS along with immune effector cell-associated neurotoxicity syndrome (ICANS) events via their periodic safety reports in the postmarketing setting (refer to FDA Pharmacovigilance plan review memo for this BLA).

FDA does not consider capillary leak syndrome (CLS) a significant risk of the lifileucel regimen based on the occurrence rate of CLS and severity. Most of the CLS cases were Grade 2 and were

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resolved. Only two CLS cases (Grade 2) were not resolved to Grade 1 or lower per Applicant's data.

8.2.5.3. Cytopenias

Data

Myelosuppression, including leukopenia, neutropenia, thrombocytopenia, and anemia, has been reported in patients treated with cyclophosphamide and fludarabine, which are the components of the NMA-LD preparative regimen used in Study C-144-01. The nadirs of the reduction in leukocyte count and thrombocyte count are usually reached in weeks 1 and 2 of treatment with cyclophosphamide, and peripheral blood cell counts are expected to normalize after approximately 20 days per the cyclophosphamide prescribing information. With fludarabine, the median time to nadir counts is 13 days for granulocytes and 16 days for platelets, and the duration of clinically significant cytopenia has ranged from approximately 2 months to approximately 1 year per the fludarabine prescribing information.

The following MedDRA PTs related to cytopenias were grouped together:

Table 54. Applicant – MedDRA PTs Related to Cytopenias

Grouped Term Preferred Term	Included in the Grouped AE Term
Cytopenia	-
Leukopenia	MedDRA PTs of White Blood Cell Count Decreased and Leukopenia
Neutropenia	MedDRA PTs of Neutrophil Count Decreased and Neutropenia
Lymphopenia	MedDRA PTs of Lymphocyte Count Decreased and Lymphopenia
Thrombocytopenia	MedDRA PTs of Platelet Count Decreased and Thrombocytopenia

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term

As expected, the cytopenia grouped terms were among the most common TEAEs (i.e., incidence of ≥30%) and Grade 3 or 4 TEAEs (i.e., incidence of ≥10%) in Study C-144-01:

- Thrombocytopenia (82.7%, Grade 3/4 76.9%)
- Neutropenia (42.3%, Grade 3/4 28.8%)
- Leukopenia (34.6%, Grade 3/4 26.9%)
- Lymphopenia (31.4%, Grade 3/4 24.4%)

Overall, 86.5% (135/156) of the subjects had a treatment-emergent cytopenia; 82.7% (129/156) of the subjects experienced a Grade 3 or Grade 4 event. Cytopenia SAEs were reported in 5.8% (9/156) of the subjects, none of which were reported as related to lifileucel.

There were 35 subjects (22.4%) who experienced post-treatment-emergent cytopenias.

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The Applicant's Position

Based on both the TEAE patterns observed and laboratory assessments (see "Laboratory Findings" in Section 8.2.4), the cytopenic events reported in subjects receiving the lifileucel regimen are as expected per the desired and well-characterized effect of the NMA-LD preparative regimen (i.e., cyclophosphamide and fludarabine) administered per protocol and as described in the respective prescribing information.

The FDA's Assessment

FDA concurs that cytopenias were expected events in lifileucel trials. However, severe or prolonged cytopenias increased the risk of severe infections and internal organ hemorrhage (e.g., intracranial or abdominal hemorrhage) which were associated with deaths in Study C-144-01 (Subjects (b) (6)

FDA found that in 45.5% (71/156) of subjects with ≥ Grade 3 cytopenia, it lasted for more than 30 days post lifileucel infusion or did not resolve to ≤ Grade 2 (Refer to Table 53). FDA also found that among 10 subjects who received lifileucel and whose deaths were at least possibly related to the lifileucel regimen, 7 had Grade 3 or 4 cytopenia that were not resolved to Grade 2 or lower at the time of death.

FDA assessed the contribution of the lifileucel regimen (NMA-LD, lifileucel, and IL-2) as one entity for severe and fatal adverse events given that the Applicant has no clinical data to demonstrate the contribution of individual components of the lifileucel regimen to the overall safety.

Also refer to FDA comments under "Study Treatment-Related Deaths," "Unresolved Grade 3 or 4 TEAEs at Time of Death," and "Laboratory Findings" in Section 8.2.4.

8.2.5.4. Cardiac Arrythmias

Data

The NMA-LD preparative treatment and IL-2, which are included in the lifileucel regimen, are known to have cardiotoxic effects. Arrhythmia is one of the most common manifestations of cardiotoxicity caused by cyclophosphamide. IL-2 is associated with severe cardiotoxicity, including arrhythmias. In addition to the cardiotoxic effects of the NMA-LD preparative treatment and IL-2, aging is associated with a functional decline of the cardiovascular system; people over the age of 60 years are more likely to develop more serious arrhythmias and often take medications that can affect the heart's rhythm.

The following MedDRA terms related to cardiac arrhythmias were grouped together:

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Table 55. Applicant – MedDRA Terms Related to Cardiac Arrhythmias

Grouped Term	Included in the Grouped AE Term
Cardiac arrhythmia	Standardised MedDRA Query: Cardiac arrhythmia terms (incl bradyarrhythmias and tachycardias) MedDRA PT: Bradycardia MedDRA PT: Tachycardia

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term

Treatment-emergent cardiac arrhythmias occurred in 47.4% (74/156) of the subjects in Study C-144-01. The majority (62/74) of the subjects experienced arrhythmia events that were mild to moderate in intensity. 7.1% (11/156) of the subjects experienced a Grade 3 (n=10) or Grade 4 (n=1) event. The most commonly reported arrhythmias were tachycardia (28.8% of subjects) and sinus tachycardia (14.7%). SAEs were reported in 1.3% (2/156) of the subjects. One of the events of arrhythmia was fatal; the death was due to cardiac dysrhythmia (PT arrhythmia), which was likely secondary to the subject's underlying cyclophosphamide-related cardiomyopathy as assessed by the investigator and Applicant. The other SAE was AF, which was reported as related to IL-2.

The median age of the subjects who experienced arrhythmias was 57 years (min, max: 25, 79; Q1, Q3: 47, 64). Of the 74 subjects who experienced arrhythmia TEAEs, 63 had recovered or were recovering at the time of the data cutoff, with only 10 remaining who had not yet recovered and 1 who died due to an arrhythmia TEAE.

The median time to onset of any treatment-emergent cardiac arrhythmia event was 2 days (min, max: 1 to 56 days). There were 5 subjects (3.2%) who experienced post-treatment-emergent cardiac arrhythmias.

The Applicant's Position

Based on the TEAE patterns observed, the cardiac arrhythmias reported in patients receiving the lifileucel regimen are as expected per the safety profile of cyclophosphamide and IL-2 as described in the respective prescribing information for the products. The data did not suggest that there was an increased incidence or severity of these AEs in patients receiving the lifileucel regimen when compared to the incidence and severity in patients receiving cyclophosphamide or IL-2.

The FDA's Assessment

Using the Applicant's data, FDA identified 16 (16/156=10.3%) subjects in Study C-144-01 who experienced Grade 3 or higher cardiac disorder (regardless of relatedness to the lifileucel regimen as assessed by the Applicant) during the first 30 days post lifileucel infusion (TEAE) including 15 subjects with cardiac arrhythmia (tachycardia, supraventricular tachycardia, AF, and QT-prolongation), 1 subject with cardiac ventricular thrombosis, 1 subject with

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cardiomyopathy, and 1 subject with acute myocardial infarction (of note, some subjects had more than one event).

