Clinical Pharmacology BLA Review

Office of Clinical Evaluation (OCE)

Office of Therapeutic Products (OTP)

Submission Number: 125773

Product Name: Lifileucel [AMTAGVI]

Proposed Indication: 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.

Applicant: Iovance Biotherapeutics, Inc.

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RPM: Catherine Tran

Reviewer: Million Tegenge, PhD

Clinical Pharmacology Reviewer, OCE, OTP

Through: Asha Das, M.D.

Director, Division of Clinical Evaluation Oncology, OCE, OTP

Table of Contents

List of Tables 3

List of Figures 3

1. Executive Summary 4

2. Recommendations 4

3. Background 5

4. Summary of Clinical Pharmacology Findings 5

5. Clinical Pharmacology Labeling Comments 8

6. Comprehensive Clinical Pharmacology Review 8

6.1. General Pharmacology 8

6.2. Study Design 9

6.3. Pharmacokinetics 10

6.3.1. Lifileucel Expansion and Persistence 10

6.3.2. Impact of Intrinsic and Extrinsic Factors on Persistence 14

6.4. Pharmacodynamics 18

6.5. Dose-Response Assessment 20

6.5.1. Dose-Efficacy 20

6.5.2. Dose-Exposure and Exposure-Efficacy 24

7. Appendix 28

7.1. Study C-144-01 28

List of Tables

Table 1: Demographics for Cohort 4, Cohort 2, and Pooled Cohorts 2 & 4 (Full Analysis Set)..... 10
Table 2: Summary of Shared Clones Between the Lifileucel Product Lot and PBMC at Various Timepoints (Cohort 4) 13
Table 3: Summary of Shared Clones Between the Lifileucel Product Lot and PBMC at Various Timepoints (Pooled Cohort 2 & 4)..... 13
Table 4: Summary Statistics for Total Infused Cells Grouped by Duration of Response 22
Table 5: Summary Statistics for Total Infused Cells Grouped by Response 23
Table 6: Statistical Analysis Results of Lifileucel Dose Versus Day 42 Persistence Relationship With or Without Factor of IL-2 Dose Group..... 25

List of Figures

Figure 1: Schematic of Planned Study Cohorts..... 10
Figure 2: Mean Shared TCR Repertoire Over Time (Cohort 4)..... 13
Figure 3: The Shared TCR Clonal Frequencies for Individual Patients Over Time (Cohort 2 & 4)..... 14
Figure 4: Intrinsic Factors and Lifileucel Persistence (Pooled Cohort 2 and Cohort 4) . 15
Figure 5: Day 42 Lifileucel Persistence for Patients by PD-L1 TPS 15
Figure 6: Extrinsic Factors and Lifileucel Persistence (for Samples in Cohort 2 and Cohort 4) 16
Figure 7: Day 42 Lifileucel Persistence by Number of IL-2 Doses 18
Figure 8: Circulating Cytokine and Chemokine Levels (Cohort 2 & 4) 20
Figure 9: Box Plot of Total Infused Cells by Disease Control by IRC per RECIST v1.1 Pooled Cohorts 2 & 4 (Full Analysis Set) 22
Figure 10: Association Between Best Overall Response and Total Infused Cells..... 23
Figure 11: Regression Analysis Between Response and Total Infused Cells (Cohort 2 & 4)..... 24
Figure 12: Mean Lifileucel Persistence by Response (Pooled Cohort 2 & 4) 26
Figure 13: Summary of Exploratory Dose-Exposure Assessment (Cohort 2 & 4) 27
Figure 14: Summary of Lifileucel Persistence in Subjects who Received Lower and Higher Than Median Dose of 30x10^9 Lifileucel (Cohort 2 & 4)..... 27

1. Executive Summary

Lifileucel (AMTAGVI) is an autologous tumor-derived T cell immunotherapy comprised primarily of T cells of the CD4+T and CD8+T cell lineages. It may also contain monocytes and other lymphocytes including B cells and NK cells.

Lifileucel is manufactured from patient tumor tissue removed from one or more tumor lesions by surgical procedure(s). The final product is a cryopreserved suspension of tumor-derived T cells that is formulated in (b) (4) to 4 infusion bags for intravenous infusion. In this BLA submission, the Applicant proposes lifileucel for 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 mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor. The Applicant is seeking accelerated approval based on overall response rate.

The data supporting clinical pharmacology of lifileucel is based one clinical study (C-144-01) that included pharmacokinetics (i.e., expansion and persistence), pharmacodynamics, and dose-response assessments. Prior to lifileucel infusion, tumor-derived clonotypes can be detected in peripheral blood at a mean proportion of 16% which was increased to 83% at Day 4 post-infusion of lifileucel. The clonotypes declined to 51% at Day 14 and persisted in the range of 37% to 41% up to Month 12 post-infusion of lifileucel. None of the analyzed cytokines and chemokines were able to provide evidence of pharmacodynamic activity of lifileucel that distinguish responding versus non-responding group.

Analysis of the dose-efficacy relationship based on duration of response (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/partial response (CR/PR) is 30x10^9 cells (range: 6.2 x10^9 to 72 x10^9) and a higher probability of CR/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 higher dose. The mean lifileucel persistence was 36 ± 24% and 49 ± 25% for subjects who received lower and higher than the median lifileucel dose of 30x10^9 cells that achieved CR/PR, respectively.

Overall, the clinical pharmacology analysis supports the accelerated approval of lifileucel for 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.

2. Recommendations

This BLA is acceptable for accelerated approval from the clinical pharmacology perspective. Labeling recommendations are provided in Section 5.

3. Background

Tumor infiltrating lymphocytes is an example of adoptive cell transfer in which a patient's tumor is harvested, expanded in vitro, and administered back to the patient to exert anti-tumor response.[1] Preliminary clinical studies have demonstrated the potential of TIL in inducing cancer regression in patients with metastatic melanoma.[2,3] Despite recent advances in the treatment of unresectable or metastatic melanoma, there remains an unmet medical need as some patients fail to respond or progress after initial response with immune check point inhibitors (ICIs) and targeted agents (e.g., BRAF and MEK inhibitors).

In this BLA submission, the Applicant proposes lifileucel (AMTAGVI) for 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. The Applicant is seeking accelerated approval based on overall response rate. Lifileucel has been granted both Fast Track and Regenerative Medicine Advanced Therapy (RMAT) designations for the treatment of advanced melanoma.

Lifileucel is composed of autologous tumor-derived T cells, which are obtained from an individual patient's resected tumor and are expanded ex vivo through cell culture in the presence of IL-2, muromonab CD3 (a murine monoclonal antibody to human CD3 [OKT3]) and allogeneic mononuclear feeder cells.

4. Summary of Clinical Pharmacology Findings

The data supporting clinical pharmacology assessment of lifileucel were based on the clinical study entitled: "A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-144; Lifileucel) for Treatment of Patients with Metastatic Melanoma (Study C-144-01)". The study includes 4 cohorts:

- Cohort 1 (N=23), which was administered non-cryopreserved lifileucel product. It should be noted that the non-cryopreserved product is no longer used in clinical trials.
- Cohort 2 (N=67), which was administered cryopreserved lifileucel product (i.e., the product being pursued for product registration).
- Cohort 3 (N=11, ongoing enrollment), which comprises subjects who were previously treated in Cohort 1, Cohort 2, or Cohort 4, had progressive disease, and opted to be retreated with the lifileucel regimen, using cryopreserved lifileucel product.
- Cohort 4 (N=89), which was administered cryopreserved lifileucel product.

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[1] Lee, S and K Margolin, 2012, Tumor-Infiltrating Lymphocytes in Melanoma, Curr Oncol Rep, 14(5):468-474.

[2] Rosenberg, SA, BS Packard, PM Aebersold, D Solomon, SL Topalian, ST Toy, P Simon, MT Lotze, JC Yang, CA Seipp, C Simpson, C Carter, S Bock, D Schwartzentruber, JP Wei, DE White, 1988, Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report, N Engl J Med 319(25):1676-80.

[3] Rohaan, MW, JH van den Berg, P Kvistborg, JBAG Haanen, 2018, Adoptive transfer of tumor-infiltrating lymphocytes in melanoma: a viable treatment option, J ImmunoTher Cancer, 6(1):102.

The clinical pharmacology assessment focuses on Cohort 2 and 4 which are based on the same manufacturing process for generating cryopreserved lifileucel product. The major clinical pharmacology findings are summarized as follows.

Lifileucel Expansion and Persistence

Because of the cellular nature of lifileucel, conventional pharmacokinetic (PK) studies of absorption, distribution, metabolism, and excretion were not conducted. Clonal T cell populations were monitored through serial sampling of peripheral blood, establishing a distinct profile of in vivo expansion and persistence for the clones. Prior to lifileucel infusion, tumor-derived T cells clonotypes can be detected in peripheral blood at a mean proportion of 16% which was increased to 83% at Day 4 post-infusion of lifileucel. By Day 14, lifileucel persistence decreased to a mean of 51%, likely reflecting hematologic recovery. By Day 42, and through the last sampling time point of Month 12, the mean relative frequency stabilized around 40% which was higher than the pre-infusion level of 16%.

Overall, the maximum tumor-derived T cells frequency (83%) was observed at Day 4, declined to 51% at Day 14, and remained between 37% and 41% up to month 12 post-infusion of lifileucel; however, it is important to note the high inter-individual variability.

Impact of Intrinsic and Extrinsic Factors on Lifileucel Persistence

The impact of intrinsic (e.g., age, sex, Eastern Cooperative Oncology Group [ECOG] status, lactate dehydrogenase [LDH], target lesion sum of diameters [SOD], PD-L1 tumor proportion score [TPS]) and extrinsic (region, IL-2 dose) factors on lifileucel persistence were retrospectively explored using persistence data at Day 42. The persistence data at Day 42 is selected since it represents data from most subjects, and Day 42 is considered as a day for “stabilized” persistence and a time point for first efficacy assessment.

