Indirect Comparison of Overall Survival (OS) between Lifileucel versus Standard-of-Care (SoC) in US Real-World (RW) Settings in Anti–PD-1–Resistant Advanced Melanoma

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Background

- Patients with anti–PD-1-resistant advanced melanoma have limited treatment options, most of which are associated with poor survival outcomes. Post–PD-1 advanced melanoma management often includes rechallenge with anti–PD-1-based therapy, influenced by prior treatment history, local treatment guidelines, and reimbursement policies.[1-4]
- Lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) therapy, was evaluated in the global, multicohort, single-arm C-144-01 study (NCT02360579) in adults with advanced melanoma previously treated with ≥1 systemic regimen containing a PD-1–blocking antibody and, for those with V600–positive disease, a BRAF± MEK inhibitor.[5-7]
- Durable response and survival outcomes demonstrated in C-144-01 supported regulatory authorization of lifileucel for treatment of anti–PD-1-resistant advanced melanoma in the U.S., Canada, and Australia.[8]
- The single-arm design of C-144-01 requires indirect comparison for the assessment of comparative survival benefit of lifileucel[9]. Evidence versus contemporary SoC used prior to lifileucel availability, including anti–PD-1-based therapies and BRAF± MEK inhibitors, has not been well characterized.

Objectives

- To compare OS with lifileucel versus SoC treatments in a US RW cohort of patients with post–PD-1 advanced melanoma, adjusting for differences in baseline prognostic characteristics.
- To assess the impact of baseline prognostic covariate selection, missing data in the RW cohort, and TIL dosing range on adjusted OS outcomes for lifileucel versus RW SoC.

Data Sources & Methods

- **Pinto et al. (2022)** was selected as the source of US RW SoC data following screening of eligible studies identified from meta-analyses of post–PD-1 melanoma treatments, including anti–PD-1 rechallenge. Studies were evaluated based on **sample size, duration of follow-up, representation of contemporary US SoC, and national coverage**.[10-12]
- **The RW cohort (median follow-up: 5.1 months) included 304 patients** with advanced melanoma who progressed after first- or second-line anti–PD-1 therapy and received subsequent systemic treatment, identified from the Flatiron Health Network (>280 cancer clinics and ~800 sites of care).[1]
- Post-PD-1 treatments in the RW cohort included **immunotherapy (50%), BRAF±MEK inhibitors (36%), and other therapies (14%)**; median OS from initiation of subsequent therapy was 7.2 months.
- The indirect OS comparison adjusted for observed differences in baseline distributions of a priori selected covariates between C-144-01 and the RW cohort (**Table 1**).
- Data availability and consistency of definitions across data sources, prognostic relevance, and baseline imbalances guided covariate selection. Covariates were classified as primary or secondary based on prognostic strength, while balancing the covariate set with the C-144-01 FAS sample size.
- Analyses focused on patients infused with lifileucel in C-144-01 (**median follow-up: 57.9 months**) including the **Full Analysis Set (FAS; n=153; 1.2 × 10^9 to 99.5 × 10^9 viable TIL cells)** and **Commercially Compliant Set (CCS; n=106; 7.5 × 10^9–72 × 10^9 viable TIL cells)**. In CCS, patients received lifileucel within the FDA-approved dose and manufactured at commercially approved sites.[13]
- For the indirect comparison, multivariable Cox proportional hazards models were fitted separately to individual patient-level data from FAS and CCS to characterize the associations between baseline covariates and OS. The calibrated Cox models were then used to predict lifileucel OS in a hypothetical target population standardized to the baseline characteristics of the RW cohort.[14-16]
- Comparative outcomes included **OS hazard ratio (HR)** estimated from Cox models, **4-year OS rate, and 4-year restricted mean survival time (RMST)**, enabled by the **maximum follow-up of 50.1 months in the RW cohort**.
- Sensitivity analyses assessed **individual exclusion of primary covariates, addition of secondary covariates, and alternative definitions for selected covariates for FAS**. **Missing values were** proportionally allocated across observed covariate categories in the base case and **assigned to categories favoring SoC in a conservative scenario for both FAS and CCS**.