Although the Applicant assessed the fatal cardiac arrhythmia event occurring on Day 24 in Subject (b) (6) as likely related to cyclophosphamide, FDA was unable to determine whether lifileucel exacerbated the clinical course given that the subject also received lifileucel. A summary of the case follows:

Subject (b) (6) received NMA-LD and lifileucel but did not receive IL-2 due to signs of cardiomyopathy. Adverse events ≥ Grade 3 experienced by the subject included adrenal insufficiency, AF, cardiac ventricular thrombosis, cardiomyopathy, hypotension, and neutropenia. The subject developed AF on Day 20 and died on Day 24.

As FDA noted earlier, FDA assessed the contribution of lifileucel regimen (NMA-LD, lifileucel, and IL-2) as one entity for severe, life-threatening, and fatal adverse events.

The Applicant assessed most of these severe cardiac disorders as either related to NMA-LD or IL-2. FDA acknowledges that myocardial toxicities have been reported in patients treated with IL-2 and cyclophosphamide, respectively, in the literature or FDA labels for these drugs. However, for severe, life-threatening, and fatal cardiac disorders, FDA assessed the lifileucel regimen as one entity.

8.2.5.5. Vascular Hypotensive Disorders

Data

Therapeutic doses of IL-2 (defined as 600,000 IU/kg) have been associated with vascular hypotensive disorders, including hypotension, capillary leak syndrome, and orthostatic hypotension. Capillary leak syndrome is marked by increased capillary permeability to protein and fluids and reduced vascular tone. In most patients, this results in a concomitant drop in mean arterial blood pressure within 2 to 12 hours after the start of treatment. Per the Proleukin prescribing information, clinically significant hypotension and hypoperfusion can occur with continued therapy.

The following MedDRA terms related to vascular hypotensive disorders were grouped together:

Table 56. Applicant – MedDRA Terms Related to Vascular Hypotensive Disorders

Grouped Term	Included in the Grouped AE Term
Vascular hypotensive disorders	MedDRA HLT: Vascular hypotensive disorders

Abbreviations: AE = adverse event; HLT = High Level Term; MedDRA = Medical Dictionary for Regulatory Activities

Treatment-emergent vascular hypotensive disorders were reported in 41.0% (64/156) of the subjects; 14.7% (23/156) of the subjects experienced a Grade 3 or 4 event. SAEs were reported in 3.2% (5/156) of the subjects, none of which was fatal.

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The majority (84.4%; n=54/64) of subjects who experienced TEAEs within vascular hypotensive disorders had recovered or were recovering at the time of the data cutoff in Study C-144-01. The median time to resolution of the events within vascular hypotensive disorders was 4 days (min, max: 1 [same day], 28). There were 10 subjects with vascular hypotensive events that had not yet recovered by the time the subjects exited the study, and 6 of those 10 subjects had events that were mild to moderate in intensity, while the remaining 4 subjects had events that were considered by the Investigator to be severe in intensity. Of note, 9 vascular hypotensive events that were persisting at the time of the data cutoff were nonserious.

Further investigation of the most severe treatment-emergent vascular hypotensive events (i.e., those events that were assessed as being of Grade 3 severity or higher) showed that the median time to onset was 3 days (min, max: 1 [same day], 6) from the time of lifileucel infusion. Given that IL-2 is administered within 24 hours of the lifileucel infusion and every 8 to 12 hours for up to 6 doses thereafter, the time to onset of these vascular hypotensive events is consistent with what would be expected with IL-2.

The median time to onset of any events within vascular hypotensive disorders was 3.0 days (min, max: 1 to 751).

There were 3 subjects (1.9%) who experienced post-treatment-emergent vascular hypotensive disorders.

The Applicant's Position

The clinical course of the vascular hypotensive disorders reported in subjects receiving the lifileucel regimen was as expected per the safety profile of IL-2 as described in the prescribing information. In clinical studies, 71% of subjects who received IL-2 experienced hypotension of any grade, and 3% of subjects experienced Grade 4 hypotension (Proleukin prescribing information). Hypotension during Study C-144-01 occurred less frequently and was less severe than described in IL-2 clinical studies, with hypotension of any grade occurring in 33% (n=52/156) of subjects receiving the TIL regimen and only 2 of 156 subjects experiencing Grade 4 hypotension.

The FDA's Assessment

FDA acknowledges that vascular hypotensive disorders observed in lifileucel trials were less frequent and severe than those presented in the Proleukin (IL-2) label. However, comparing occurrence rates of AEs in the lifileucel trials to those in the Proleukin (IL-2) prescribing label is potentially misleading because AEs reported in the Proleukin label are usually associated with high dose of IL-2 treatment as a single agent and for a significantly longer treatment period (if patients tolerate IL-2 related toxicities) than the abbreviated IL-2 regimen in lifileucel trials.

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Furthermore, FDA notes that vascular hypotensive disorders are not unique to IL-2 alone, i.e., they occur with many immunotherapies. Therefore, FDA considers the contribution of the lifileucel regimen as one entity when assessing severe vascular hypotensive disorders.

8.2.5.6. Noninfectious Encephalopathy/Delirium

Data

The therapeutic dose of IL-2 is 600,000 IU/kg per dose, administered IV over 15 minutes, every 8 hours for a maximum of 14 consecutive doses per treatment cycle; treatment courses consist of two 5-day treatment cycles separated by a rest period and are repeated if tolerated. This therapy has been associated with alterations in cognitive and affective functioning in approximately 80% of patients with metastatic melanoma and metastatic renal cell carcinoma, with more than one-fourth experiencing moderate to severe cognitive alterations. Altered cognition includes changes in concentration, attention, short-term memory, confusion, mental fatigue, executive functioning, abstraction, language, basic arithmetic, and orientation, whereas affective symptoms include mood alterations, depression, anxiety, psychosis, hallucinations, aggression, suicide ideation, and coma (Mann et al. 2016). Although generally occurring later in a cycle, gradual decay does not always occur, and an additional dose may cause an acute worsening of symptoms (Dutcher et al. 2014). Additionally, age is an important risk factor for alterations in cognitive function, with the incidence of events, such as delirium or acute confusional state, increasing progressively after the fourth decade of life (Espino et al. 1998).

The following MedDRA terms related to noninfectious encephalopathy and delirium were grouped together:

Table 57. Applicant – MedDRA Terms Related to Noninfectious Encephalopathy and Delirium

Grouped Term	Included in the Grouped AE Term
Noninfectious encephalopathy/delirium	SMQ: Noninfectious encephalopathy/ delirium

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Query

Treatment-emergent noninfectious encephalopathy/delirium was reported in 32.1% (50/156) of the subjects; 9.0% (14/156) of the subjects experienced a Grade 3 or 4 event. SAEs were reported in 3.2% (5/156) of the subjects, none of which was fatal.

The median age of the subjects who experienced TEAEs within the Noninfectious encephalopathy/delirium Standardised MedDRA Query (SMQ) was 59.5 years (min, max: 39,79; Q1, Q3: 53, 66). The majority (72%; n=36/50) of subjects who experienced events within the Noninfectious encephalopathy/delirium MedDRA SMQ had recovered or were recovering at the time of the data cutoff. The median time to resolution of the events within the Noninfectious encephalopathy/delirium MedDRA SMQ that resolved was 3 days (min, max: 1 [same day], 23). There were 14 subjects with events within the Noninfectious encephalopathy/delirium MedDRA SMQ that had not yet recovered by the time the subjects exited the study, and 9 of

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those 14 subjects had events that were mild to moderate in intensity, while the remaining 5 subjects had events that were considered by the Investigator to be severe in intensity. Of note, all but 2 of the events within the Noninfectious encephalopathy/delirium MedDRA SMQ that were persisting at the time of the data cutoff were nonserious.