- No association was observed between Day 42 persistence and age (≥65 versus <65 years old), baseline ECOG performance status (0 versus ≥1), baseline LDH value (≤ upper limit of normal [ULN] versus >ULN), baseline target lesion SOD (<70 mm versus ≥70 mm), and region (U.S. versus Europe).
- A trend for higher persistence of lifileucel for subjects in Cohort 4 with PD-L1 TPS (≥5%, n=18) versus PD-L1(<5%, n=34). However, this was not the case for subjects in Cohort 2 and there was no notable impact of PD-L1 TPS on persistence based on the pooled Cohort 2 & 4 data.
- A trend was observed for sex with male subjects showing higher persistence versus female subjects. The clinical implication of this difference in lifileucel persistence in male versus female is not known.
- A trend was observed for IL-2 doses administered when analyzed in 2 groups: 1 to 4 versus 5 to 6 IL-2 infusions. Patients that received 1 to 4 dose of IL-2 appear to have higher persistence than those who received 5 to 6 doses of IL-2. Most subjects with best overall response data (n=53 out of 85) received 6 infusions of IL-2 in Cohort 4

and pooled Cohort 2 & 4 (n=85 out of 151). Since some subjects did not tolerate 6 infusions of IL-2, they received either 1 to 3 (n=9) or 4 to 5 (n=23) infusions in Cohort 4. The persistence of lifileucel is comparable among subjects that received 1 to 3 versus 4 to 5 versus 6 infusions of IL-2.

Overall, the sub-group analysis of lifileucel persistence for different dosing regimens of IL-2 is viewed as exploratory, considering the higher variability of persistence and small sample size of subjects that received fewer than 6 infusions of IL-2. Based on the current lifileucel persistence data, the Applicant proposed dosing regimen of IL-2 (i.e., up to a maximum of 6 infusions of IL-2 at a dose of 600,000 IU/kg every 8 to 12 hours based on tolerability) is acceptable. We recommend monitoring of safety, efficacy, and persistence in future trial(s) to optimize IL-2 dosing regimen.

Pharmacodynamics:

Longitudinal cytokines and chemokines (IL-15, IL-6, IL-7, IL-9, IL-10, IL-12(p40), CCL2, CXCL10, IFN-γ, and TNF-α) were explored using plasma samples collected at baseline and post-infusion of lifileucel at Day 1, 4, 14, 42, and 84.

- The mean level of IL-15 peaked following lymphodepletion on Day 1 of the lifileucel regimen, decreased over time, and returned to baseline levels by Day 42. These observed kinetics of circulating IL-15 may reflect the lymphodepletion mechanism of action. Mean circulating levels of IL-15 were similar between the responder and non-responder groups.
- The mean IFN-γ level was below baseline post lymphodepletion and lifileucel infusion at Day 1 to 4 and returned to baseline by Day 14. The decrease in IFN-γ observed at Day 1 and Day 4 relative to baseline may also reflect the effect of lymphodepletion, since T cells are the primary source of IFN-γ. The mean IFN-γ levels were similar between responder and non-responder groups.
- The mean CXCL10 level was elevated following lymphodepletion and lifileucel infusion at Day 1 compared to baseline levels and increased further at Day 4 before gradually returning to near baseline levels at Day 84. Mean circulating levels of CXCL10 were similar between the responding and non-responding group.
- Other cytokines and chemokines analyzed did not show any noticeable changes.

Overall, none of the analyzed cytokines and chemokines were able to provide evidence of pharmacodynamic activity of lifileucel that distinguish responding versus non-responding group.

Dose/Exposure-Efficacy:

For pooled Cohorts 2 & 4, the median dose of lifileucel was 20.87 × 10^9 viable cells (min, max: 0.4 × 10^9, 99.5 × 10^9). The wide dose range administered in Study C-144-01 allowed the Applicant and FDA to conduct a retrospective dose-efficacy analysis using DOR and objective response rate (ORR) as efficacy assessment.

- Analysis of 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 BOR in Cohort 4 and a similar trend was observed for Cohort 2.
- Based on pooled analysis of Cohort 2 & 4, the median dose resulting in CR/PR is 30x10^9 cells (range: 6.2 x10^9 to 72 x10^9) and higher probability of CR/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 higher dose. The mean lifileucel persistence was 36 ± 24% and 49 ± 25% for subjects who received lower and higher than the median dose of 30.6x10^9 cells that achieved CR/PR, respectively.

Overall, the CMC, clinical and clinical pharmacology teams discussed the dose range proposed by the Applicant (b) (4) viable cells. Considering the CMC data and dose-response relationship the lifileucel dose should reflect the dose range that show CR/PR in Cohort 4. Accordingly, the FDA recommended lifileucel dose range is 7.5 x10^9 to 72x10^9 viable cells.

5. Clinical Pharmacology Labeling Comments

Section 2.1: Dose

- Requested to update dose range to 7.5x10^9 to 72x10^9 viable cells based on CMC data and clinical data for Cohort 4.

Section 12.1. Mechanism of Action

- Requested to include data supported statement to describe the mechanism of action and avoid speculative claims of untested mechanism of action.

Section 12.2. Pharmacodynamics

- Recommended moving the persistence results to section 12.3.

Section 12.3. Pharmacokinetics

- Requested to summarize the results for lifileucel persistence from Cohort 2 & 4.

6. Comprehensive Clinical Pharmacology Review

6.1. General Pharmacology

AMTAGVI (lifileucel) is a tumor-derived autologous T cell immunotherapy comprised of a suspension of tumor-derived T cells for intravenous infusion. Lifileucel is manufactured from patient tumor tissue removed from one or more tumor lesions by surgical procedure(s). Immune cells derived from a patient's tumor(s) are expanded in cell culture,

washed, formulated as a cell suspension, and cryopreserved. Lifileucel is composed primarily of T cells of the CD4+T and CD8+T cell lineages. Lifileucel may also contain monocytes and other lymphocytes including B cells and NK cells. The specific mechanism of action of lifileucel is unknown.

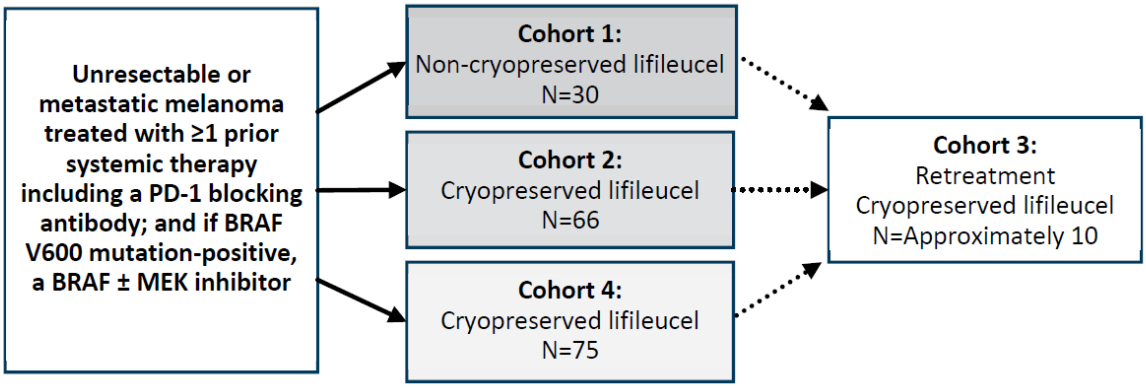
Preparation of the patient with the nonmyeloablative lymphodepletion (NMA-LD) regimen immediately prior to the infusion of lifileucel is proposed to eliminate suppressive influences (e.g., regulatory T cells and cytokine depletion [e.g., IL-15] to provide an optimal milieu supporting the expansion, trafficking, and antitumor cytotoxicity of the transferred lifileucel. The doses of the components of the NMA-LD preparative regimen (i.e., cyclophosphamide 60 mg/kg intravenously [IV] with mesna daily for 2 days followed by fludarabine 25 mg/m^2 IV daily for 5 days) are based on prior published studies in patients with metastatic melanoma. After lifileucel infusion, IL-2 is administered IV at 600,000 IU/kg every 8 to 12 hours for up to a maximum of 6 doses. Hepatic and renal impairment studies were not performed and the lifileucel regimen is not expected to be used in patients with renal or hepatic impairment, given the guidance in the FDA Prescribing Information for cyclophosphamide, fludarabine, and IL-2 for these patient populations. Accordingly, Study C-144-01 required patients to have adequate organ function, which excluded patients with evidence of clinically relevant hepatic and renal impairment.

Reviewer comments: Infusion of IL-2 is believed to support the in vivo persistence of lifileucel, and the dosing regimen justification was supported by efficacy, safety, and persistence data (see pharmacokinetics Section 6.3).

6.2. Study Design

Study C-144-01 is an ongoing Phase 2, prospective, interventional, multicenter study evaluating the efficacy and safety of treatment with lifileucel in adult patients with unresectable or metastatic melanoma who progressed following treatment on at least one systemic therapy, including a PD-1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor or BRAF inhibitor with a MEK inhibitor. The total number of patients that were planned to receive lifileucel in this study was approximately 171. As illustrated in Figure 1, the study includes Cohort 1 to 4 but the clinical pharmacology evaluation for the current submission is based on Cohort 2 & 4 (primary evidence for efficacy is based on Cohort 4). The clinical pharmacology review focuses on pharmacokinetics, pharmacodynamics, and dose-response assessments of pooled results from Cohort 2 & 4. The demographics and other relevant baseline disease characteristics of subjects in the full analysis set (FAS) are provided in Table 1.

Figure 1: **Schematic of Planned Study Cohorts**



Source: Figure 1; Study report C-144-01-14

Table 1: Demographics for Cohort 4, Cohort 2, and Pooled Cohorts 2 & 4 (Full Analysis Set)

Characteristic	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled Cohorts 2 & 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	-	-	-
Mean (SD)	55.4 (11.9)	54.3 (11.5)	54.9 (11.7)
Median	58.0	55.0	56.0
Min, Max	25, 74	20, 79	20, 79
Age, n (%)	-	-	-
<40	9 (10.3)	7 (10.6)	16 (10.5)
≥40 - <65	56 (64.4)	45 (68.2)	101 (66.0)
≥65	22 (25.3)	14 (21.2)	36 (23.5)
Race, n (%)	-	-	-
American Indian or Alaska Native	0	0	0
Asian	1 (1.1)	2 (3.0)	3 (2.0)
Black or African American	2 (2.3)	1 (1.5)	3 (2.0)
White	83 (95.4)	63 (95.5)	146 (95.4)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (1.1)	0	1 (0.7)
Region, n (%)	-	-	-
U.S.	54 (62.1)	55 (83.3)	109 (71.2)
Europe	33 (37.9)	11 (16.7)	44 (28.8)

Source: Table 14.1.5.2.1; Study report C-144-01-14
Abbreviations: SD, standard deviation

6.3. Pharmacokinetics

6.3.1. Lifileucel Expansion and Persistence

In Study C-144-01, clonal T cell populations were monitored through serial sampling of peripheral blood, establishing a distinct profile of in vivo expansion and persistence for the clones. Lifileucel is composed of polyclonal T cells that can be distinguished from one another since each T cell clone expresses a unique T cell receptor (TCR). The TCR is (b) (4)

(b) (4) by which the T cell repertoire of any T cell-containing sample can be defined. A semi-quantitative polymerase chain reaction followed by next generation sequencing was used to define the T cell repertoire of lifileucel and the corresponding pre- and post-infusion peripheral blood mononuclear cell (PBMC) samples in Study C-144-01. However, it is important to note methodological limitations for the PK analysis:

- The most sensitive and accurate method of TCR detection involves (b) (4) (b) (4) For details on the (b) (4) assay, refer to CMC/bioinformatics review.
- The absence of a lifileucel product-specific marker (such as the common transgene shared by chimeric antigen receptor T cells [CAR-T]) prevents the unequivocal identification of circulating product-derived clones, as the same clones may arise endogenously.
- The semi-quantifications involved are not only representative of concentrations (cell number/µL), but also measure the level of TCR expression in each T cell which may vary depending on the cell state.

