

Lifileucel versus ipilimumab in metastatic or unresectable melanoma previously treated with immune checkpoint inhibitors: A simulated treatment comparison approach

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Background and study selection

• Treatment options for advanced (unresectable or metastatic) melanoma patients who are previously treated with immune checkpoint inhibitors are highly limited regardless of their BRAF-mutation status.

• Lifileucel – an autologous tumor-infiltrating lymphocyte cell therapy – showed clinically meaningful and durable survival benefits in the treatment of advanced melanoma after progression on immune checkpoint inhibitors in the C-144-01 trial.¹ C-144-01 (NCT02360579) is a global, Phase II, open-label, multicohort, multicentre, single-arm trial evaluating the efficacy and safety of lifileucel in adult patients with advanced melanoma treated with ≥1 systemic prior therapy containing an anti-PD1 therapy and, if BRAF V600 mutation-positive, a BRAF inhibitor (BRAFi) +/- a MEK inhibitor (MEKi). Based on the results from C-144-01 study, lifileucel is approved by FDA and Health Canada for the treatment of adults in this population.^{2,3}

• Based on published treatment guidelines^{4,5} and clinical expert opinion, for advanced melanoma patients who are previously treated with an anti-PD1 treatment, ipilimumab (IPI) monotherapy can be a viable treatment option depending on their treatment history (i.e. IPI in combination with or without an anti-PD1 therapy) and eligibility for treatment according to their physical fitness, local reimbursement patterns and physician choices. Therefore, IPI can be considered as a relevant comparator to lifileucel for treatment of previously treated advanced melanoma.

• In the absence of head-to-head clinical trial data for lifileucel versus IPI from the C-144-01 study, a systematic literature review was conducted in January 2025 to identify all published clinical evidence to inform an indirect treatment comparison (ITC) of progression-free survival (PFS) and overall survival (OS) for lifileucel versus IPI in patients with previously treated advanced melanoma.

• The systematic literature review identified 32 studies investigating IPI in the population of interest, among which an initial feasibility assessment identified 5 studies published between 2020 and 2022 as suitable candidates for the ITC based on 1) Study sites (including European sites), 2) Prior anti-PD1 treatment, if BRAF V600 mutation-positive, treatment with a BRAFi +/- MEKi, and 3) Availability of Kaplan-Meier curves for PFS and OS

• The most suitable source of data for IPI to inform the ITC was da Silva et al. (2021)⁶, which was a multi-region, multi-center, retrospective, cohort study comparing IPI plus anti-PD1 treatment to IPI. Other candidate studies and reasons for their exclusion from ITC are summarized in **Table 1**.

Table 1. Assessment of IPI studies identified in the systematic literature review for use in the ITC

Publication/Source	Study type	Rationale for exclusion from ITC
Cybulska-Stopa et al. (2020) ⁷	Retrospective RWE study	Patients received only one prior line of therapy. BRAF V600 mutation-positive patients who had not received BRAFi/MEKi were included.
Long et al. (2022), ⁸ KEYNOTE-006, (NCT01866319)	Randomised clinical trial	BRAF V600 mutation-positive patients who had not received BRAFi/MEKi were included. Limited reporting of data on baseline characteristics due to post-hoc nature of the analysis and reporting of PFS outcomes.
Rohaam et al. (2022) ⁹ (NCT02278887)	Randomised clinical trial	Patients were treatment-naïve or received just one prior line of therapy. Limited overlap in patients' key baseline characteristics (particularly ECOG performance status [PS] and lactate dehydrogenase [LDH] levels) when compared with the lifileucel population.
Wilson et al. (2021) ¹⁰	Retrospective RWE study	Small population size (N=11) in the IPI arm and limited reporting of data on baseline characteristics.

Results

• In the base case analysis, STC led to a PFS HR of 0.40 (95% CI: 0.34-0.61) and an OS HR of 0.46 (95% CI: 0.34-0.61) for lifileucel versus IPI. Given the 95% CIs of the estimated HRs from the adjusted analyses are entirely <1, results demonstrate statistically significant improvements in both PFS and OS with lifileucel versus IPI (see **Table 3**).

• **Figure 1** (PFS) and **Figure 2** (OS) present the reported Kaplan-Meier curves for IPI from da Silva et al. (2021), and the Kaplan-Meier curves for lifileucel before and after STC.