Further investigation of the most severe treatment-emergent events within the Noninfectious encephalopathy/delirium MedDRA SMQ (i.e., those events that were assessed as being of Grade 3 severity or higher) showed that the median time to onset was 5 days (min, max: 2, 22) from the time of lifileucel infusion. Given that IL-2 is administered within 24 hours of the lifileucel infusion and every 8 to 12 hours for up to 6 doses thereafter, the time to onset of these events is consistent with what would be expected with IL-2.

The median time to onset of any noninfectious encephalopathy/delirium event was 5.0 days (min, max: 2 to 130 days).

There were 10 subjects (6.4%) who experienced post-treatment-emergent noninfectious encephalopathy/delirium AEs.

The Applicant's Position

The reported terms within the Noninfectious encephalopathy/ delirium MedDRA SMQ were consistent with but occurred less frequently than the alterations in cognitive and affective functioning that are expected to occur in patients who receive IL-2 therapy. Of note, subjects receiving IL-2 as part of the lifileucel regimen administered in this study receive a maximum of 6 consecutive doses, possibly explaining the lower frequency of events associated with alterations in cognitive and affective functioning.

The FDA's Assessment

FDA does not agree that noninfectious encephalopathy observed in Study C-144-01 was only related to IL-2.

Using Applicant submitted data, FDA identified 10 (10/156=6.4%) cases of non-infectious encephalopathy (encephalopathy, seizure, and ICANS) among subjects who received lifileucel in Study C-144-01. All 10 cases had an onset during the TEAE period (Day 0 to Day 30). Among these 10 cases, 3 (2 Grade 3, 1 Grade 2) were assessed by the investigators as related to lifileucel in addition to other components of the lifileucel regimen (IL-2 and/or NMA-LD).

Using the Applicant's grouped AE terms, FDA identified 30 cases of non-infectious encephalopathy/delirium (encephalopathy, seizure, ICANS, lethargy, tremor, confusion, somnolence, amnesia, memory impairment, aphasia, delirium, hallucination, lethargy, aphasia, seizure, depression, dysarthria, etc.), 5 (3 encephalopathy, 1 memory impairment, and 1 lethargy) of which were assessed by the investigators as related to lifileucel in addition to other component(s) of the lifileucel treatment regimen.

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8.2.5.7. Immune-Mediated/Autoimmune Disorders

Data

The following MedDRA terms related to immune-mediated and autoimmune disorders were grouped together:

Table 58. Applicant – MedDRA Terms Related to Immune-Mediated and Autoimmune Disorders

Grouped Term	Included in the Grouped AE Term
Immune-mediated/autoimmune disorders	SMQ (Narrow): Immune-mediated/autoimmune disorders

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Query

Treatment-emergent immune-mediated/autoimmune disorders were reported in 6.4% (10/156) of the subjects. None of the events were Grade 3 or 4 or reported as an SAE. The only two TEAEs within the Immune-mediated/autoimmune disorders MedDRA SMQ were vitiligo (n=9) and cutaneous vasculitis (n=1).

The median time to onset of any immune-mediated/autoimmune disorder event was 19.5 days (min, max: 6 to 88).

There were 5 subjects (3.2%) who experienced post-treatment-emergent immune-mediated/ autoimmune disorder AEs.

Vitiligo, which occurred in 9 of the 10 subjects and is an identified risk for lifileucel, is discussed further in Section 8.2.4 under "Significant Adverse Events."

The Applicant's Position

There were no significant immune-mediated or autoimmune disorders reported in subjects receiving the TIL regimen. All events were mild to moderate in severity and manageable per current treatment guidelines.

The FDA's Assessment

The Applicant retrieved 10 cases of immune-mediated or autoimmune AEs in Study C-144-01 using MedDRA SMQ analysis, including 9 cases of low-grade vitiligo and 1 case of low-grade cutaneous vasculitis. However, this SMQ analysis and reporting may have underreported immune-mediated and immune-related AEs.

Immune-mediated or immune-related AEs are common in immunotherapy and can occur in any body system and organ. Examples include, but are not limited to, dermatomyositis, myocarditis, pneumonitis, colitis, hepatitis, nephritis, encephalitis, HLH, adrenal insufficiency, hyperglycemic conditions such as glucose intolerance, hypo- or hyperthyroidism, vitiligo, and cutaneous vasculitis.

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Due to limited information submitted in the BLA, it remains unclear to FDA if many of the AEs reported in lifileucel trials were immune-mediated or immune-related in addition to the 10 cases noted by the Applicant above, e.g., pneumonitis, non-infectious colitis, cholestasis, non-infectious encephalopathy, HLH, acute myocardial infarction, pruritus, hyperglycemia, and adrenal insufficiency.

8.2.6. FDA Assessments of Additional High-Grade Adverse Events

Febrile Neutropenia

High grade febrile neutropenia was a significant adverse reaction in lifileucel trials which were likely associated with severe infections. Based on FDA assessment, 46.8% of study subjects in Study C-144-01 experienced febrile neutropenia within 6 months post lifileucel infusion and assessed as related to the lifileucel regimen by the Applicant (refer to Table 51).

A total of 74 (74/156=47.4%, Refer to Table 47 in Section 8.2.4.3) subjects from the safety analysis set (N=156) of Study C-144-01 experienced Grade 3 (no Grade 4 or 5) febrile neutropenia during the first 30 days post lifileucel infusion (TEAE), among whom 5 (5/156=3.2%) events were onset prior to lifileucel infusion and 69 (69/156=44.2%) events were onset within 30 days post lifileucel.

Based on the Applicant's assessment, all components of the lifileucel regimen contributed to the febrile neutropenia events observed in Study C-144-01. Specifically, among all 74 events, 51 (51/156=32.7%) events were assessed by the Applicant as related to NMA-LD, 42 (42/156=26.9%) as related to IL-2, and 18(18/156=11.5%) as related to lifileucel.

Pleural Effusion During TEAE Period

Among safety reports submitted to lifileucel INDs (IND 16317, (b) (4), and (b) (4)), several study subjects with lung lesions and pleural effusion died after receiving lifileucel regimen. To help understand the overall benefit/risk among subjects with pleural effusion who received lifileucel regimen, FDA assessed the occurrence rate of pleural effusion in Study C-144-01 during TEAE period and the outcomes.

Using submitted data, FDA identified 18 (18/156=11.5%) subjects from the primary safety analysis set (N=156) who had pleural effusion during TEAE period, onset before or after lifileucel infusion), 4 (4/156=2.6%) of which were Grade 3 and none were Grade 4 or higher.

Among these 18 subjects with pleural effusion, 5 had pleural effusion onset prior to lifileucel effusion. None of these five subjects received more than four doses of IL-2 due to toxicity. Specifically, Subject (b) (6) received lifileucel but not IL-2 due to renal tubular necrosis and renal failure and died on Day 12 post lifileucel infusion. The remaining four subjects (b) (6) (b) (6) with Grade 2 to 3 pleural effusion received lifileucel, but only

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two to four doses of IL-2. The Applicant's data also indicate that three of the five subjects had worsened pleural effusion after receiving lifileucel infusion.

Among these 18 subjects, 6 subjects did not recover from the pleural effusion, which included 1 subject (b) (6) who died on Day 12, 1 subject (b) (6) who died on day 14, and the other 4 subjects (b) (6) had PD and died 112 to 246 days post lifileucel infusion.

However, among the 18 subjects with pleural effusion, 4 (4/18=22.2%) achieved a PR assessed by IRC, and these subjects received 4 to 6 doses of IL-2.

FDA found that proportionally more subjects with pleural effusion received less than 5 doses of IL-2 (8/18=44.4%) compared with subjects without pleural effusion (37/138=26.8%), apparently indicating that subjects with pleural effusion were likely to experience severe toxicity which resulted in a discontinuation of further administration of IL-2.