Table 1. Baseline characteristics considered for adjustment between C-144-01 populations and the RW cohort.

Characteristic	C-144-01 FAS (n = 153)	C-144-01 CCS (n = 106)	Pinto et al. (2022) (n = 304)
Primary covariates			
Age group, years			
<65	76%	77%	45%
≥65	24%	23%	55%
Sex			
Male	54%	57%	65%
Female	46%	43%	35%
ECOG performance status*			
0	55%	53%	40%
≥1	45%	47%	60%
LDH level*			
Normal	46%	47%	58%
Elevated	54%	53%	42%
Brain metastases			
Yes	18%	21%	28%
No	82%	79%	72%
BRAF mutation status*			
Mutated	27%	26%	54%
Wild type	73%	74%	46%
Prior anti–CTLA-4 therapy†			
Yes	82%	87%	21%
No	18%	13%	79%
Primary resistance to prior anti–PD-1 therapy *,††			
Yes	55%	47%	64%
No	45%	53%	36%
Number of prior lines of anti–PD-1 therapy in the metastatic setting			
≤1	43%	52%	100%
>1	57%	48%	0%
Melanoma subtype			
Cutaneous	79%	80%	100%
Other	21%	20%	0%
Secondary covariates			
Disease stage at initial diagnosis			
Stage III/IV	58%	60%	67%
Stage <III	42%	40%	33%
Duration of baseline anti–PD-1 therapy			
<6 months	73%	73%	62%
≥6 months	27%	27%	38%
Number of prior lines of systemic therapy in the metastatic setting			
≤1	22%	23%	75%
>1	78%	77%	25%

Abbreviations: CCS, commercially compliant set; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; SoC, standard of care. **Note:** Missingness in the RW cohort was 23% for ECOG performance status, 21% for LDH, 6% for BRAF status, and 15% for primary anti–PD-1 resistance. Covariates with missing values in the RW cohort are denoted by *. †: Alternative variable: Baseline anti–PD-1 therapy with or without anti–CTLA-4; ††: Alternative definition per 2020 SITC Immunotherapy Resistance Taskforce

Table 2. Summary of adjusted survival outcomes between lifileucel and SoC in the RW Cohort

Outcome	Lifileucel, FAS	Lifileucel, CCS	RW SoC
HR (lifileucel vs SoC) (95% CI)	0.551 (0.375–0.859)	0.532 (0.320–0.946)	—
4-year OS rate, % (95% CI)	27.0 (13.1–42.1)	30.7 (13.6–49.7)	13.3 (8.8–20.2)
4-year RMST, months	22.6	23.6	13.9

Abbreviations: CCS, commercially compliant set; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; OS, overall survival; RMST, restricted mean survival time; SoC, standard of care. 4-year RMST was calculated as the area under the Kaplan–Meier OS curve from time 0 through year 4