• The estimation of adjusted survival distributions for lifileucel was limited to the duration of follow-up for the IPI study cohort, which was shorter than the duration of follow-up in the lifileucel study cohort. In addition, in the STC, prediction of survival probabilities were based on the time interval including uncensored events in the lifileucel arm. Therefore, adjusted PFS and OS curves for lifileucel were projected up to ~44 months which approximately corresponds to the timing of last uncensored event in the corresponding data sets.

• Results of the STC were in line with clinical expert opinion sought in an advisory board prior to the conduct of the analyses. Due to differences in mechanisms of actions of lifileucel and IPI, after balancing out the differences between the two study cohorts, consulted clinical experts expected significantly longer survival and time to progression with lifileucel, when compared to IPI

Figure 1. Adjusted and unadjusted Kaplan-Meier curves of PFS for lifileucel versus Kaplan-Meier curve of PFS for IPI, base case analysis

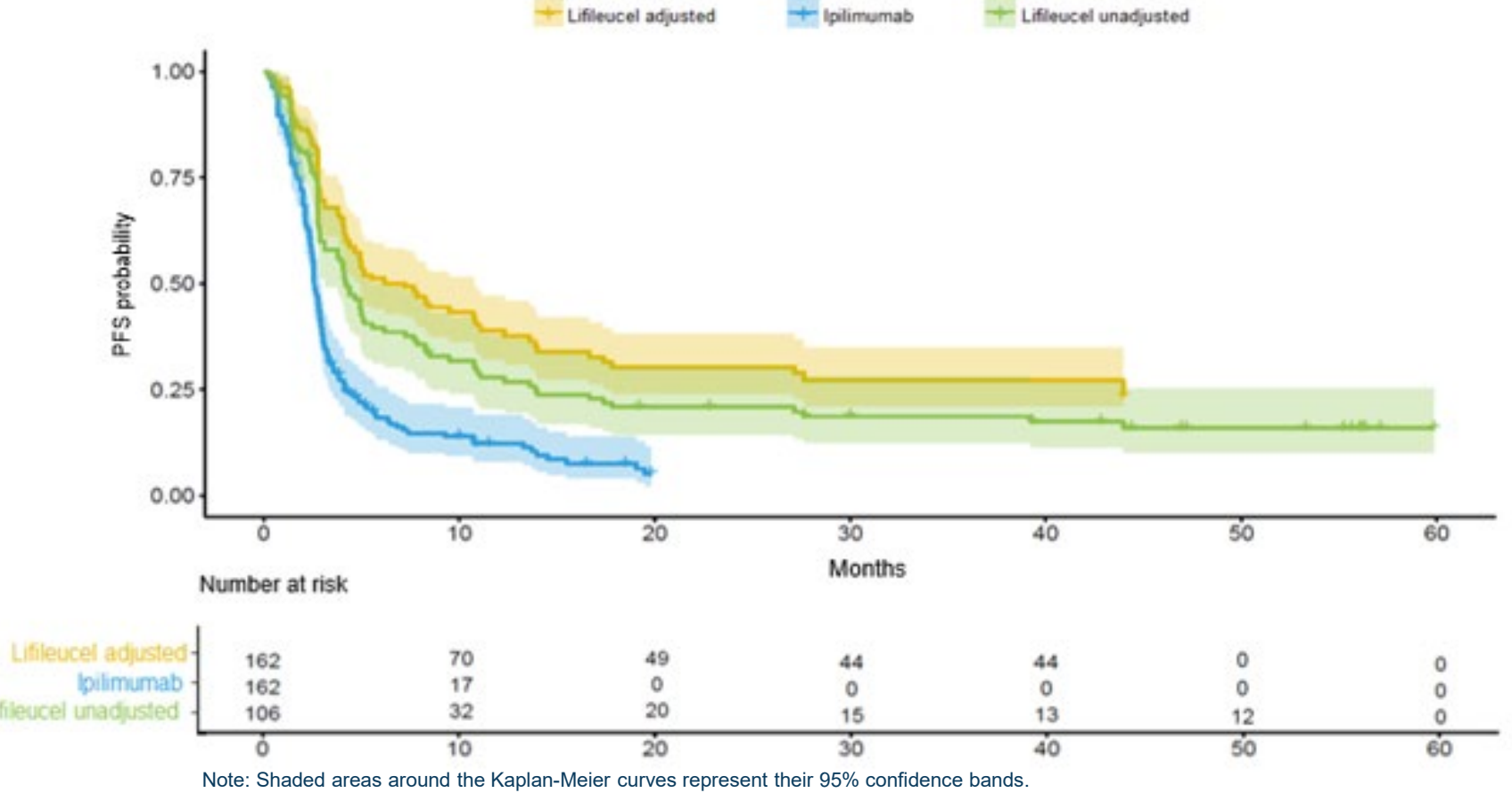


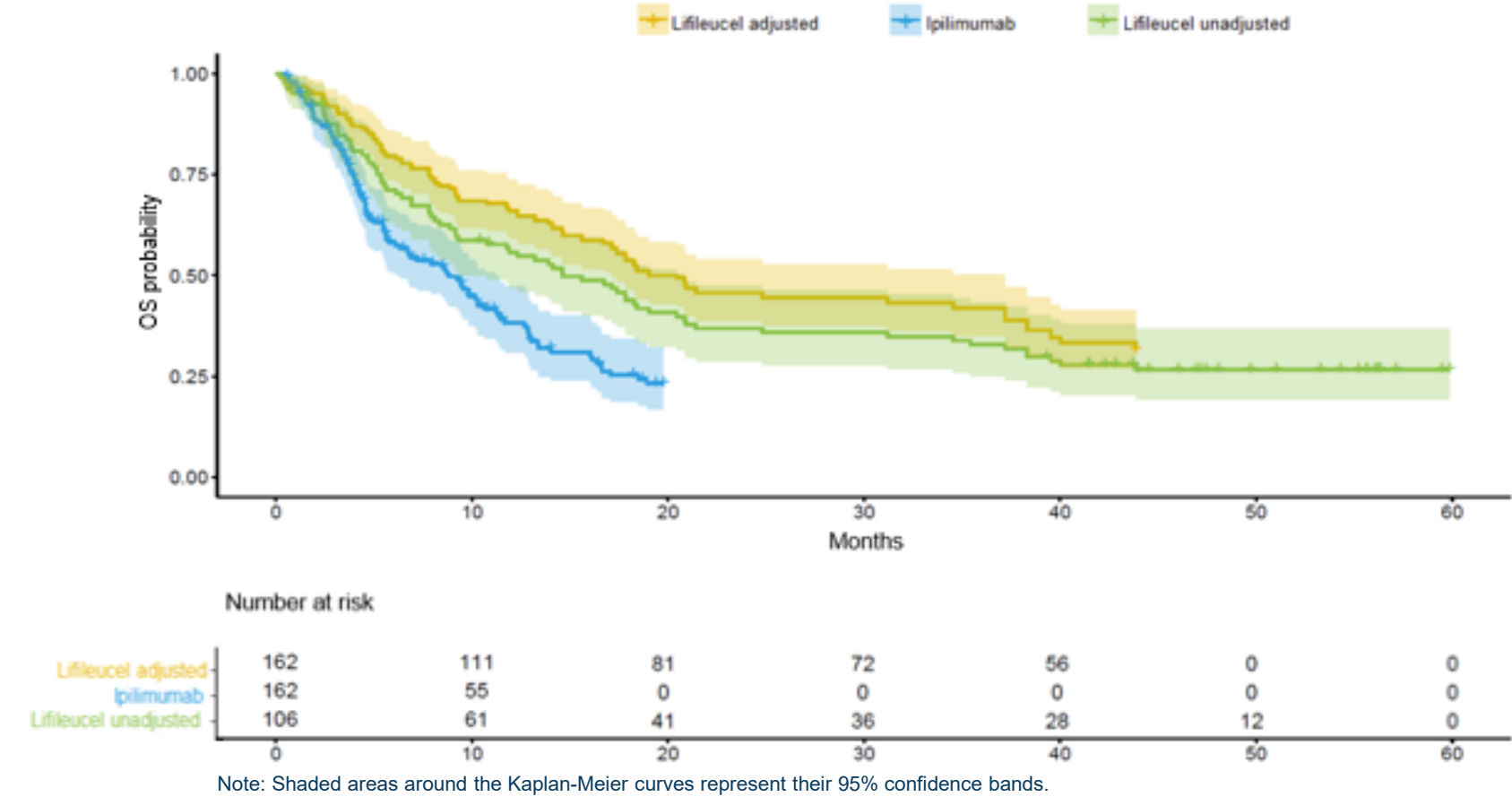
Table 3. Summary of results from unadjusted and adjusted comparison of PFS and OS for lifileucel versus IPI