Therefore, based on data from Study C-144-01 alone, there is not enough evidence to suggest that subjects with pleural effusion had an unfavorable benefit-risk profile with the lifileucel treatment regimen.

Respiratory Failure

In the safety analysis set of Study C-144-01, FDA identified 9 (6%=9/156) subjects with Grade 3 or higher treatment-emergent respiratory dysfunction, including respiratory failure, edema, embolism, and hemorrhage. Including Grade 3 or higher hypoxia and dyspnea TEAEs, a total of 35 (22%=35/156) subjects from Cohort 2 and 4 experienced treatment-emergent Grade 3 or higher respiratory adverse events within 30 days following lifileucel infusion.

Also refer to FDA comments on Applicant Table 46 under "Treatment-emergent SAEs Reported in ≥2 Subjects in Pooled Cohorts 2 and 4 by Preferred Term (Safety Analysis Set)."

Therefore, respiratory dysfunction was a significant adverse reaction in lifileucel trials, and the risk was particularly high among subjects with NSCLC from Study IOV-LUN-202 trial. Refer to FDA assessment under "Safety profile across lifileucel trials" in Section 8.2.4.4.

Renal Injury

In the safety analysis set of Study C-144-01, 7.1% (11/156) of subjects experienced treatment-emergent Grade 3 or higher renal injury, including renal failure, oliguria, and renal tubular necrosis within 30 days post initiating the lifileucel regimen. Renal injury was a significant adverse reaction directly associated with at least two deaths of several study subjects in Study C-144-01. For patients with severe renal injury prior to lifileucel infusion, potential risks may outweigh potential clinical benefit based on limited data from Study C-144-01.

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Based on limited data, the following are two examples (Subjects (b) (6) identified by FDA for in subjects with renal injury prior to lifileucel infusion.

- Subject (b) (6) (41-year-old male, died on Day 12) did not receive the last dose of fludarabine due to renal tubular necrosis, which would likely prevent the subject from receiving IL-2 in the clinical setting. However, the subject was proceeded to lifileucel infusion, but was unable to receive IL-2 due to renal tubular necrosis and increased creatinine. The subject also had pleural effusion on Day -1 (prior to lifileucel). The subject probably should not have been proceeded to lifileucel infusion which made it difficult to exclude the role of lifileucel in his death (also refer to "Dose Interruption/Reduction Due to Adverse Effects" in Section 8.2.4.6 and "Dropouts and/or Discontinuations Due to Adverse Effects" in Section 8.2.4.5)
- Subject (b) (6) (66-year-old male, died on Day 24) had increased creatinine prior to lifileucel day. The Subject only received two of five fludarabine doses due to adrenal insufficiency and cardiomyopathy. However, the subject was proceeded to lifileucel infusion. IL-2 was not started due to cardiomyopathy. AEs ≥ Grade 3 included: adrenal insufficiency, atrial fibrillation, cardiac ventricular thrombosis, cardiomyopathy, hypotension, and neutropenia.

Also refer to FDA comments on the impact of lack of specific criteria for administering each component of the lifileucel regimen under "Dose Interruption/Reduction Due to Adverse Effects" and "Dropouts and/or Discontinuations Due to Adverse Effects" in Section 8.2.4.6.

Internal Organ Hemorrhage

Internal organ hemorrhage was a significant adverse reaction associated with at least two deaths (Subject (b) (6) in Study C-144-01.

FDA identified five subjects with Grade 3 or higher internal organ hemorrhage occurring during the first 30 days post lifileucel infusion: three (intra-abdominal hemorrhage, pulmonary alveolar hemorrhage, upper gastrointestinal hemorrhage in Subject (b) (6) respectively) of which were assessed as related to IL-2, and two (rectal hemorrhage, tumor hemorrhage in Subject (b) (6) respectively) as not related to any study drug by the Applicant. The intra-abdominal hemorrhage that occurred in Subject (b) (6) was fatal and was assessed as related to IL-2 by the Applicant.

FDA also identified three subjects (Subject (b) (6) with internal organ hemorrhage (intracranial) onset during the post treatment-emergent period (Day 31 up to 6 months), two of which were fatal. The fatal intracranial hemorrhage (Day 58) in Subject (b) (6) (b) (6) was assessed by FDA as related to study treatment (refer to FDA Table 45). Subject (b) (6) was also diagnosed with tuberculosis on Day 32, with no history of tuberculosis, or other severe infections. The fatal event of intracranial hemorrhage in Subject (b) (6) on Day 94 was complicated by the concurrent use of anti-coagulant rivaroxaban. Subject (b) (6) experienced

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a Grade 3 cerebral hemorrhage onset on Day 95, which resolved on Day 100 post lifileucel infusion and was assessed as related to NMA-LD by the Applicant.

Subject (b) (6) and (b) (6) are included in Table 45.

Anemia

Grade 3 or higher anemia is a significant risk following receiving the lifileucel regimen. It occurred in 106 (67.9%) study subjects in Study C-144-01 after initiating the lifileucel regimen including 104 (66.7%) occurring within 30 days post lifileucel (TEAE period, refer to Table 47). Additionally, 58.3% of study subjects who received lifileucel experienced Grade 3 or higher anemia within 6 months post lifileucel infusion assessed by the Applicant as related to study treatment (refer to Table 53). Although anemia was not found to be directly related to deaths of subjects treated in Study C-144-01, six subjects with Grade 3 or higher anemia during the TEAE period unresolved to Grade 2 or lower by the time of death (refer to FDA Figure 9).

Fatal Bone Marrow Failure

Bone marrow failure was a rare event in lifileucel trials. However, a fatal bone marrow failure was reported in Study C-144-01, assessed as related to all components of the lifileucel regimen by the investigator. The subject died on Day 150 after lifileucel infusion (refer to FDA Table 45).

Hemophagocytic Lymphohistiocytosis

HLH was a rare adverse reaction in Study C-144-01 and was not associated with death of study subjects with melanoma. However, high-grade HLH was observed in subjects with NSCLC and oropharyngeal squamous cell carcinoma in other lifileucel trials and is associated with at least two deaths.

FDA identified three HLH or suspected HLH cases among melanoma subjects across lifileucel trials:

- Subject (b) (6) from Cohort 2 experienced Grade 1 HLH. The subject died from intracranial hemorrhage with unresolved HLH. FDA notes that the low grade HLH was unlikely to be directly associated with the death of the subject based on information received from the Applicant.
- Subject (b) (6) from Cohort 2 who died from bone marrow failure was suspected by the investigator to have HLH but did not meet the HLH diagnosis criteria.
- Subject (b) (6) with stage IV melanoma enrolled to IOV-COM-202 experienced a serious event of HLH onset 49 days post lifileucel infusion. However, the subject also received several doses of pembrolizumab in addition to the lifileucel regimen. Therefore, it is unclear to FDA whether the serious HLH event in Subject (b) (6) was

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related to the lifileucel regimen as the subject received a combination of lifileucel and pembrolizumab therapy. The event was reported as resolved.

In contrast to subjects with melanoma enrolled to lifileucel trials, serious HLH was associated with two deaths of subjects with NSCLC who received lifileucel regimen as a monotherapy in Study IOV-COM-202 Cohort 3B. Based on information provided by the Applicant, one of these two subjects died from HLH, and the other subject died from HLH-related complications (intestine perforation and cytomegalovirus viremia). Refer to FDA Table 59 below for additional details.

