Evaluating Long-Term Overall Survival (OS) Potential of Lifileucel versus Standard-of-Care (SoC) for Anti-PD-1 Advanced Resistant Melanoma in US Real-World (RW) Settings

James Smithy[1], Barbara Ma[2], Josh Wang[3], Brian Gastman[3], Murat Kurt[3]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Weill Cornell Medicine, New York, NY, USA; [3]Iovance Biotherapeutics, Philadelphia, PA, USA

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Background

- Patients with anti–PD-1–resistant advanced melanoma have limited treatment options. Lifileucel—a one-time, autologous, tumor-infiltrating lymphocyte (TIL) therapy—was evaluated in the global, single-arm C-144-01 study (NCT02360579). The trial was pivotal in supporting regulatory authorization of lifileucel in the US, Canada, and Australia, based on the durable responses observed.[1-5]
- Pinto et al. (2022) evaluated survival in a US RW cohort of patients with anti–PD-1–resistant advanced melanoma receiving contemporary SoC treatments before availability of lifileucel (immunotherapy, 50%; BRAF±MEK inhibitors, 36%; other therapies, 14%).[6] Data were obtained from the Flatiron Health Advanced Melanoma Core Registry.
- A previously published indirect treatment comparison (ITC) of OS between lifileucel and this RW cohort,[7] adjusting for baseline differences, favored lifileucel over this mix of SoC treatments. While curative potential and long-term survival profile of lifileucel have been previously explored,[8] comparative long-term survival and life-year (LY) gains versus SoC have not been well characterized.

Objectives

- **Primary objective:** To compare projected long-term survival outcomes of lifileucel versus RW SoC and characterize how OS improvements estimated from the prior ITC translate into long-term survival benefits.
- **Secondary objective:** To assess the impact of missing key baseline covariates in the RW SoC cohort and alternative excess mortality assumptions for long-term survivors (LTS) on the projected long-term survival benefit of lifileucel versus RW SoC.

Data Sources & Methods

- Given maturity of C-144-01 and RW survival data (median and maximum follow-up: 57.8 and 50.1 months, respectively), a piecewise approach maximized the use of adjusted Kaplan-Meier estimates, with long-term OS extrapolated beyond observed follow-up using conditional survival probabilities.[9,10]
- For RW SoC, conditional survival probabilities for extrapolation were derived from the best-fitting survival model to the data[11] accounting for the observed survival plateau and presence of LTS.
- The proportion of LTS and OS among non-LTS in the RW cohort were jointly estimated using mixture-cure models (MCMs).[12] LTS were assumed to follow age- and sex-adjusted US general population mortality (standardized mortality ratio [SMR]=1); sensitivity analysis applied an SMR of 1.57, representing 57% higher mortality than the general population.[13]
- Indirect comparison of OS between lifileucel and RW SoC adjusted for differences in key prognostic factors, including age, sex, ECOG performance status (PS), LDH, brain metastases, BRAF status, prior CTLA-4 exposure, PD-1 resistance, melanoma subtype, and prior metastatic PD-1 lines.
- Analyses focused on lifileucel-infused patients in C-144-01:
  - Full Analysis Set (FAS, n=153): 1.2–99.5 × 10^9 viable TIL cells.
  - Commercially Compliant Set (CCS, n=106): FDA-approved dose range (7.5 × 10^9 – 72 × 10^9 viable TIL cells), manufactured at commercially approved sites.[14]
- The RW SoC data had missingness in key baseline covariates, ranging from 6%–23% (ECOG PS: 23%; LDH level: 21%; BRAF-status: 6%; prior anti–PD-1 resistance: 15%).

Table 1: Adjusted OS HRs for lifileucel vs RW SoC from the ITC

Population	Base Case	Conservative Case
FAS	0.551	0.597
CCS	0.532	0.589

- In the ITC, missing values were proportionally allocated across observed categories in the base case and assigned to categories favoring SoC in sensitivity analysis. For example, missing ECOG PS values were assumed >0, resulting in lifileucel outcomes being predicted for a relatively less healthy population in the ITC.
- For lifileucel, survival through available follow-up was derived from the previously published ITC of OS with RW SoC. Beyond observed follow-up, estimated HRs (**Table 1**) were applied to SoC conditional survival probabilities derived from MCMs to project long-term OS.

Conclusions & Limitations

- Findings demonstrate the projected long-term life-extending benefit of lifileucel versus SoC in a nationally representative RW cohort following anti–PD-1 failure, supporting clinical and health economic decision-making and value-based payer discussions in practice.
- Given the frequent use of anti–PD-1 rechallenge in the RW SoC cohort (50%), findings provide insights into lifileucel's projected long-term survival benefit in settings where rechallenge is common.
- Differences in patient characteristics and treatment patterns across RW populations may yield different projected long-term survival gains with lifileucel, limiting generalizability.
- Pinto et al. (2022) was selected as the RW SoC comparator for its large sample (n=304), extended follow-up and OS Kaplan-Meier curve, national representativeness, and frequent anti–PD-1 rechallenge. Mature survival data from additional RW cohorts could further strengthen these findings.
- Survival projections assume a constant treatment effect for lifileucel versus RW SoC over time, representing a key limitation of the analysis.