At each timepoint for Cohort 4, the number of PBMC samples available for analysis varied from 11 (Month12) to 74 (Day 42). The "Enroll" and the "D-7" (Day-7) timepoints were used as a baseline to reflect the native TCR repertoire, prior to infusion. At these early timepoints, an average of 7,071 unique clones were identified (Table 2). The post-infusion timepoints showed lower average unique clone counts, ranging from 774 (Day 0/Day 1) to 4,326 (Month 12) with an average of 2,333 clones, which may attribute to decreased clonal T cell diversity following recovery from lymphopenia in adults. Before lifileucel infusion, the number of clones in common between the circulating blood and the product lot averaged 189 clones and represented 2.67% of the mean number of unique clones present in the Enroll and Day-7 timepoints. These shared clones contributed 11.6% of the total TCR population prior to infusion (calculated by the sum of frequencies of the shared clones). Post-infusion, the average number of shared clones varied from 89 (Day 0/Day 1) to 570 (Day 4) with an average of 257 clones. The shared clones represented as much as 78.6% of the total population at Day 4, and as little as 24.7% at Month 12 (Table 2 & Figure 2). All post-infusion timepoints show a greater average overlap with the lifileucel product lots than the pre-infusion timepoints, supporting that post-infusion shared clones were lifileucel product lot-derived and represented a measure of in vivo persistence. The similarity of the PBMCs to the lifileucel product lot peaks during the Day 4 to Day 14 timepoints, with Day 4 showing an average of 78.6% of the determined TCR repertoires composed of clonotypes also identified in the lifileucel product lots. Lifileucel persistence levels off with an average of 30.8% post Day 14, continuing to show a greater similarity to the product lots than prior to lifileucel infusion. This suggests that the lifileucel product lot can contribute T cell clones to the patient circulation and that the clones persist to Month 12 after treatment (the last timepoint evaluated). The early timepoints correspond to patients before recovery from lymphopenia and the decrease in shared TCR repertoire

after Day 14 may be attributed to immune reconstitution and T cell recovery; it could be seen as a dilution effect due to lymphocyte recovery.

The same trend was observed for subjects in Cohort 2. Based on the data available, similarity of the PBMCs to the lifileucel product lot peaks at Day 4 showing an average of 93% lifileucel clonotypes. Lifileucel persistence levels off with an average of 51% post Day 14, continuing to show a greater similarity to the product lots than prior to lifileucel infusion.

Reviewer comments: Because of the nature of lifileucel, conventional studies on pharmacokinetics (absorption, distribution, metabolism, and excretion) are not applicable. Previous clinical studies via imaging and biopsy analysis demonstrated that autologous tumor infiltrating lymphocytes selectively localize to metastatic tumor sites based on their unique ability to distinguish tumor from normal tissue[4],[5]. The kinetic profile of lifileucel in PBMC samples, as depicted in Figure 2, appear to constitute initial decline between Day 4 and 14, and persistence between Day 42 and Month 12.

The following can be concluded based on combined analysis (Cohort 2 & 4; Table 3, Figure 3, &Figure 4):

- The available samples for in vivo persistence analysis of lifileucel decreased over time (e.g., n=120 at 42 days versus n=34 at 6 months versus n=22 at 12 months)**.**
- Prior to lifileucel infusion, TCR clonotypes can be detected in peripheral blood at a mean proportion of 16% that was increased to 83% at Day 4 (~ maximum time to expansion, Tmax) post-infusion of lifileucel.
- By Day 14, lifileucel persistence decreased to a mean of 51%. By Day 42 and through the last sampling time point of Month 12, the mean relative frequency stabilized around 40% which was higher than the pre-infusion level of 16% (Table 3).
- Overall, the maximum lifileucel frequency (83%) was observed at Day 4, declined to 51% at Day 14, and remained 37 to 41% up to Month 12 post-infusion of lifileucel; however, it is important to note the high inter-individual variability (Figure 3).

[4] Griffith, KD, EJ Read, JA Carrasquillo, CS Carter, JC Yang, B Fisher, P Aebersold, BS Packard, MY Yu, SA Rosenberg, 1989, In Vivo Distribution of Adoptively Transferred Indium-Ill-Labeled Tumor Infiltrating Lymphocytes and Peripheral Blood Lymphocytes in Patients With Metastatic Melanoma, J Natl Cancer Inst, 81(22):1709-17.

[5] Pockaj, BA, RM Sherry, JP Wei, JR Yannelli, CS Carter, SF Leitman, JA Carasquillo, SM Steinberg, SA Rosenberg, JC Yang, 1994, Localization of 111indium-Labeled Tumor Infiltrating Lymphocytes to Tumor in Patients Receiving Adoptive Immunotherapy. Augmentation with cyclophosphamide and correlation with response, Cancer, 73(6):1731-7.

Table 2: Summary of Shared Clones Between the Lifileucel Product Lot and PBMC at Various Timepoints (Cohort 4)

Subject	Enroll	D-7	D0/D1	D4	D14	D42	D84	M6	M9	M12
No. samples	64	17	22	32	64	74	43	22	14	11
Mean No. uCDR3	6805	8074	774	1285	1447	1958	2106	2728	4040	4326
No. samples with shared clones	64	17	22	32	64	74	43	22	14	11
Mean No. uCDR3 shared	178.64	225.76	89.27	570.78	345.25	241.28	210.81	212.14	214.00	175.91
Mean % TCR shared	11.44	12.17	61.69	78.63	47.24	34.09	32.04	35.99	27.19	24.68

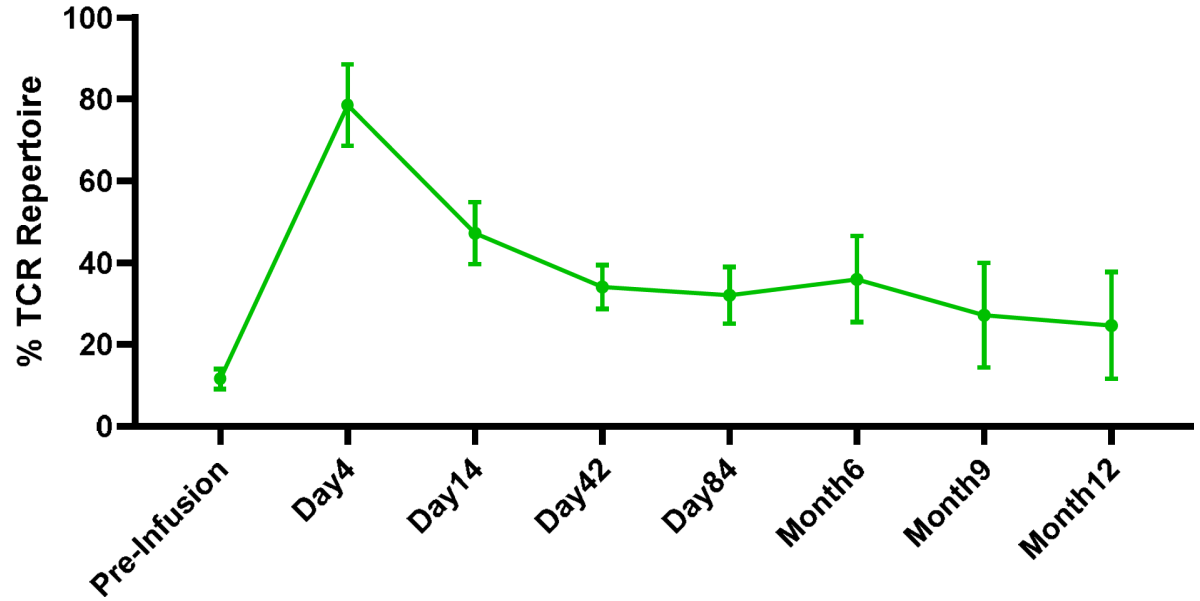
Source: Table 2; rep-0272.
Note: TCR repertoires were established for **lifileucel** product lots and available, corresponding PBMC samples. Number of samples available at each timepoint is indicated in "# samples" row. Mean numbers of uCDR3 clones detected at each timepoint are indicated in "Mean # uCDR3". The number of samples with shared/persisting clonotypes between a timepoint sample and the **lifileucel** product is indicated in "# samples with shared clones". The mean number of shared uCDR3s and the mean of the sums of the frequencies of the shared uCDR3s with the respective product lots are indicated in the last two rows, "Mean # uCDR3 shared" and "Mean % TCR shared".
Abbreviations: PBMC, post-infusion peripheral blood mononuclear cell; TCR, T cell receptor

Table 3: Summary of Shared Clones Between the Lifileucel Product Lot and PBMC at Various Timepoints (Pooled Cohort 2 & 4)

Statistic	Pre-Infusion (n=125)	Day 4 (n=45)	Day 14 (n=96)	Day 42 (n=120)	Day 84 (n=73)	Month 6 (n=34)	Month 9 (n=26)	Month 12 (n=22)
%Mean (SD)	16 (15)	83 (24)	51 (30)	40 (25)	40 (24)	41 (26)	40 (26)	37 (27)