Table 59. FDA – Fatal HLH Events in Patients with NSCLC Treated with Lifileucel Regimen as Monotherapy

Subject ID	Study ID	Adverse Event	Outcome	Information from Applicant
(b) (6) (b) (6) (NSCLC)	IOV-COM-202 Cohort 3B	HLH Grade 5: met 5 of 8 criteria: Fever up to 40°C Splenomegaly Bicytopenia Hypertriglyceridemia Elevated ferritin-onset day -2	Died on Day 36 post lifileucel infusion	CMV reactivation secondary to lymphodepletion. CMV reactivation may have led to the development of HLH.
(b) (6) (b) (6) (lung carcinoma, Stage IIIA)	IOV-COM-202 Cohort 3B	HLH Grade 3: met 5 of 8 criteria: Fever Splenomegaly Pancytopenia Elevated ferritin Elevated sCD25	Grade 3 HLH was not resolved. Subject died on Day 116.	CMV viremia secondary to lymphodepletion. HLH onset on Day 57. Subject died from small bowel perforation with unresolved CMV viremia and HLH.

Source: Additional Information submitted by Applicant per FDA Information Request
Abbreviations: CMV = cytomegalovirus; HLH = hemophagocytic lymphohistiocytosis; NSCLC = non-small cell lung cancer

For the above reasons, FDA recommends that the Applicant continue to assess and report HLH events via their periodic safety reports in the postmarketing setting (Refer to FDA Pharmacovigilance plan review memo for this BLA.)

8.2.7. COA Analyses Informing Safety/Tolerability

Data and The Applicant's Position

Not applicable. The EORTC QLC-C30 HRQoL results are presented in Section 8.1.2.

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The FDA's Assessment

FDA concurs.

8.2.8. Safety Analyses by Demographic Subgroups

The datasets for the following analyses are ADSL and ADAE.

Data

Age

The incidence of TEAEs was similar between the age subgroups except for the following:

- When comparing subjects who were at least 65 years of age (n=37) to those who were <65 years of age (n=119), there was a higher incidence of asthenia (27.0% versus 10.1%), hypertension (32.4% versus 11.8%), encephalopathy (13.5% versus 3.4%), and hallucination (8.1% versus 0.8%); however, the incidence of each of these events generally increases with increasing age independently of lifileucel administration. Thus, an increased incidence of these TEAEs in subjects who were at least 65 years of age does not suggest that the overall safety profile in these subjects is different from that of subjects who were <65 years of age.
- When comparing subjects who were <65 years of age to subjects who were at least 65 years of age, rash maculo-papular was the only TEAE that had a higher incidence (19.3% versus 2.7%); however, when evaluating this event and other similar events (i.e., rash, rash erythematous, rash follicular, rash macular, rash papular, and rash pruritic), there was no pattern that would suggest that these events were clinically meaningful, with most subjects experiencing events that were mild to moderate in intensity.

Sex

The incidence of TEAEs was similar between the sex subgroups except for the following:

- When comparing male subjects (n=84) to female subjects (n=72), there was a higher incidence of chills (83.3% versus 65.3%), decreased appetite (26.2% versus 11.1%), and weight decreased (16.7% versus 4.2%); however, there was no pattern that would suggest that these events were clinically meaningful, as most subjects experienced events that were mild to moderate in intensity and there were no meaningful differences when comparing the incidence of Grade 3 or higher events.

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Race

Subgroup analyses by race were not performed for Study C-144-01 since 95.4% of the subjects in Cohorts 2 and 4 were white.

The Applicant's Position

There were no clinically meaningful differences in safety, as observed in the incidence of TEAEs, between the age and sex subgroups.

The FDA's Assessment

FDA concurs that there were no clinically meaningful differences in safety between different age and sex subgroups. Given that melanoma predominantly occurs in the White population and 95.4% of study subjects in Study C-144-01 were White, FDA agrees that subgroup analysis by race is unnecessary.

8.2.9. Specific Safety Studies/Clinical Trials

Data and The Applicant's Position

Not applicable.

The FDA's Assessment

FDA concurs there are no separate safety trials to support this BLA submission.

8.2.10. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data and The Applicant's Position

Not applicable.

The FDA's Assessment

The carcinogenicity of lifileucel was not studied. However, FDA considers the risk as low because lifileucel is autologous tumor-derived T cells without in vitro genetic modification.

Human Reproduction and Pregnancy

Data and The Applicant's Position:

Not applicable.

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The FDA's Assessment

The impact on human reproduction and pregnancy has not been studied in lifileucel trials. FDA concurs that this is acceptable due to the seriousness of the disease and a high unmet medical need for patients with unresectable or metastatic melanoma previously treated with at least one systemic therapy, including a PD-1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

Pediatrics and Assessment of Effects on Growth

Data and The Applicant's Position

Not applicable.

The FDA's Assessment

Study C-144-01 did not enroll any pediatric subjects. Therefore, this section is not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data and The Applicant's Position

Not applicable.

The FDA's Assessment

FDA concurs.

8.2.11. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data and the Applicant's Position

Not applicable as lifileucel is not yet marketed in any region.

The FDA's Assessment

FDA concurs.

Expectations on Safety in the Postmarket Setting

Data and the Applicant's Position

Not applicable.

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The FDA's Assessment

FDA concurs.

8.2.12. Integrated Assessment of Safety

Data

Additional supportive safety data are presented in Table 60 from the monotherapy cohorts with the following data cutoff dates:

- 9/15/2021 for melanoma Study C-144-01
- 10/12/2022 (final data extract) for the completed HNSCC Study C-145-03
- 1/29/2023 for all other non-melanoma monotherapy Gen 2 TIL cohorts (see Table 5)

This analysis presents the Safety Population which consists of subjects who received any component of study treatment (i.e., NMA-LD, TIL, or IL-2).

Table 60. Applicant – Adverse Events of Any Grade Reported by Preferred Term at an Incidence of ≥30% in the Gen 2 TIL Monotherapy Studies (Safety Population)

Preferred Term	Melanoma C-144-01 Cohorts 2+4 (N=160)	Cervical Cancer C-145-04 Cohorts 1+2+4 (N=107)	NSCLC IOV-LUN-202 Cohorts 1+2 + IOV-COM-202 Cohort 3B (N=59)	HNSCC C-145-03 Cohort 2 (N=18)
Thrombocytopenia [1]	134 (83.8)	68 (63.6)	47 (79.7)	16 (88.9)
Anaemia	124 (77.5)	88 (82.2)	47 (79.7)	16 (88.9)
Chills	120 (75.0)	68 (63.6)	41 (69.5)	12 (66.7)
Nausea	118 (73.8)	80 (74.8)	39 (66.1)	11 (61.1)
Neutropenia [2]	118 (73.8)	62 (57.9)	42 (71.2)	13 (72.2)
Pyrexia	109 (68.1)	68 (63.6)	39 (66.1)	13 (72.2)
Diarrhoea	86 (53.8)	63 (58.9)	32 (54.2)	11 (61.1)
Leukopenia [3]	81 (50.6)	35 (32.7)	30 (50.8)	9 (50.0)
Fatigue	80 (50.0)	51 (47.7)	27 (45.8)	7 (38.9)
Febrile neutropenia	75 (46.9)	43 (40.2)	17 (28.8)	8 (44.4)
Vomiting	74 (46.3)	51 (47.7)	28 (47.5)	4 (22.2)
Lymphopenia [4]	73 (45.6)	48 (44.9)	28 (47.5)	11 (61.1)
Hypokalaemia	71 (44.4)	38 (35.5)	34 (57.6)	5 (27.8)
Hypophosphataemia	71 (44.4)	43 (40.2)	22 (37.3)	8 (44.4)
Hypotension	65 (40.6)	53 (49.5)	33 (55.9)	6 (33.3)
Tachycardia	61 (38.1)	33 (30.8)	7 (11.9)	3 (16.7)
Decreased appetite	59 (36.9)	42 (39.3)	25 (42.4)	4 (22.2)
Headache	57 (35.6)	36 (33.6)	18 (30.5)	3 (16.7)
Constipation	54 (33.8)	41 (38.3)	17 (28.8)	6 (33.3)
Alopecia	48 (30.0)	26 (24.3)	18 (30.5)	2 (11.1)
Hypomagnesaemia	48 (30.0)	41 (38.3)	23 (39.0)	6 (33.3)
Oedema peripheral	47 (29.4)	36 (33.6)	26 (44.1)	4 (22.2)