Results

Figure 1: Long-term OS projections for lifileucel versus RW SoC (SMR=1): (A) base-case; (B) conservative case

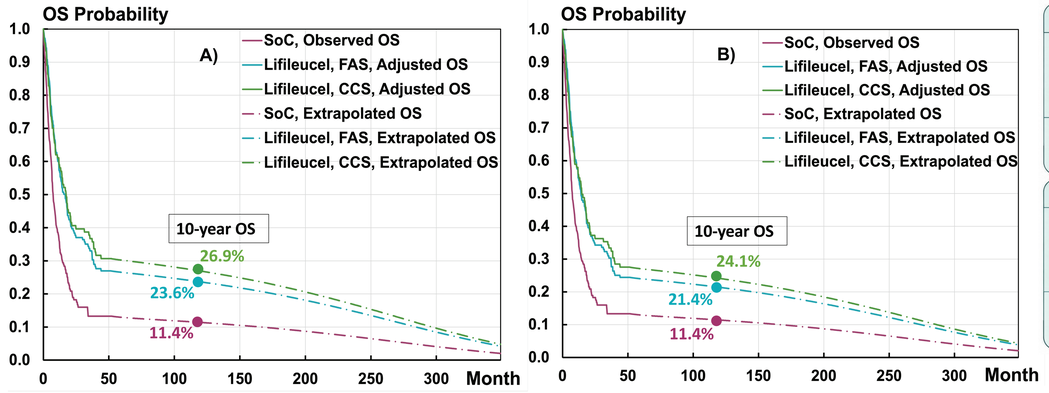
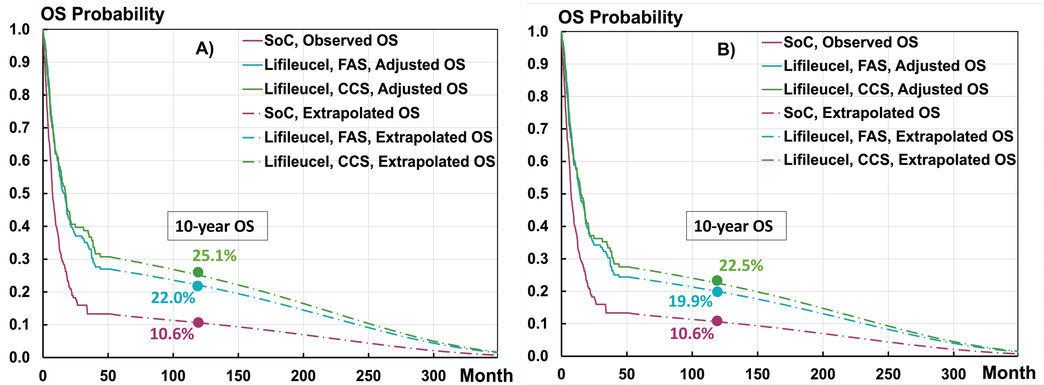


Figure 2: Long-term OS projections for lifileucel versus RW SoC (SMR=1.57): (A) base-case; (B) conservative case



- Across clinically plausible models capturing observed survival plateau and underlying hazard trend in the RW SoC arm, estimated fractions of LTS ranged from 12.8%–13.5% with SMR=1 and 13.1%–13.9% with SMR=1.57.
- Lifileucel was associated with substantial long-term survival gains versus RW SoC. In both FAS and CCS populations, projected 5- and 10-year OS rates were more than doubled compared with the RW cohort (**Table 2**).
- Mean LY gains with lifileucel versus RW SoC increased with longer time horizons: from 0.86 years at 5 years to 3.01 years over a lifetime for FAS (conservative: 0.74–2.49 years) and from 0.98 to 3.71 years for CCS (conservative: 0.78–3.06 years).
- Across time horizons and scenarios, estimated long-term LY gains and improvements in OS rates were consistently greater for CCS than FAS (**Tables 2, 3**).
- Projected long-term OS benefits with lifileucel were only modestly affected by alternative assumptions regarding missing covariates in the RW SoC cohort and the survival of LTS, supporting the stability of findings (**Tables 2, 3**).

Table 2: Mean OS and OS rate projections (SMR=1)

Measure	Base Case	RW SoC	Lifileucel (CCS)	Lifileucel (FAS)
Mean OS (years)	5 years	1.31	2.29	2.17
	10 years	1.91	3.72	3.43
	Lifetime	3.32	7.03	6.33
OS Rate (%)	5 years	12.9	30.2	26.5
	10 years	11.4	26.9	23.6

Measure	Conservative Case	RW SoC	Lifileucel (CCS)	Lifileucel (FAS)
Mean OS (years)	5 years	1.31	2.13	2.05
	10 years	1.91	3.41	3.18
	Lifetime	3.32	6.38	5.81
OS Rate (%)	5 years	12.9	27.0	24.0
	10 years	11.4	24.1	21.4

Durations shown for mean OS estimates (5 years, 10 years, and lifetime) represent the follow-up horizon. Lifetime horizon = 35.2 years based on mean baseline age of 64.8 in the RW cohort.

Table 3: Mean OS and OS rate projections (SMR=1.57)

Measure	Base Case	RW SoC	Lifileucel (CCS)	Lifileucel (FAS)
Mean OS (years)	5 years	1.31	2.29	2.17
	10 years	1.89	3.67	3.38
	Lifetime	2.92	6.11	5.53
OS Rate (%)	5 years	12.8	30.0	26.4
	10 years	10.6	25.1	22.0

Measure	Conservative Case	RW SoC	Lifileucel (CCS)	Lifileucel (FAS)
Mean OS (years)	5 years	1.31	2.13	2.05
	10 years	1.89	3.37	3.14
	Lifetime	2.92	5.55	5.08
OS Rate (%)	5 years	12.8	26.9	23.9
	10 years	10.6	22.5	19.9

Durations shown for mean OS estimates (5 years, 10 years, and lifetime) represent the follow-up horizon. Lifetime horizon = 35.2 years based on mean baseline age of 64.8 in the RW cohort.

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