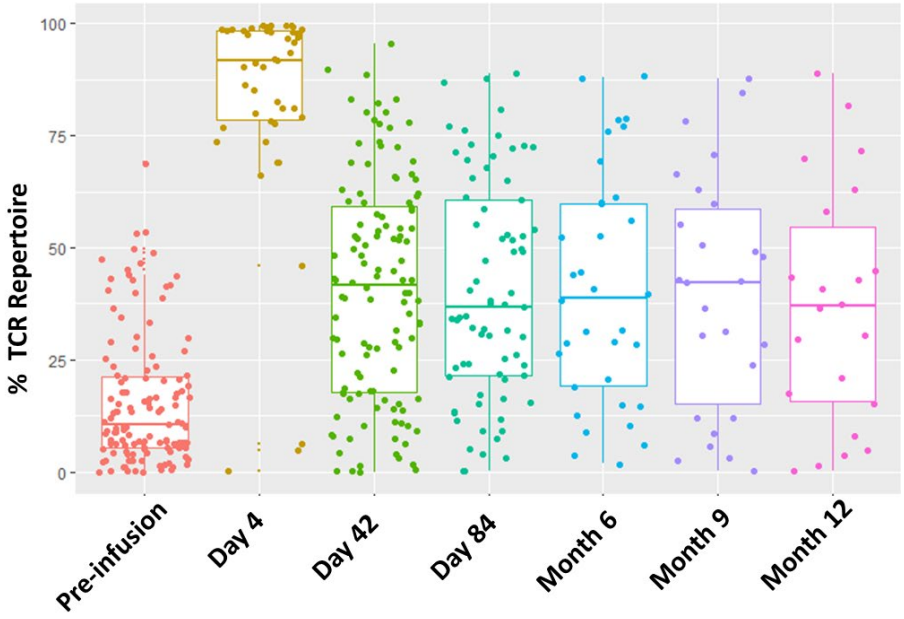
Source: Table 2; Applicant response to clin pharm IR#1
Abbreviations: PBMC, post-infusion peripheral blood mononuclear cell; SD, standard deviation

Figure 2: Mean Shared TCR Repertoire Over Time (Cohort 4)



Source: Figure 4; rep-0272
Note: The mean portion of TCR repertoire, as defined by (b) (4) clonotypes, shared between the individual PBMC timepoint repertoires and the lifileucel product lot, for all samples available with pre- or post-infusion PBMC samples available is shown. The 95% confidence interval is shown with the error bars at each timepoint assessed.
Abbreviations: TCR, T cell receptor

Figure 3: The Shared TCR Clonal Frequencies for Individual Patients Over Time (Cohort 2 & 4)



Source: FDA Reviewer Analysis
Abbreviations: TCR, T cell receptor

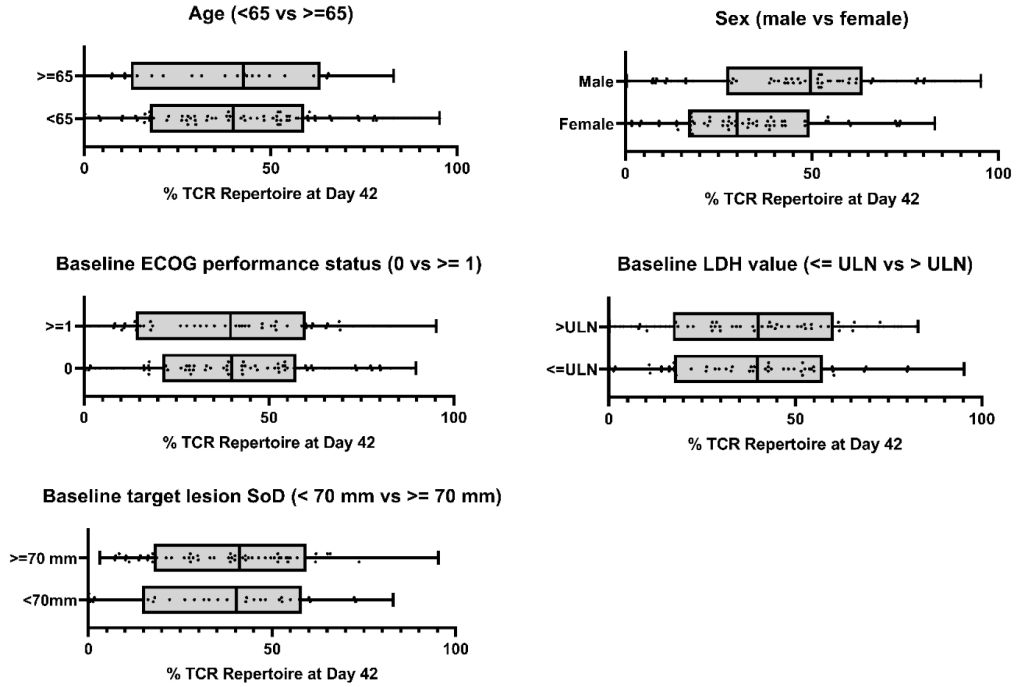
6.3.2. Impact of Intrinsic and Extrinsic Factors on Persistence

The impact of intrinsic (e.g., age, sex, ECOG status, LDH, target lesion SOD, PD-L1 TPS) and extrinsic (region, IL-2 dose) factors on lifileucel persistence was retrospectively explored using persistence data at Day 42. The persistence data at Day 42 was selected since it represents data from most subjects' first efficacy assessment, and Day 42 is considered for "stabilized" lifileucel persistence. The impact of intrinsic and extrinsic factors is displayed in Figure 4, Figure 5, Figure 6, and Figure 7, and is summarized below:

- No association was observed between Day 42 persistence and age (≥65 versus <65 years old), baseline ECOG performance status (0 versus ≥1), baseline LDH value (≤ULN versus >ULN), baseline target lesion SOD (<70 mm versus ≥70 mm), and region (U.S. versus Europe).
- A trend for higher persistence of lifileucel for subjects in Cohort 4 with PD-L1 TPS (≥5%, n=18) versus PD-L1(<5%, n=34) was observed. However, this was not the case for subjects in Cohort 2 and there was no impact of PD-L1 TPS on persistence based on the pooled Cohort 2&4 data.
- A statistically significant difference in lifileucel persistence between males versus females for Cohort 4 and pooled Cohort 2 & 4 was observed. The analysis showed a higher lifileucel persistence in males than females.
- A trend of higher persistence was observed for IL-2 doses administered when analyzed in 2 groups: 1 to 4 versus 5 to 6 infusions. Patients that received 1 to 4 doses of IL-2 appear to have higher persistence than those who received 5 to 6 doses of IL-

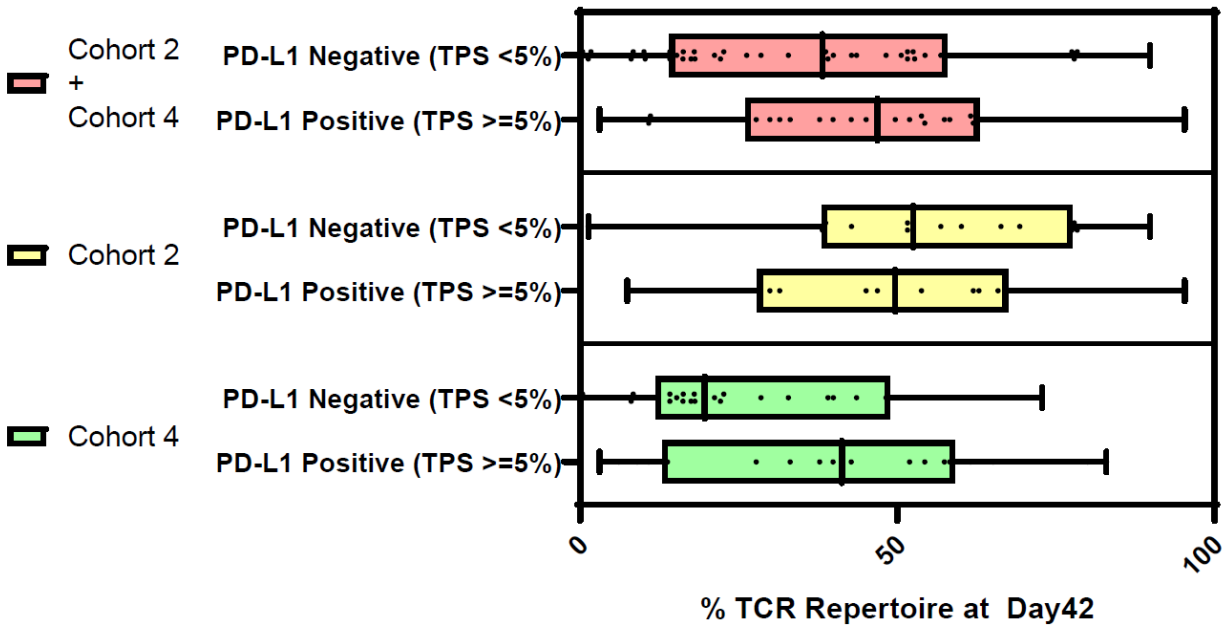
2. No association was observed between Day 42 persistence and number of IL-2 doses administered when analyzed in 3 groups of 1 to 2, 3 to 4, and 5 to 6 doses.