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Preferred Term	Melanoma C-144-01 Cohorts 2+4 (N=160)	Cervical Cancer C-145-04 Cohorts 1+2+4 (N=107)	NSCLC IOV-LUN-202 Cohorts 1+2 + IOV-COM-202 Cohort 3B (N=59)	HNSCC C-145-03 Cohort 2 (N=18)
Dyspnoea	45 (28.1)	28 (26.2)	31 (52.5)	4 (22.2)
Hypocalcaemia	40 (25.0)	26 (24.3)	13 (22.0)	7 (38.9)
Hypoxia	39 (24.4)	28 (26.2)	30 (50.8)	3 (16.7)
Hypoalbuminaemia	38 (23.8)	28 (26.2)	10 (16.9)	6 (33.3)
Hypertension	35 (21.9)	13 (12.1)	20 (33.9)	7 (38.9)
Sinus tachycardia	35 (21.9)	21 (19.6)	19 (32.2)	5 (27.8)
Hyponatraemia	33 (20.6)	16 (15.0)	11 (18.6)	7 (38.9)

Source: Program: t2-ae-soc-hlt-pt-safpop.sas, Data: ADSL and ADAE
Notes: The Safety Population consists of subjects who received any component of study treatment.
AEs are coded based on MedDRA v24.0.
All AEs that occurred after the start of NMA-LD and up to start of new anti-cancer therapy or data cutoff date are included.
AEs are sorted by decreasing frequency of PT in the Melanoma C-144-01 Cohorts 2+4 group.
[1] AE grouped terms of platelet count decreased and thrombocytopenia.
[2] AE grouped terms of neutrophil count decreased and neutropenia.
[3] AE grouped terms of white blood cell count decreased and leukopenia.
[4] AE grouped terms of lymphocyte count decreased and lymphopenia.
Abbreviations: AE = adverse event; Gen = Generation; HNSCC = head-and-neck squamous cell carcinoma; MedDRA = Medical Dictionary for Regulatory Activities; NMA-LD = nonmyeloablative lymphodepletion; NSCLC = non-small cell lung cancer; PT = Preferred Term; TIL = tumor-infiltrating lymphocytes

The Applicant's Position

Based on the safety analyses conducted across the Gen 2 TIL monotherapy studies, the safety profile observed across the cervical cancer, NSCLC, and HNSCC tumor cohorts was consistent with that observed in the Study C-144-01 melanoma cohorts except for differences related to the underlying disease being treated. The AEs reported were generally hematological toxicities, such as the grouped term of thrombocytopenia and anaemia, that are known to be commonly observed in patients who have been administered the components of the NMA-LD preparative regimen (i.e., cyclophosphamide and fludarabine) and nonhematological toxicities, such as chills, nausea, pyrexia, diarrhea, fatigue, vomiting, hypotension, tachycardia, decreased appetite, electrolyte disturbances, and peripheral edema, that are commonly observed in patients who have been administered the components of the NMA LD preparative regimen or IL-2 therapy.

Based on the safety data collected in Cohort 4 of Study C-144-01 and supporting data from Cohort 2 and across the Gen 2 TIL monotherapy studies, the lifileucel regimen has a safety profile for which routine risk mitigation measures, such as providing health care providers with risk information through FDA-approved prescribing information, are sufficient to preserve its benefits while minimizing risk.

The FDA's Assessment

FDA concurs that most common AEs were consistent across lifileucel trials.

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However, serious safety risks may vary across lifileucel trials depending on disease indication-related risk factors. As FDA assessed earlier in this document, study subjects with lung cancer (IOV-LUN-202) appeared to be more susceptible to pulmonary toxicity which was associated with approximately 12% death rate during the first 30 days post receiving lifileucel (refer to FDA assessment under "Safety profile across lifileucel trials" in Section 8.2.4.4). In addition, serious HLH event occurred in two study subjects with lung cancer and was associated with the deaths of these two study subjects [refer to "Hemophagocytic Lymphohistiocytosis" under "FDA Assessments of additional High-Grade Adverse Events" in Section 8.2.6].

As FDA has noted throughout this memo, for severe, life-threatening, and fatal adverse events, FDA assessed the contribution of the multi-component lifileucel regimen as one entity. This is because there were no clinical data from the lifileucel trials to discern the contribution of individual components of the lifileucel regimen to these severe or serious adverse events.

FDA concurs that risk mitigation measures should be provided to healthcare providers. Refer to FDA conclusions and recommendations in the next section. Refer to FDA labeling recommendations for risk mitigation measures in Section 12.

Also refer to Table 47, Table 48, Figure 10, Table 51, and Table 53.

9 Summary and Conclusions

9.1. Statistical Issues

The FDA's Assessment

FDA verified the results of ORR, DOR, DCR, PFS, and OS provided by the Applicant, and did not find significant issues. With respect to the Applicant's null hypothesis of ORR ≤10%, please refer to Section 8.1.1.4. for FDA comments. Of note, FDA considers DCR, PFS, and OS endpoints from single arm trials exploratory and not adequate to be used as measures of efficacy to support the approval of lifileucel. Refer to FDA Statistics review memo for details.

9.2. Conclusions and Recommendations

The FDA's Assessment

Based on FDA assessments of efficacy and safety data from Study C-144-01, as well as additional safety summaries of other lifileucel studies under IND (b) (4) and IND (b) (4), FDA concurs that Study C-144-01 has established clinically important improvement in ORR for the treatment of unresectable or metastatic melanoma previously treated with at least one systemic therapy, including a PD-1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. The ORR was 28.0% (95% CI: 18.7% to 39.1%)

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based on the primary efficacy analysis set (N=82, Cohort 4 with lifileucel manufactured at (b) (4) facility). The primary ORR result was supported by ORR observed in Cohort 2 efficacy analysis set [34.8% (95% CI: 23.5% to 47.6%), N=66] and pooled Cohort 2 and 4 full efficacy analysis set [31.4% (95% CI: 24.1% to 39.4%), N=153].

FDA identified significant risks associated with the lifileucel regimen. There were 12 (12/160=7.5%) study treatment-related deaths in Study C-144-01 as assessed by FDA, which included 10 deaths that occurred after lifileucel infusion and 2 deaths that occurred during lymphodepleting period before lifileucel infusion.

However, study subjects in Study C-144-01 had previously received a median of two lines of anti-PD1-based immunotherapies, and there is no FDA-approved treatment available for this patient population. Therefore, FDA concludes that the benefit-risk profile of the lifileucel regimen is acceptable for an AA. The Applicant is required to verify the clinical benefit of lifileucel in improving PFS without a detriment to OS, and overall benefit-risk through a confirmatory RCT (refer to the status update of Phase 3 confirmatory trial IOV-MEL-301 in "Summary of Pre-submission/Submission Regulatory Activity" under Section 3.2).

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10 Advisory Committee (AC) Meeting and Other External Consultations

The FDA's Assessment

There was no AC meeting or other external consultations for this BLA submission.

11 Pediatrics

The Applicant's Position

On 4/7/2022, the FDA provided an agreement letter to the Applicant's amendment to the initial pediatric study plan (iPSP), which includes a plan to request a waiver for pediatric assessments for lifileucel in children <8 kg and a request for deferral to initiate the Phase 1 clinical studies until nonclinical feasibility has been established. A request for a partial pediatric waiver and pediatric deferral consistent with the agreed iPSP is provided in this BLA.