Setting	PFS		OS	
	Est. HR (95% CI)	p-value	Est. HR (95% CI)	p-value
Base case				
Unadjusted	0.54 (0.41-0.71)	<0.001	0.62 (0.45-0.85)	0.003
Adjusted	0.40 (0.31-0.51)	<0.001	0.46 (0.34-0.61)	<0.001
Sensitivity analysis: Including BRAF-mutation status as an additional covariate				
Adjusted	0.37 (0.29-0.48)	<0.001	0.45 (0.34-0.61)	<0.001

Est. HR: Estimated hazard ratio, IPI: Ipilimumab

• Compared to unadjusted analysis, results of adjusted analysis point out more favorable PFS and OS outcomes for lifileucel versus IPI, emphasizing the statistical importance and value of STC in addressing differences in the baseline characteristics between two studies.

Figure 2. Adjusted and unadjusted Kaplan-Meier curves of OS for lifileucel versus Kaplan-Meier curve of OS for IPI, base case analysis



Methods

• With the exception of Rohaan et al. (2022), there was an absence of head-to-head clinical trial data between lifileucel versus IPI or another relevant comparator (e.g. Nivolumab, Pembrolizumab or chemotherapy) in previously treated advanced melanoma. In addition, because C-144-01 was a single arm trial, it was not possible to construct a connected network enabling an ITC of lifileucel versus IPI. Therefore, an unanchored population-adjusted ITC was considered as the most suitable approach to analyze the comparative effectiveness of lifileucel versus IPI.

• There were noticeable differences in the key baseline characteristics of study populations from C-144-01 and da Silva et al. (2021), including ECOG PS and LDH levels at baseline (see **Table 2**). Therefore, a simulated treatment comparison (STC) was preferred over a match-adjusted indirect comparison. This preference was also based on published evidence suggesting STCs may perform statistically more reliable than match-adjusted indirect comparison when there is poor overlap in baseline characteristics across datasets with low sample sizes.¹¹

• For STC, based on the prognostic importance of covariates and data availability, expert clinical opinion from UK outlined age, sex, ECOG PS score, LDH levels, target lesion sum diameter and line of treatment as key prognostic variables based on their clinical importance. Among these, target lesion sum diameter and prior line of treatment information were both excluded from the analysis as they were available from C-144-01 study but not reported in da Silva et al. (2021).

• The STC employed a regression model associating PFS and OS outcomes with selected covariates. The model was trained with the individual patient level data (IPD) corresponding to patients within Cohort 2 and Cohort 4 of C-144-01 study who received lifileucel within proposed dosing range specified in summary of product characteristics and manufactured at commercially-approved facilities (N=106). Calibrated model was used to predict PFS and OS outcomes for a hypothetical population with baseline characteristics of IPI study cohort treated with lifileucel.

Table 2. Covariates used in the STC for lifileucel versus IPI, and comparison of their baseline values between the studies

Covariate used in STC	C-144-01, pooled Cohorts 2 and 4 (N=106)	da Silva et al. (2021) (N=162)
Age, median	55.2	67.0
Sex, n (%)	Male: 60 (56.6), Female: 46 (43.4)	Male: 103 (64), Female: 59 (36)
Disease stage, n (%)	IIIC: 10 (9.4), IV: 96 (90.6)	III/M1a/M1b: 44 (27), M1c/M1d: 118 (73)
ECOG PS, n (%)	0: 56 (52.8), 1: 50 (47.2)	0: 64 (40), ≥1: 95 (60)
High LDH levels, n (%)	≤ULN: 50 (47.2), >ULN: 56 (52.8)	Normal: 95 (62.5), >ULN: 57 (37.5)

• As summarised in **Table 3**, including BRAF-mutation status as a covariate in the STC did not affect the statistical significance of results. Moreover, it generated slightly more favorable PFS HR (0.37, 95% CI: 0.29-0.48) and OS HR (0.45, 95% CI: 0.34-0.61) for lifileucel versus IPI.