Figure 4: Intrinsic Factors and Lifileucel Persistence (Pooled Cohort 2 and Cohort 4)



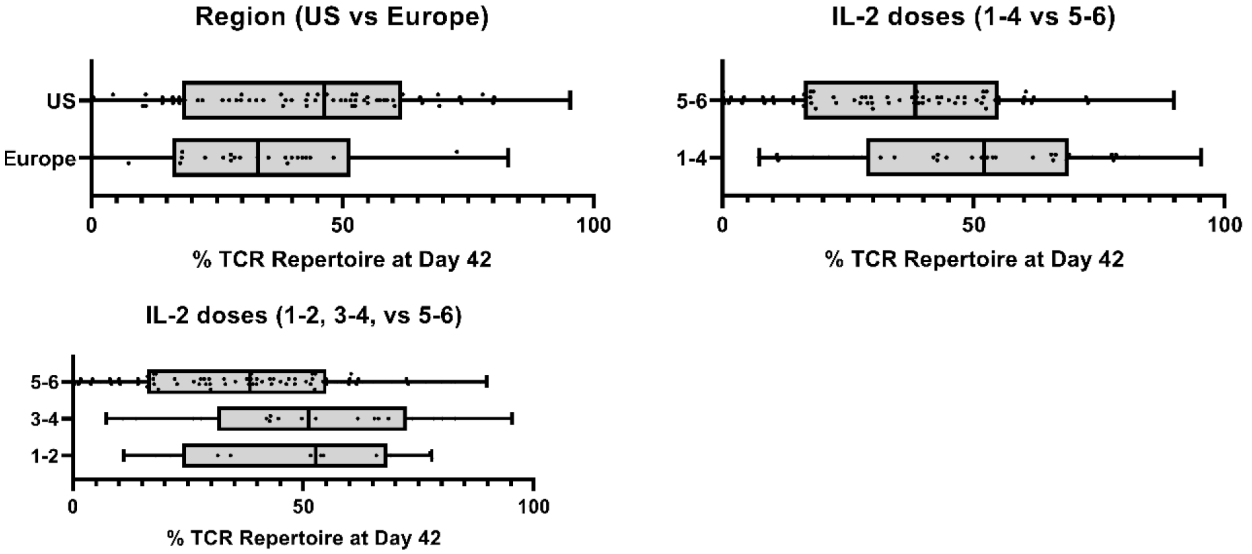
Source: Figure 7; Applicant response to clin pharm IR#1
Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; TCR, T cell receptor; ULN, upper limit of normal

Figure 5: Day 42 Lifileucel Persistence for Patients by PD-L1 TPS



Source: Figure 2; Applicant response to clin pharm IR#2
Abbreviations: TCR, T cell receptor; TPS, tumor proportion score

Figure 6: Extrinsic Factors and Lifileucel Persistence (for Samples in Cohort 2 and Cohort 4)



Source: Figure 8; Applicant response to clin pharm IR#1
Abbreviations: TCR, T cell receptor

<u>Reviewer comments:</u> The clinical implication of higher lifileucel persistence in males versus females is not known. The BOR appears comparable between males and females. For the combined Cohort 2 & 4, subjects that received 1 to 4 infusions of IL-2 appear to have a better persistence as compared to subjects that received 5 to 6 infusions of IL-2. Previous studies have shown a lack of clear correlation between the number of IL-2 infusions and clinical response, and it has been suggested to reconsider the role of high dose of IL-2 infusion in combination with tumor infiltrating lymphocytes[6]. Considering the potential for toxicity of IL-2 and the relatively higher lifileucel persistence in subjects that received up to 4 infusions of IL-2 versus 5 to 6 infusions, we requested additional analysis and justification for IL-2 dosing up to 6 infusions. The results of the additional analysis and the Applicant justification for the dosing regimen of IL-2 are summarized below.

<u>Applicant Justification of IL-2 Dosing Regimen:</u>

It should be noted that up to 6 doses of IL-2 post-lifileucel were planned in Study C-144-01, but the actual number of IL-2 doses administered was based on adverse events (AEs) and tolerability per IL-2 local prescribing information and institutional standards. Thus, the reported dosing groups are not prospectively defined for the purpose of dose-finding but are defined by differences in safety experience after IL-2 dosing, which limits the ability to draw conclusions on dose-safety relationships. The persistence data for lifileucel are presented by number of IL-2 doses (i.e., 1 to 3, 4 to 5, and 6 doses) in <u>Figure 7</u> for Cohort 2, Cohort 4, and the pooled Cohort 2 & 4. No associations were observed between the number of IL-2 doses and lifileucel persistence at Day 42, with overlapping distributions

[6] Rohaan, MW, JH van den Berg, P Kvistborg, JBAG Haanen, 2018, Adoptive transfer of tumor-infiltrating lymphocytes in melanoma: a viable treatment option, J ImmunoTher Cancer, 6(1):102.

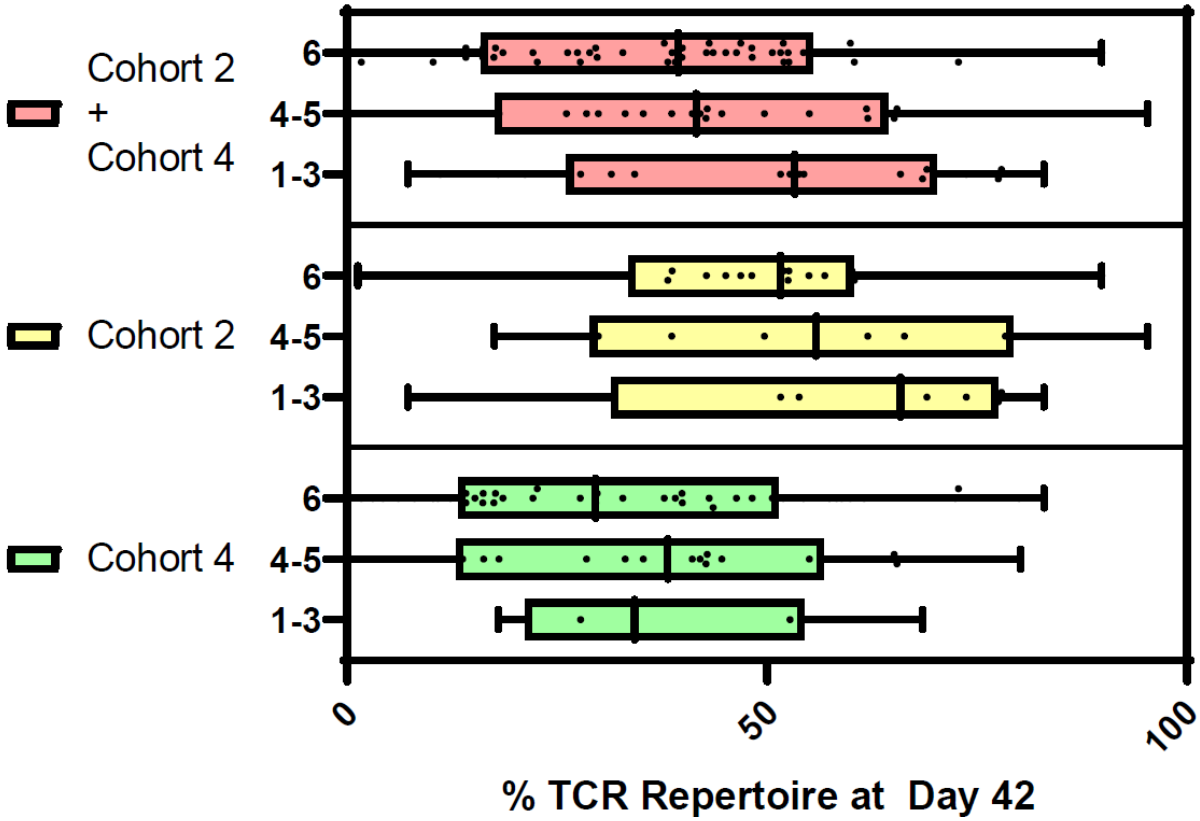
of relative persistence among the different IL-2 dose groups. In the pooled Cohorts 2 & 4 group, clinical response rates were observed across all 3 IL-2 dose subgroups (≥25%) with the highest response rate being observed in the 6 infusions of IL-2 group.

The IL-2 dose and schedule used in Study C-144-01 was selected based upon review of clinical studies in patients with metastatic melanoma. These data suggest that a higher dose or cumulative exposure is not associated with improved clinical benefit. Higher doses of IL-2 may be associated with increased toxicity. Given these findings, to optimize the benefit-risk of IL-2 exposure, with the goal of minimizing toxicity yet providing an exposure that supports the clinical benefit of adoptive cell therapy with lifileucel, the lifileucel regimen includes up to a maximum of 6 doses of IL-2 (at a dose of 600,000 IU/kg every 8 to 12 hours based on tolerability). Safety data from the Study C-144-01 show no meaningful difference in frequency or severity of AEs when comparing subjects who received 1 to 3 doses versus 4 to 5 doses versus 6 doses of IL-2. Taken together, the safety, efficacy, and persistence data presented above do not support changing the targeted number of up to 6 IL-2 doses in the lifileucel regimen. The data do, however, support the management of AEs with discontinuation of IL-2 as needed. The persistence and efficacy data show that, in subjects managed in this manner, there was no obvious loss of benefit associated with the reduced number of administered doses.

Reviewer comments: **Most subjects with best overall response data (n= 53 out of 85) received 6 infusions of IL-2 in Cohort 4 and pooled Cohort 2 & 4 (n=85 out of 151), suggesting that 6 infusion of IL-2 was tolerated. Since some subjects did not tolerate 6 infusions of IL-2, they received either 1 to 3 (n=9) or 4 to 5 (n=23) infusions in Cohort 4. The comparable lifileucel persistence data among the three cohorts of the IL-2 dosing regimen (1 to 3, 4 to 5, and 6 infusions), and a trend for higher lifileucel persistence among those who received 1 to 4 versus 5 to 6 infusions, can provide supportive evidence of clinical benefit for those subjects that don't tolerate up to 6 infusions of IL-2.**

Overall, caution is needed in interpreting the sub-group analysis of lifileucel persistence for different dosing regimens of IL-2 due to the higher variability of persistence and small sample size of subjects that received less than 6 infusions of IL-2. Based on the current lifileucel persistence data, the Applicant-proposed dosing regimen of IL-2 (i.e., up to a maximum of 6 infusions of IL-2 at a dose of 600,000 IU/kg every 8 to 12 hours based on tolerability) is acceptable. We recommend monitoring of safety, efficacy, and lifileucel persistence to determine the optimum IL-2 dosing regimen.

Figure 7: Day 42 Lifileucel Persistence by Number of IL-2 Doses



Source: Figure 1; Applicant response to clin Pharm IR#2
Abbreviations: TCR, T cell receptor; TIL, tumor infiltrating lymphocytes

6.4. Pharmacodynamics

Exploratory longitudinal cytokines and chemokines (IL-15, IL-6, IL-7, IL-9, IL-10, IL-12(p40), CCL2, CXCL10, IFN-γ, and TNF-α) analyses were preformed using plasma samples collected at baseline and post-infusion of TIL at Day 1, 4, 14, 42, and 84. The longitudinal data for all subjects and the data in relation to clinical response status (responder versus non-responder) were analyzed (Figure 8).

IL-15 levels in plasma were measured to evaluate changes during and after administration of the lifileucel regimen. Lymphodepletion prior to adoptive cell transfer of tumor infiltrating lymphocytes has been shown to contribute to persistence of infused cells and duration of response to therapy. This effect is believed to be due to the elimination of cellular “sinks” for homeostatic cytokines such as IL-15. In Study C-144-01, the mean level of IL-15 peaked following lymphodepletion on Day 1 of the lifileucel regimen, decreased over time, and returned to baseline levels by Day 42 (Figure 8). Mean circulating levels of IL-15 were similar between the responder and non-responder groups. The observed kinetics of circulating IL-15 are consistent with the lymphodepletion mechanism of action.