The FDA's Assessment

The Applicant had an Agreed iPSP with FDA (4/7/2022) to study the safety and efficacy of lifileucel in children (≥8 kg to <21 years) with recurrent or refractory soft tissue sarcoma (rhabdomyosarcoma and Ewing sarcoma) or primary central nervous system malignancies. The Applicant submitted Phase 1 pediatric study protocol (IOV-PED-101) on 6/29/2023.

However, FDA CBER does not consider lifileucel to be a molecularly targeted product for the following reason: lifileucel is an unmodified tumor-derived T cell immunotherapy. There are no genetic modifications or lymphocytes selection process to direct the T cells to specific molecular target(s) on the tumor. Therefore, Section 505B(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (i.e., Pediatric Research Equity Act [PREA]), as amended by the FDA Reauthorization Act of 2017 (FDARA), does not apply to lifileucel.

In addition, lifileucel had been granted orphan drug designation (ODD#154772) for the treatment of Stage IIB-Stage IV melanoma before the BLA submission, including the indication sought for approval in BLA 125773. Therefore, according to PREA and 21 CFR 601.27(d), lifileucel is exempt from requirements for pediatric assessments under PREA.

As such, FDA notified the Applicant on 1/30/2024 that all pediatric studies (IOV-PED-101 and IOV-PED-201) including timelines proposed by the Applicant are considered voluntary.

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12 Labeling Recommendations

Data

Not applicable as this is a new label.

The Applicant's Position

A draft USPI for lifileucel has been submitted for FDA's consideration.

The FDA's Assessment

There are several major issues with the Applicant's draft USPI for lifileucel:

1. "Warnings and Precautions" section only included hypersensitivity reaction. FDA believes that the Applicant severely underestimated risks associated with the lifileucel regimen.
2. In summary tables for adverse reactions, the Applicant only included TEAEs which were related to the lifileucel regimen and occurred during the first 30 days post lifileucel infusion (defined as TEAE by the Applicant). FDA believes that both TEAEs and post TEAEs (up to 6 months as defined by the Applicant) that were related to the lifileucel regimen should be included in the safety summary tables.
3. The Applicant did not group individual infection events and summarize them as a single group (i.e., infection) in the safety summary tables. However, FDA found that 26.9% (42/156) of study subjects treated with lifileucel in Study C-144-01 experienced treatment-related infection (of any origin), including 13.5% (21/156) with Grade 3 or higher infection.
4. The draft USPI submitted by the Applicant did not describe serious adverse reactions (SARs). FDA was unable to summarize SAEs or SARs in a meaningful way because SAEs were apparently underreported in Study C-144-01 (refer to FDA comments in Section 8.2.4.2).
5. The Applicant proposed to provide lifileucel only to "Authorized Treatment Center."
6. The Applicant proposed a lifileucel dose of (b) (4) for commercial release. This proposed lifileucel dose range reflected doses administered to all but two study subjects from the pooled full efficacy analysis set. These two subjects received less than (b) (4) viable cells (Subject (b) (6) from Cohort 2 and (b) (6) from Cohort 4).

To address issues 1, 2, 3, and 4, and to enhance characterization of risks associated with the lifileucel treatment regimen, FDA made the following revisions to the Applicant's draft USPI:

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a. Included significant adverse reactions which were associated with deaths in the Boxed Warning section.
b. Revised all safety summary tables by including both TEAEs and post TEAEs.
c. Summarized the most common adverse reactions that occurred in ≥20% of study subjects in C-144-01, as opposed to ≥30% proposed by the Applicant.
d. Added additional grouped safety events (e.g., infections) not characterized by the Applicant in the draft USPI.
e. In the USPI, FDA listed adverse reactions that were assessed by FDA as related to the deaths of study subjects in Study C-144-01 as SARs. FDA believes that these were not the only SARs from Study C-144-01, but they were the most serious ones associated with fatal outcomes.

To mitigate serious risks associated with the lifileucel regimen, FDA takes the following risk mitigation measures through FDA-approved label:

a. Providing healthcare providers with accurate risk information associated with the lifileucel regimen.
b. Mitigating risks through Boxed Warning and Warnings and Precautions.
c. Mitigating risks through administering the lifileucel regimen in a hospital inpatient setting with immediate access to ICU.
d. Recommending that healthcare providers assess benefit/risk for each patient before and during the administration of the lifileucel regimen, and in the event of a SAR, re-assess the benefit/risk of completing the regimen.

To address issue 5, because FDA is unable to restrict drug distribution without implementation of risk evaluation and mitigation strategy (REMS), FDA removed the Applicant-proposed "Authorized Treatment Center" from the USPI.

To address issue 6, FDA assessed clinical, clinical pharmacological, and cell markers data provided by the Applicant. The following are FDA's findings:

a. There was no correlation between lifileucel persistence and objective tumor response, i.e., lifileucel persistency was observed in both responders and non-responders.
b. The Applicant has not identified a meaningful cell marker on lifileucel that was correlated with the observed objective response.
c. Responders appeared to have received higher lifileucel doses than non-responders overall (refer to Figure 2 in Section 6.3.2.2), although the correlation between lifileucel dose and the likelihood of objective response was weak (odds ratio =1.03 for each increase of 1 billion viable cells, 95% CI: 1.009 to 1.052, p=0.0057).
d. The lowest and highest lifileucel dose that has shown an objective response in the primary efficacy Cohort 4 was 7.5 x 10^9 and 72 x 10^9 viable cells, respectively.

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Under the circumstance that the Applicant has not demonstrated the MOA of lifileucel, relatively high risks associated with the lifileucel regimen, and an apparent trend that responders received higher lifileucel doses than non-responders overall, FDA recommends 7.5 x 10^9 to 72 x 10^ 9 viable cells for commercial release of lifileucel under the initial AA. A subset of the primary efficacy Cohort 4 subjects received lifileucel within the FDA-recommended dosing range. The ORR for this subset (i.e., efficacy set, refer to Figure 4) was 31.5% (95% CI: 21.1% to 43.4%, N=73) including 3 (4.1%) CR and 20 (27.4%) PR. Among the 23 responders, 56.6%, 47.8% and 43.5% achieved durable responses at 6, 9, and 12 months following confirmed initial responses, respectively. All 73 (100%) patients received prior anti-PD-(L)1 therapy, 63 (86.3%) received prior anti-CTLA-4 therapy, 42 (57.5%) received anti-PD1/anti-CTLA-4 combination therapy and 20 (27.4%) received a BRAF inhibitor or combination therapy with BRAF and MEK inhibitors. The median age was 58 years (min, max:25, 74 years), with 26.0% age 65 or older, 52.1% were male, 94.5% were white, 2.7% were black, and 1.4% were Asian. Patients received a median of 3 prior lines of therapy and a median of 2 prior lines of anti-PD(L)1 containing therapies. Main disease characteristics were: BRAF V600 mutation-positive: 27.4%; PD-L1 TPS greater than or equal 5%: 23.3%; elevated LDH: 63.0%; brain and/or liver metastases: 54.8%. The median target lesion sum of diameters was 108.7 mm (min, max: 15.7, 552.9). The performance status prior to tumor procurement was ECOG 0 (71.2%) and ECOG 1 (28.8%).