• Results of leave-one-out sensitivity analyses are summarised in **Table 4**. Removing covariates from the STC unilaterally had no effect on the pattern of statistical significance for PFS HR (range: 0.37-0.52) or OS HR (range: 0.45-0.62)

• In the leave-one-out sensitivity analyses, unilateral removal of LDH levels in the STC led to highest marginal deviation from the base case estimates of PFS HR (0.12 absolute deviation) and OS HR (0.16 absolute deviation). Unilateral removal of all other individual covariates had only modest impact on both PFS HR (≤0.03 absolute deviation from the base-case) and OS HR (≤0.07 absolute deviation from the base-case).

Table 4. Summary of leave-one-out sensitivity analyses using the list of base case covariates

Excluded Covariate	PFS		OS	
	Est. HR (95% CI)	p-value	Est. HR (95% CI)	p-value
Age	0.38 (0.30-0.50)	<0.001	0.47 (0.35-0.63)	<0.001
Sex	0.40 (0.31-0.51)	<0.001	0.53 (0.39-0.70)	<0.001
ECOG	0.37 (0.28-0.47)	<0.001	0.45 (0.34-0.61)	<0.001
LDH	0.52 (0.41-0.67)	<0.001	0.62 (0.47-0.82)	<0.001
Disease stage	0.37 (0.28-0.47)	<0.001	0.48 (0.35-0.64)	<0.001

Est. HR: Estimated hazard ratio, IPI: Ipilimumab

Limitations

• Compared with the duration of follow-up in C-144-01 study, where Kaplan-Meier curves for PFS and OS exhibited visible plateaus, limited follow-up in the comparator da Silva et al. (2021) study may constitute a cause of uncertainty for long-term relative treatment effect of lifileucel versus IPI

• Differences in geographic enrollments between the two studies were not considered in the STC. C-144-01 study population was predominantly enrolled from the US whereas in the IPI arm of da Silva et al. (2021) study only a minority of patients were from the US. These differences, due to availability of treatments beyond progression across regions, may be a source of additional uncertainty around the OS results.

• Classification of disease stages was slightly dissimilar between the studies. Staging at baseline was reported as III/M1a/M1b and M1c/M1d in da Silva et al. (2021) whereas in C-144-01 study, staging classification by metastases was available for Cohort 4 but not reported for Cohort 2.

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Limitations (cont'd)

• Association of covariates in the STC with the predicted outcomes was specific to the outcome of interest (i.e. PFS and OS) and in a pre-specified structural form in a regression model (i.e. linear, logistic).

• STC assumed shared-effect modification between the study cohorts, implying selected covariates for STC influence the outcomes of both treatments in a similar fashion despite differences in their mechanisms of actions.

• Simulating pseudo patient-level data for baseline characteristics from published aggregate level data for the IPI cohort relied on normality assumption around average baseline values and could not account for possible dependencies between the distributions of covariates.

Conclusions

• By utilizing IPD from C-144-01 study and aggregate-level data from da Silva et al (2021), STC aimed to reduce risk of potential bias from unobserved confounders in pairwise comparison of lifileucel versus IPI while balancing differences between the prognostic variables and treatment effect modifiers between the two study cohorts.

• Through STC, lifileucel was predicted to be associated with superior PFS and OS outcomes compared with IPI.

• Leave-one-out sensitivity analyses and inclusion of BRAF-mutation status in the STC emphasized the stability of the results, particularly the statistical significance of estimated PFS HR and OS HR between the two treatments, with respect to covariate selection.

• Based on the covariates studied in the STC, IPI cohort from da Silva et al. (2021) was fitter and had a better prognosis than the lifileucel cohort, which translated to an upward shift in the Kaplan-Meier curves of PFS and OS curves for lifileucel after adjustment with STC.

• Results emphasize lifileucel's potential to address unmet need in previously treated advanced melanoma.

• In the absence of head-to-head clinical trial data, the results also offer insights for advanced melanoma practitioners and payers in treatment selection, while enabling long-term clinical and economic evaluation of lifileucel vs IPI.

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