IFN-γ is primarily produced by activated T cells, CD4+ Th1 cells, and CD8+ cytotoxic T cells. IFN-γ functions as a key mediator of immune response by influencing activation and

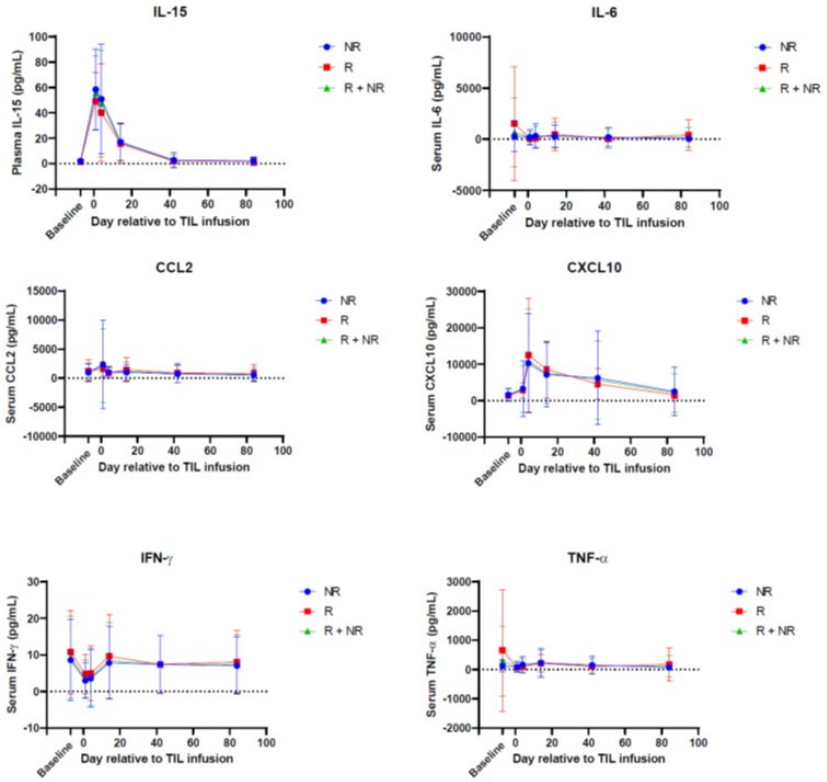
differentiation of T cells and plays a critical role in immune surveillance against tumors. In Study C-144-01, the mean IFN-γ level was below baseline post lymphodepletion and lifileucel infusion at Day 1 and Day 4 and returned to baseline by Day 14 (Figure 8). Mean IFN-γ levels were similar between responder and non-responder groups. The decrease of IFN-γ observed at Day 1 and Day 4 relative to baseline may also reflect the pharmacodynamic effect of lymphodepletion, since T cells are the primary source of IFN-γ.

The chemokine CXCL10, also known as interferon gamma-induced protein (IP-10), is a chemokine that plays a role in recruiting immune cells to the site of inflammation or tumors. In Study C-144-01, the mean CXCL10 level was elevated following lymphodepletion and lifileucel infusion at Day 1 compared to baseline levels and increased further at Day 4 before gradually returning to near baseline levels at Day 84 (Figure 8). Mean circulating levels of CXCL10 were similar between the responding and non-responding groups. Other cytokines and chemokines analyzed did not show any noticeable change.

Reviewer comments: The IL-15 data may provide evidence for the mechanism of action of lymphodepletion prior to lifileucel infusion. The time course of IFN-γ also appear to follow lymphodepletion (a decrease from baseline within 1 to 4 days of lifileucel infusion) and return to baseline levels at Day 14. The return to baseline may be related to pharmacodynamic activity of lifileucel but the IFN-γ level was comparable in responding versus nonresponding groups.

Overall, none of the analyzed cytokines and chemokines were able to provide evidence of pharmacodynamic activity of lifileucel that distinguish the responding from the nonresponding group.

Figure 8: Circulating Cytokine and Chemokine Levels (Cohort 2 & 4)



Source: Figure 6; Applicant response to clin Pharm IR#2
Abbreviations: TIL, tumor infiltrating lymphocytes

6.5. Dose-Response Assessment

6.5.1. Dose-Efficacy

Each dose of lifileucel in Study C-144-01 was to contain between 1 × 10^9 to 150 × 10^9 total viable cells. The proposed labeling of lifileucel recommends (b) (4) viable cells for a single intravenous administration.

For Cohort 4, the median dose of lifileucel was 20.5 × 10^9 viable cells (min, max: 1.3 × 10^9, 72 × 10^9; Table 3), which fell within the manufacturing product specifications. All but 3 subjects (96.6%) received the entire planned lifileucel infusion, with a median relative infusion of 100.00% (min, max: 66.7%,100%).

For Cohort 2, the median dose of lifileucel was 23.28 × 10^9 viable cells (min, max: 0.4 × 10^9, 99.5 × 10^9, Table 3) and 88.1% of the subjects received the entire planned lifileucel infusion, with a median relative infusion of 100.00% (min, max: 3.5%, 100%). For pooled Cohorts 2 & 4, the median dose of lifileucel was 20.87 × 10^9 viable cells (min, max: 0.4 × 10^9, 99.5 × 10^9).

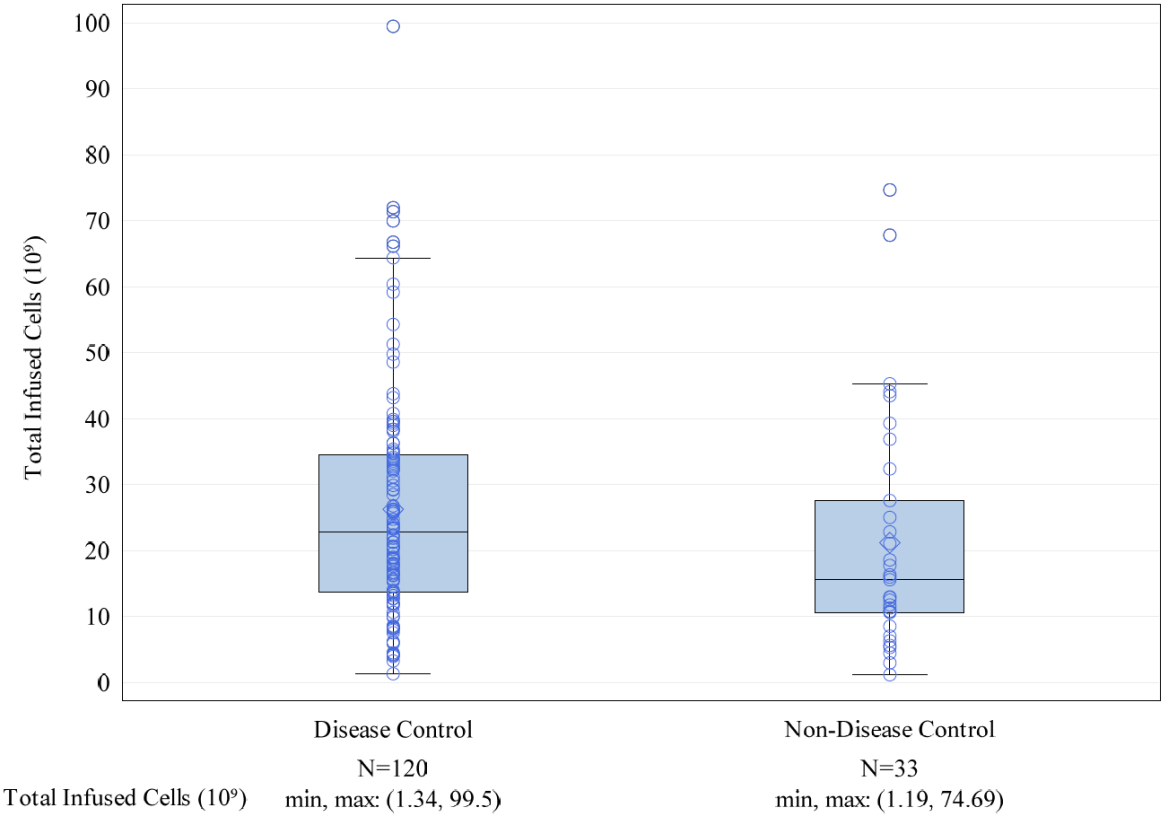
The wide dose range administered in Study C-144-01 allowed for the conduction of a retrospective exploratory dose-efficacy analysis. The Applicant used disease control rate (DCR) for efficacy assessment. The DCR is defined as patients with best overall response

of CR (n=8), PR (n=40), stable disease (SD, n=71), and non-CR/non-PD (NN, n=1). Non-disease control includes progressive disease (PD, n=27) and not evaluable (NE, n=6). For the FAS of pooled Cohorts 2 & 4, the distribution of the lifileucel dose in the disease control (N=120) and non-disease control (N=33) groups was largely overlapping (Figure 9).