However, for the following reasons, FDA recognizes uncertainties of the recommended lifileucel dosing range:

e. Different lifileucel dosing ranges did not yield meaningful differences in ORR due to the well overlapping 95% CIs of the ORRs.

   i. ORR =31.5% (95% CI: 21.1% to 43.4%, N=73) for Cohort 4 with a lifileucel dose of 7.5 x 10^9 to 72 x 10^9 cells
   ii. ORR =31.4% (95% CI: 24.1% to 39.4%, N=153) for the pooled full Cohort 2 and 4 analysis set with a lifileucel dose of 1.2 x 10^9 to99.5 x 10^9 viable cells
   iii. ORR =34.3% (95% CI: 26.5% to 42.8%), N=140) for a subset of the pooled full Cohort 2 and 4 efficacy set with a dose of 6.16 x 10^9 to 99.5 x 10^9 viable cells
   iv. ORR =35.7% (95% CI: 27.4% to 44.7%, N=126) for a subset of the pooled full Cohort 2 and 4 efficacy set with a dose of 10.0 x 10^9 to 99.5 x 10^9 viable cells

f. Lifileucel dose had no correlation with DOR.
g. Lifileucel dose had a weak correlation with lifileucel persistence (p=0.0118, R^2=0.0525).
h. Lifileucel dose did not appear to be related to the seriousness of adverse events.
i. There were a limited number of study subjects across different dose ranges.

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j. Correlation between dose and objective response across patients should be interpreted with caution given the patient-specific, autologous, non-genetic modification and non-molecularly targeted nature of lifileucel.

In summary, considering the lack of understanding of MOA of lifileucel, and overall risks associated with the lifileucel treatment, FDA recommends approving the lifileucel dose range (min =7.5 x 10^9, max =72 x 10^9 viable cells) which has shown objective tumor responses among study subjects enrolled to the primary efficacy Cohort 4.

FDA suggests the Applicant to continue to collect both clinical and non-clinical data via its planned post-marketing expanded access program and the ongoing Phase 3 confirmatory trial (IOV-MEL-301). The Applicant may request to extend or narrow the dosing range through a supplemental BLA submission if new evidence supports a new dosing range in the future.

Refer to FDA-approved USPI for lifileucel.

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13 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment

Several safety profiles drawn from Study C-144-01 are concerning:

1. Study treatment was possibly related to the deaths of 7.5% (12/160) of study subjects who initiated the lifileucel treatment regimen including 5% (8/160) died during the first 30 days after receiving NMA-LD or lifileucel.
2. 23.6% (21/89) of study subjects in Cohort 4 had an ICU stay for non-infusion related events such as managing specific adverse events and stabilizing the condition of study subjects.
3. 82.1% (128/156) of study subjects experienced at least one Grade 4 or 5 adverse event related to the study treatment (assessed by Applicant) during the first 30 days after lifileucel infusion (defined as TEAE by the Applicant).
4. 25.0% (39/156) of study subjects had at least one Grade 3 or 4 TEAE unresolved at the time of death, some of which contributed to their deaths.

The most SARs of the lifileucel treatment regimen associated with deaths included both acute toxicities (e.g., acute respiratory failure, acute renal failure, and septic shock) and delayed toxicities (e.g., intracranial hemorrhage, severe infection, multi-organ failure, bone marrow failure).

Although the types of primary risks of the lifileucel regimen are not different from the known risks associated with cyclophosphamide, fludarabine, IL-2 or other immunotherapies, it is difficult to exclude the contribution of lifileucel to these risks, particularly fatal risks. Therefore, FDA assessed the safety profile of the lifileucel regimen as one entity for severe, life-threatening, and fatal adverse events.

REMS was not recommended for lifileucel due to the lack of specific serious risks. Instead, FDA recommends risk mitigation measures via labeling. Refer to FDA recommended risk mitigation measures in Section 12 "Labeling Recommendations." Also refer to USPI for lifileucel.

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14 Postmarketing Requirements and Commitment

The FDA's Assessment

Postmarketing Requirement (PMR):

As a PMR, the Applicant is conducting a confirmatory trial (IOV-MEL-301) to verify the clinical benefit of lifileucel in improving PFS without a detriment to OS among adult patients with untreated unresectable or metastatic melanoma(refer to Section 3.2 for details of the study design).

The required timelines for completing the ongoing Trial IOV-MEL-301 are as follows:

- Study Completion: 3/31/2030 based on the final OS analysis
- Final Study Report Submission: 3/31/2031

Postmarketing Commitment (PMC):

The Applicant has agreed to two CMC PMCs (Refer to FDA CMC review memo for details).

1) To perform a study to develop and evaluate the suitability of (b) (4) (b) (4) control for (b) (4) analysis of (b) (4) on the drug product with the following timelines:
   - Study Protocol Submission: 4/30/2024
   - Final Study Report Submission: 4/30/2025
2) To execute a (b) (4) organic and elemental leachables study for lifileucel over the manufacturing, storage, and in-use period (i.e., for cumulative leachables in the drug product) with the following timelines:
   - Final Study Report Submission: 2/28/2025

In addition, the Applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80, and enhanced pharmacovigilance for the following:

1) Expedited (15-day) reporting (regardless of seriousness or expectedness) to the FDA Adverse Event Reporting System for three years post-licensure for Uveitis, Cytokine Release Syndrome, ICANS, and HLH.
2) Provide aggregate safety assessments (based on interval and cumulative postmarketing safety data) in periodic safety reports for the above adverse events in individuals who receive lifileucel.

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The sponsor plans to conduct a voluntary non-interventional observational postmarketing safety surveillance study (IOV-MEL-401) for long term follow-up of patients with metastatic melanoma who receive treatment with commercial lifileucel in routine clinical practice in the United States. Study IOV-MEL-401 will enroll approximately 300 adult patients, and each patient will be followed up for 5 years.

Proposed study milestones are as follows:

- Final protocol submission: 4/30/2024
- Study completion date: 11/30/2031
- Final Study Report completion: 11/30/2032

The proposed pharmacovigilance plan for lifileucel is adequate for the labeled indication. The available data do not indicate a safety signal which would require either a REMS, or a PMR study that is specifically designed to evaluate a particular safety issue as a primary endpoint. There is no agreed-upon postmarketing commitment (PMC) for a safety study for this product.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes _X_ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g., race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _X_ No
□	Other considerations (e.g., PK/PD), if applicable:	__ Yes _X_ No

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15 Clinical Review and Clinical Team Leaders

X

Clinical Reviewer

X

Clinical Team Leader

X

OCE MORE Team Leader

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16 Oncology Branch 1 Chief

X

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17 Division of Clinical Evaluation Oncology Director

X

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18 Oncology Center of Excellence (OCE) Director (or designee)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

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19 Office of Therapeutic Products Director (or Designated Signatory Authority)

X

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20 Appendices

20.1. References

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20.2. Financial Disclosure

The Applicant's Position

The Applicant has adequately assessed clinical investigators from covered Study C-144-01 (Cohort 2 and 4) for any financial interests/arrangements as defined in 21 CFR Part 54.

Two US investigators disclosed significant payments over (b) (4) United States dollars. These investigators participated as subinvestigators at the time of financial disclosure then subsequently were Principal Investigators at a second study site. In total these investigators screened 21 patients and enrolled/treated 12 patients across 2 study sites in Study C-144-01 (Cohort 2 and Cohort 4 combined). Financial certifications and disclosures are provided.

The FDA's Assessment

Covered Clinical Study (C-144-01):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 664		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)

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Number of investigators with certification of due diligence (Form FDA 3454, box 3) 17		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant)

*The table above was filled by the Applicant and confirmed and edited by the FDA.

20.3. Nonclinical Pharmacology/Toxicology

Data and The Applicant's Position

Not applicable.

The FDA's Assessment

Refer to FDA Pharmacology/Toxicology review memo.

20.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

20.4.1. Population PK Analysis

Not applicable.

20.4.2. Exposure-Response Analysis

Not applicable.

20.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment

Results of safety analyses conducted by FDA are reported under Section 8.2 of this memo.

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