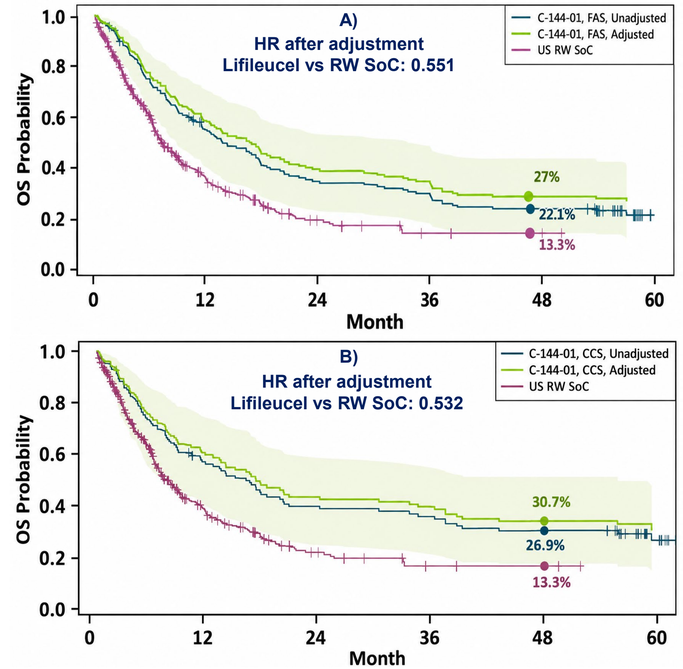
Conclusions

- In the absence of head-to-head data, analyses provide supportive, hypothesis-generating comparative evidence between lifileucel and US RW SoC settings where most patients receive anti–PD-1-based therapies or BRAF±MEK inhibitors following anti–PD-1 failure study.
- Findings fill an important evidence gap by demonstrating lifileucel's potential to address unmet need in anti-PD-1 resistant advanced melanoma, provide insights for treatment selection and inform value-based decision-making.
- Mature survival data and indirect comparisons from additional RW cohorts may broaden generalizability of findings and provide insights into the potential impact of residual confounding from unmeasured covariates.

Results

- **Notable baseline differences were observed between the C-144-01 populations and the RW cohort**, underscoring the need for adjustment (**Table 1**).
- Compared with the RW cohort, both FAS and CCS had higher proportions of patients aged <65 years and with prior anti-CTLA-4 exposure, and lower proportions with BRAF-mutant disease, ≤1 prior metastatic anti-PD-1 therapy, and cutaneous melanoma (**Table 1**).
- Differences across cohorts were less pronounced for sex, ECOG performance status, LDH level, brain metastases, and primary anti–PD-1 resistance (absolute differences: 7%–17%)
- For both FAS and CCS, **lifileucel was estimated to improve OS versus RW SoC** before and after adjustment, with **improvements statistically significant at the 95% confidence level** (**Table 2, Figure 1**).
- Following adjustment, **lifileucel was estimated to increase 4-year OS rates** by an absolute **13.7% and 17.4%,** and **4-year RMST by 8.7 and 9.7 months versus RW SoC** for FAS and CCS, respectively (**Table 2**).
- **For FAS, exclusion of LDH and prior anti–CTLA-4 exposure had the greatest impact on adjusted HRs (0.611 and 0.658, respectively)**; **HRs ranged from 0.522–0.590** with exclusion of other primary covariates and **0.501–0.665** with individual addition of secondary covariates or use of alternative variable definitions. **Improvements remained statistically significant across all sensitivity analyses.**
- **In the conservative scenario, adjusted comparisons continued to favor lifileucel versus RW SoC in both FAS and CCS**, with only modest changes from the base-case treatment effects (**HRs: 0.597 and 0.589, respectively**).

Figure 1. Comparison of unadjusted and adjusted Kaplan-Meier OS curves for lifileucel versus RW SoC. A) C-144-01 FAS, B) C-144-01 CCS



*Shaded areas represent the 95% confidence band for the adjusted Kaplan-Meier OS curves

Discussion

- **Lifileucel was estimated to significantly improve OS versus RW SoC**, with consistent findings across a broad range of sensitivity and scenario analyses supporting the robustness of the results.
- **Population adjustment improved lifileucel's comparative OS versus RW SoC in both FAS and CCS**, with adjusted OS curves exceeding unadjusted estimates, highlighting potential bias from baseline imbalances in naïve comparisons.
- The RW comparator comprised a heterogeneous mix of treatments following anti–PD-1 failure; therefore, **findings reflect lifileucel's comparative survival benefit versus the overall RW SoC mix rather than any individual treatment**.
- **Comparative OS analyses of lifileucel versus anti–PD-1 rechallenge or BRAF±MEK inhibitor subgroups within the RW cohort were not feasible** because subgroup-specific baseline characteristics were not reported, despite the availability of subgroup OS Kaplan–Meier curves.
- As the **RW cohort captures treatment patterns only through March 2019**, its survival outcomes may not be representative of patients receiving newer prior and post–anti–PD-1 therapies in the evolving advanced melanoma treatment landscape.

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