Reviewer comments: Per FDA clinical pharmacology information request, the Applicant conducted a further dose-efficacy analysis using the ORR and DOR. Results from the dose-efficacy analysis based on DOR (categorized as ≥12 months or <12 months) is shown in Table 4. The following is a summary of the dose-efficacy assessment:

- **There was no association between DOR and total infused dose (Table 4).**
- **The dose-response analysis showed a weak positive trend with BOR in Cohort 4, and a similar trend was observed for Cohort 2 (Table 5 and Figure 10).**
- **For Cohort 4, the dose range resulting in CR/PR was 7.56x10^9 to 72x10^9 cells (Table 5).**
- **A significant but weak positive correlation between dose and efficacy was observed for pooled Cohort 2 & 4 (Figure 11).**
- **Based on pooled analysis of Cohort 2 & 4, the median dose resulting in CR/PR is 30x10^9 cells (range: 6.2 x10^9 to 72 x10^9)and higher probability of CR/PR is predicted with a higher dose (Figure 11). However, it should be noted that some subjects that received higher than the median dose were also nonresponders (Figure 11).**
- **The CMC, clinical, and clinical pharmacology team discussed the dose range proposed by the Applicant (b) (4) viable cells). Considering the CMC data and dose-response relationship, the lifileucel dose should reflect the dose range that show CR/PR in Cohort 4. Accordingly, the team recommends a dose range of 7.5 x10^9 to 72x10^9 viable cells.**

Figure 9: Box Plot of Total Infused Cells by Disease Control by IRC per RECIST v1.1 Pooled Cohorts 2 & 4 (Full Analysis Set)



Source: Figure 14.2.7; Study report C-144-01-14-tables-figures
Abbreviations; IRC, Independent Review Committee

Table 4: Summary Statistics for Total Infused Cells Grouped by Duration of Response

DOR	N	Mean	STDEV	Min	Median	Max
Cohort 2 Total infused cells (10^9)	-	-	-	-	-	-
≥ 12months	15	33.86	16.01	11.91	32.40	71.40
< 12months	8	27.35	12.48	6.16	28.74	43.80
Cohort 4 Total infused cells (10^9)	-	-	-	-	-	-
≥ 12months	11	33.11	20.97	7.56	29.3	72.00
< 12months	14	28.75	13.46	12.07	28.7	64.4
Pooled Cohort 2 & 4 Total infused cells (10^9)	-	-	-	-	-	-
≥ 12months	26	33.54	17.88	7.56	30.85	72.00
< 12months	22	28.24	12.83	6.16	28.70	64.40

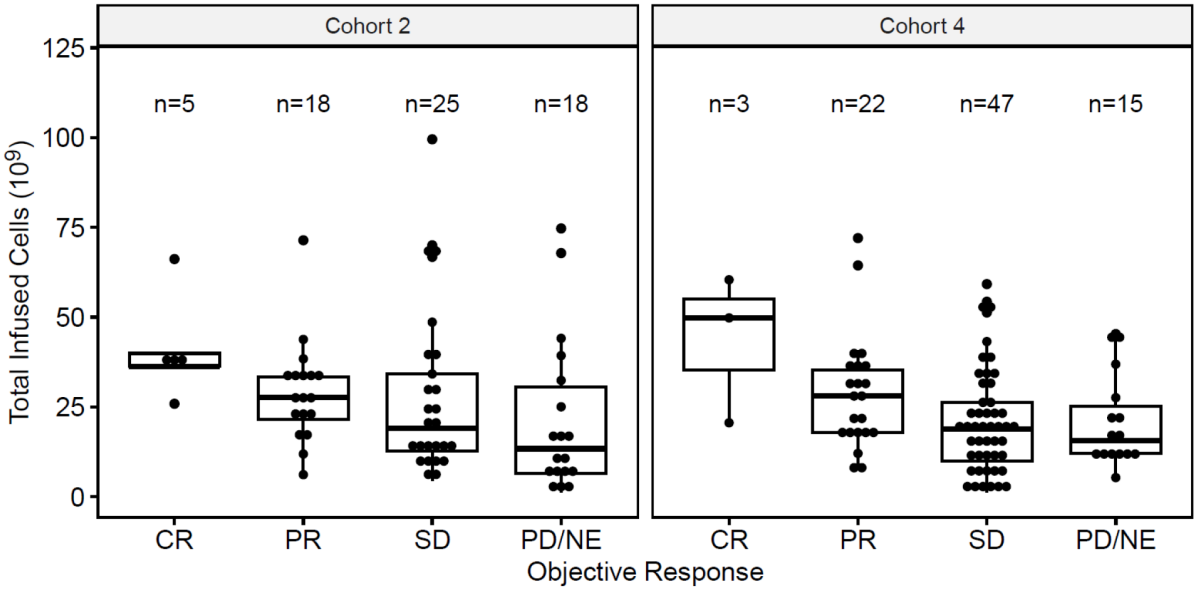
Source: Table 4; Applicant response to clin pharm IR#1
Abbreviations: DOR, duration of response

Table 5: Summary Statistics for Total Infused Cells Grouped by Response

BOR	N	Mean	STDEV	Median	Min	Max
Cohort 2 Total infused cells (10^9)	-	-	-	-	-	-
CR	5	40.91	15.06	36.30	25.89	66.16
PR	18	29.01	14.23	27.64	6.16	71.40
SD	25	27.37	23.02	18.98	4.53	99.50
PD/NE	18	21.73	21.88	13.39	1.19	74.69
Cohort 4 Total infused cells (10^9)	-	-	-	-	-	-
CR	3	43.60	20.61	49.8	20.60	60.40
PR	22	28.90	16.11	28.05	7.56	72.00
SD	47	20.75	13.85	18.8	1.34	59.20
PD/NE	15	20.60	12.42	15.60	5.34	45.30

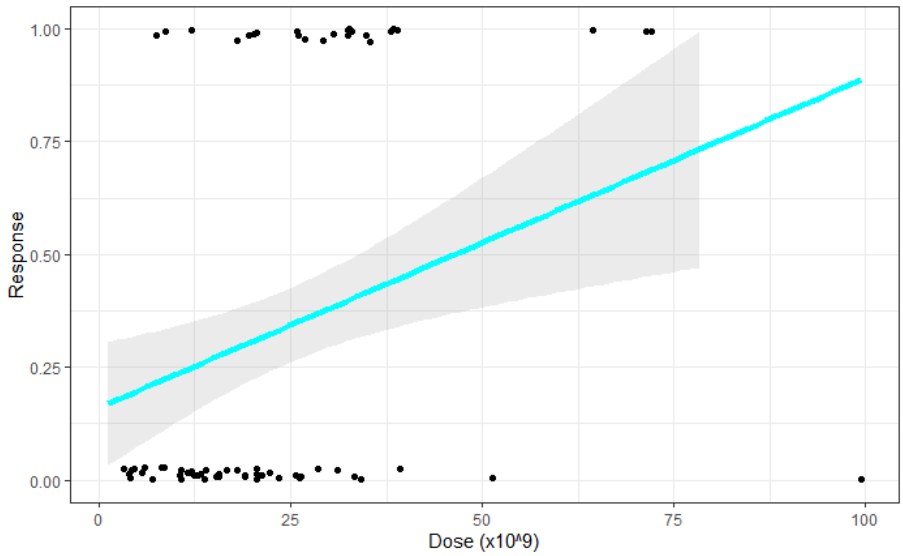
Source: Table 3; Applicant response to clin pharm IR#1
Abbreviations: BOR, best overall response; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; STDEV, standard deviation

Figure 10: Association Between Best Overall Response and Total Infused Cells



Source: Figure 9; Applicant response to clin pharm IR#1
Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; STDEV, standard deviation

Figure 11: Regression Analysis Between Response and Total Infused Cells (Cohort 2 & 4)



Source: FDA Reviewer analysis
Note: Objective response refers to patients with best overall response of CR and PR. The solid circles represent the observed data (CR/PR coded as "1" and all other response coded as "0"). The solid line represents dose-response relationship (p=0.005, odd ratio=1.03), and shaded region show 95% CI.

6.5.2. Dose-Exposure and Exposure-Efficacy

For dose-exposure assessment, the persistence data at Day 42 is selected as the exposure parameter (see pharmacokinetics Section 6.3). Statistical analysis results of the dose-persistence relationship are presented in Table 6. The linear regression Model 1 showed significant association between lifileucel persistence and the infused dose for Cohort 4 and the pooled Cohorts 2 & 4, but the association was not observed in Cohort 2. Model 2 included IL-2 dose group (1 to 3, 4 to 5, or 6 infusions) as an additional factor in the linear regression model. Compared to Model 1, Model 2 did not have meaningful improvement in terms of R^2.

The relationship between exposure (i.e., persistence) and efficacy was visually explored using pooled data from Cohort 2 & 4 (Figure 12) and no relationship between persistence and efficacy was identified.

Table 6: Statistical Analysis Results of Lifileucel Dose Versus Day 42 Persistence Relationship With or Without Factor of IL-2 Dose Group

	Cohort 4 (N=74)			Cohort 2 (N=46)			Pooled Cohorts 2&4 (N=120)		
Parameter	**Parameter Estimate**	**p-value**	**R square**	**Parameter Estimate**	**p-value**	**R square**	**Parameter Estimate**	**p-value**	**R square**
Linear Regression Model 1[a]									
Total infused cells (10^9)	0.551	0.0016	0.1307	0.010	0.9525	0.0001	0.319	0.0118	0.0525
Linear Regression Model 2[b]									
Total infused cells (10^9)	0.544	0.0025	0.1333	0.036	0.8388	0.0240	0.321	0.0112	0.0784
Number of IL-2 doses	-	0.8978	-	-	0.6014	-		0.2004	-
1-3 vs 6	4.162	-	-	7.662	-	-	11.475	-	-
4-5 vs 6	0.276	-	-	7.243	-	-	3.110	-	-

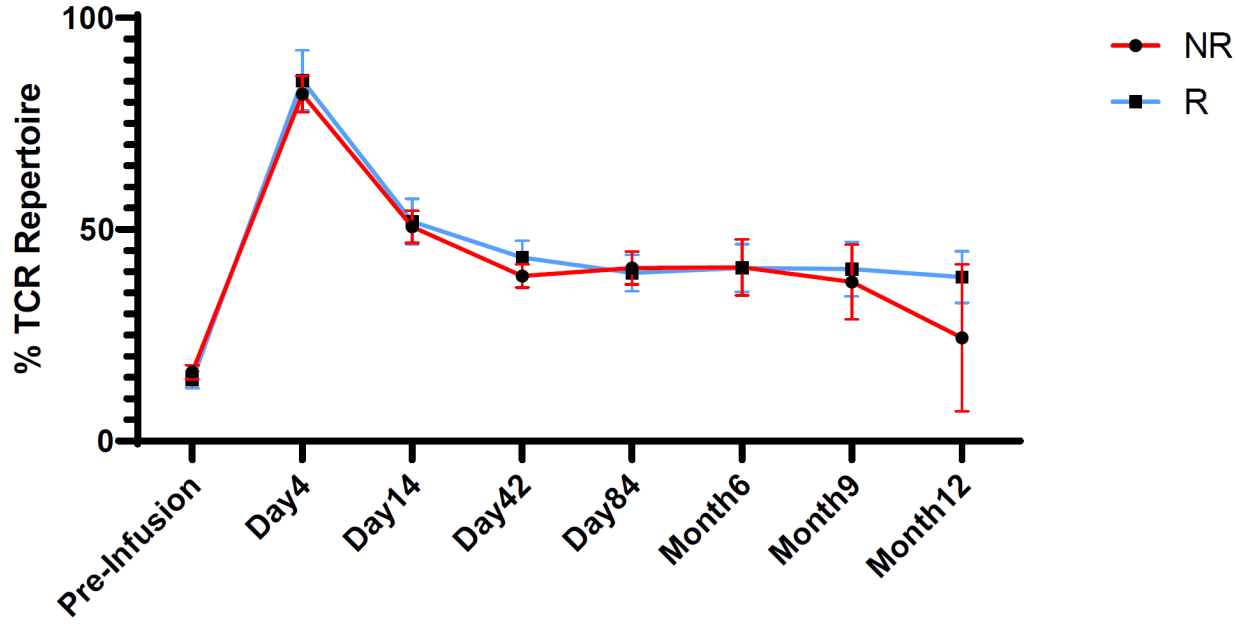
Source: Table 4; Applicant response to clin pharm IR#2

[a] Linear Regression Model 1 refers to Day42 % TCR Repertoire ~ Total infused cells (10^9)

[b] Linear Regression Model 2:refers to Day42 % TCR Repertoire ~ Total infused cells (10^9) + IL-2 group (1-3 vs 4-5 vs 6)

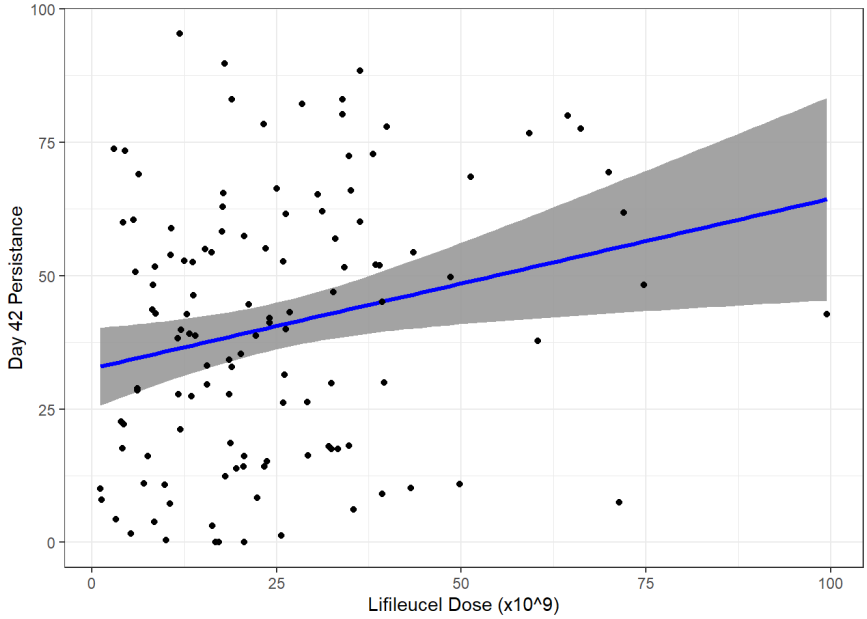
Reviewer comments: Consistent with the Applicant's analysis, FDA dose-exposure analysis showed a weak positive trend for increased persistence with increasing the infused dose of lifileucel (Figure 13). The mean lifileucel persistence was 36 ± 24% and 49 ± 25% for subjects who received lower and higher than the median lifileucel dose of 30x10^9 cells that achieved CR/PR, respectively (Figure 14). Also, subjects that received below the minimum recommended dose of 7.5 x10^9 cells had lower mean persistence (24 ± 20, n=9) as compared to the persistence of subjects (35 ± 23, n=65) that received >7.5 x10^9 cells.

Figure 12: Mean Lifileucel Persistence by Response (Pooled Cohort 2 & 4)



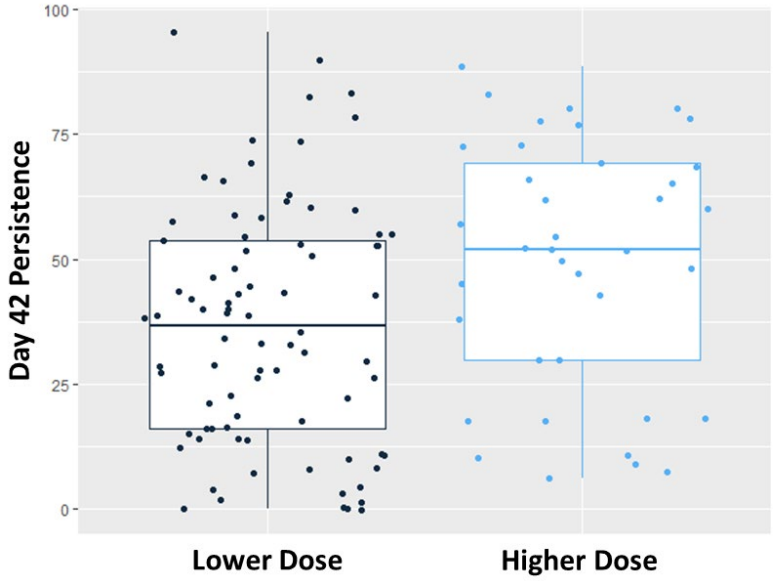
Source: Figure 6; Applicant response to clin pharm IR#1
Abbreviations: NR, non-responding; R: responding; TCR, T cell receptor

Figure 13: Summary of Exploratory Dose-Exposure Assessment (Cohort 2 & 4)



Source: FDA Reviewer analysis.
Note: Blue solid line represents the fit to linear regression and shaded region showing 95% confidence interval. Black circles represent the observed data.

Figure 14: Summary of Lifileucel Persistence in Subjects who Received Lower and Higher Than Median Dose of 30x10^9 Lifileucel (Cohort 2 & 4)



Source: FDA Reviewer analysis

7. Appendix

7.1. Study C-144-01

Title: A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-144; Lifileucel) for Treatment of Patients with Metastatic Melanoma
Objectives: The primary objective of the study is to evaluate the efficacy of lifileucel in patients with unresectable or metastatic melanoma using the objective response rate (ORR), as assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). The secondary objective of the study includes to evaluate: • Efficacy of lifileucel using duration of response (DOR), disease control rate (DCR), overall survival (OS), and progression-free survival (PFS), as assessed by the IRC per RECIST v1.1 • Efficacy by assessing ORR, DOR, DCR, and PFS, as assessed by the Investigator per RECIST v1.1 • Safety profile of lifileucel The main clinical pharmacology objective of the study is to determine the in vivo persistence of tumor-infiltrating lymphocytes (TIL) in the blood of patients with advanced melanoma treated with Lifileucel.
Methodology and Study Design: This study is an ongoing Phase 2, prospective, interventional, multicenter study evaluating the efficacy and safety of lifileucel in adult patients with unresectable or metastatic melanoma who progressed following treatment on at least 1 systemic therapy, including a programmed cell death protein-1 (PD-1) blocking antibody and, if proto-oncogene B-Raf (BRAF) V600 mutation positive, a BRAF inhibitor or BRAF inhibitor with mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor. Eligible patients had their tumor(s) harvested for the manufacture of lifileucel. Subsequently, the Treatment Period began with the preparative nonmyeloablative lymphodepletion (NMA-LD) regimen, followed by the lifileucel infusion on Day 0 and post-infusion administration of IL-2. NMA-LD and IL-2 are included in the regimen to support the engraftment, expansion, and activation of the transferred TIL. Patients were first evaluated for efficacy during the Assessment Period, following the end of the Treatment Period, at Week 6 (Day 42), then every 6 weeks until Month 6 (Week 24), and every 3 months (12 weeks) starting from Month 6 up to 5 years from Day 0 or until disease progression or the start of a new anti-cancer 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 anti-cancer therapy information. The study includes 4 cohorts:

- Cohort 1: Patients infused with non-cryopreserved lifileucel product. The non-cryopreserved product is no longer in clinical use.
- Cohort 2: Patients infused with cryopreserved lifileucel product.
- Cohort 3: Patients who were previously treated in Cohort 1, Cohort 2, or Cohort 4, had progressed, and opted to be rescreened and retreated with the lifileucel regimen, using cryopreserved lifileucel product.
- Cohort 4: Patients infused with cryopreserved lifileucel product.

The efficacy and clinical pharmacology evaluation focus on Cohort 2 (n= 67 patients) and Cohort 4 (n=89 patients) which are based on the same manufacturing process to generate cryopreserved lifileucel product.

Study Treatments:

- NMA-LD (Day-7 to Day-1; with treatment duration of 11-12 days):

Cyclophosphamide IV (60 mg/kg × 2 doses) over 2 days with mesna 15 mg/kg over the first 2 hours followed by mesna 3 mg/kg/hour over the remaining 22 hours). Followed by fludarabine IV (25 mg/m2 × 5 doses) over 5 days.

- Lifileucel infusion: After completion of NMA-LD

Lifileucel is a preparation of TIL derived from an individual patient's tumor for patient-directed immunotherapy. Lifileucel is provided as a single dose for infusion containing 1×10^9 to 150×10^9 viable cells suspended in a cryopreservation medium. Patients were to receive the full dose of product that was manufactured.

- IL-2 IV (Day 0 to Day 4): IL-2 dose of 600,000 IU/kg approximately every 8-12 hrs (maximum of 6 doses) with the first dose within 3-24 hrs after the completion of the lifileucel infusion.

Pharmacokinetics/ Evaluation of In vivo Persistence of TIL:

RNA sequencing was used to define the T cell repertoire of lifileucel in PBMC samples collected pre-and post-TIL infusion in patients treated under Cohort 2 and 4. Samples were collected at the following timepoints:

- Pre-infusion: at enrollment (i.e., at time of tumor harvest) and/or Day -7 (i.e., 7 days prior to infusion of lifileucel and prior to start of NMA-LD therapy
- Post-infusion: Days 4, 14, 42,84 and Months 6, 9 and 12.

(b) (4) from TIL product lots and PBMCs by (b) (4) using the (b) (4) according to the manufacturer's protocol (b) (4) (b) (4) (b) (4)

(b) (4)

(b) (4)

(b) (4)

Pharmacodynamics/Evaluation of Cytokines and Chemokines: Plasma samples collected pre-and post-TIL infusion in patients treated under Cohort 2 and 4 were analyzed for cytokines/chemokines (IL-15, IL-6, IL-7, IL-9, IL-10, IL-12(p40), CCL2, CXCL10, IFN-γ, and TNF-α). Samples were collected at baseline, Days 1, 4, 14, 42 and 84.