1648P Presented at the European Society for Medical Oncology (ESMO) | October 17–21, 2025 | Berlin, Germany

Evaluating curative potential of lifileucel in previously treated advanced melanoma: Analyses from C-144-01 Trial

J. Larkin[1], P. Lorigan[2], E. Dlotko[3], M. Kurt[4], L. Cox[3], D. Freigofaite[3], J. Wang[5], J. Jiang[5], X. Wu[6], P. Mohr[7]

[1] Royal Medicine Department, The Royal Marsden Hospital – Chelsea, London, United Kingdom, [2] Department of Medical Oncology, The Christie NHS Foundation Trust, and Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom, [3]Health Economics & Outcomes Research, Access, FIECON Limited, London, United Kingdom, [4] Global Health Economics & Outcomes Research, Iovance Biotherapeutics, Inc. – Headquarters, San Carlos, California, United States of America, [5] Global Patient Operations, Value & Access, Iovance Biotherapeutics, Inc. – Headquarters, San Carlos, California, United States of America, [6] Biostatistics, Iovance Biotherapeutics, Inc. – Headquarters, San Carlos, California, United States of America, [7] Biostatistics, Demato-Oncology department, Dermatologic Center Buxtehude, Germany,

Introduction

- Treatment options for patients with advanced (unresectable or metastatic) melanoma are limited after progression on immune checkpoint inhibitors (ICI).
- Lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, is a one-time treatment with a novel mechanism of action that is distinct from ICIs and targeted therapies which recently transformed the treatment landscape for advanced melanoma[1]
- Efficacy and safety of lifileucel in patients with melanoma who are relapsed or refractory to ICIs was investigated in the C-144-01 study.
- C-144-01 (NCT02360579) is a global, phase 2, open-label, multicohort, multicenter, single-arm trial[2]
- Based on the results from C-144-01 study, lifileucel is approved by FDA and Health Canada for the treatment of adults with advanced (unresectable or metastatic) melanoma who have been previously treated with anti–PD-1 therapies and BRAF+/-MEK inhibitors, if patients are BRAF V600 mutation–positive[3,4].
- In the C-144-01 trial lifileucel demonstrated durable survival and response benefits which are manifested by survival plateaus in the progression-free survival (PFS) and overall survival (OS) data.
- Survival plateaus can be attributed to survival heterogeneity borne by the existence of long-term survivors (LTS) in the trial and pose challenges in estimating long-term clinical and economic benefits of lifileucel by traditional methods due to their inability to capture sophisticated hazard trends with multiple inflection points.
- Mixture cure models (MCMs) are commonly used flexible survival modeling frameworks accommodating the underlying survival heterogeneity in broader oncology settings by probabilistically classifying patients as LTS and non-LTS[5].
- MCMs have been recently explored for several early stage and advanced melanoma studies to derive the fraction of LTS from various endpoints (i.e. recurrence-free survival, PFS, OS)
- The objective of this study was to investigate the maturity of the data in the C-144-01 trial for signs on the existence of LTS and to estimate the corresponding fractions of LTS in the C-144-01 trial (data cut-off: 30th June 2023) using MCMs

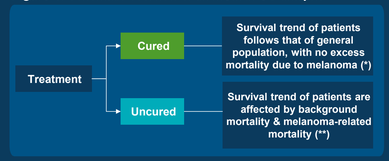
Methods

- In the MCMs[6-10] (schematic overview in **Figure 1**), PFS and OS outcomes were both assumed to be distinct between the mutually exclusive subgroups of LTS and non-LTS, where the fraction of LTSs were referred to as "statistical cure" rate.
- "Statistical cure" differs from the notion of "clinical cure" which is defined as the complete eradication of tumor cells with no signs and symptoms of disease without a further need for treatment
- In the MCMs, in both PFS and OS analysis, LTSs were subjected to only non-melanoma related mortality and non-LTS were subject to all-cause mortality. In addition, in the PFS analysis, LTS were at no risk of disease-progression while non-LTS were also subject to risk of disease progression.
- The structural form of survival in an MCM is defined as:

$$S(t) = S^*(t)[\pi + (1-\pi)S_u(t)], \text{ where}$$

  - $S^*(t)$ = survival of general population
  - π = proportion of LTS (ie. 'cure fraction')
  - $S_u(t)$ = survival of non-LTS estimated by parametric survival functions
- MCMs were performed on the patient-level PFS and OS data from PFS and OS data, corresponding to patients who received lifileucel within proposed dosing range specified in summary of product characteristics and manufactured at commercially-approved facilities (N=106), with a median 47.4 (95% CI: 44.5 -54.3) months of follow-up.
- In the base case, survival trend of LTS was assumed to be identical to the survival trend of the age- and sex-adjusted United States (US) general population and derived from US lifetables[11]
  - In a sensitivity analysis, survival of LTS was further adjusted using a standardized mortality ratio (SMR) of 1.57 (versus SMR = 1 in the base case)[12-15]
  - SMR represented the amount of excess mortality for LTS compared to general population. In reference to age- and sex-adjusted general population mortality rates, SMR = 1 implied no excess mortality for the LTS, and SMR = 1.57 indicated a higher mortality risk for LTS (i.e. hazard-ratio = 1.57 versus general population survival)
- The fractions of LTS were derived alongside the PFS and OS outcomes of non-LTS via maximum likelihood methods
- PFS and OS outcomes for non-LTS were modeled using standard parametric distributions, which enable long-term extrapolations of PFS and OS outcomes, with easily interpretable and clinically intuitive hazard functions[16]

Figure 1. Schematic overview of an MCM in OS analysis



*: Subject to no risk of progression in the PFS analysis, **: Subject to risk of progression in the PFS analysis

- Candidate MCMs were assessed based on statistical goodness-of-fit criteria, visual comparison to reported survival and underlying hazard trends from the trial and clinical plausibility which included a comparison of cure fractions estimated from PFS and OS to ensure a hierarchical order between the two endpoints

Results

- Best-fitting MCMs to the observed PFS and OS data were selected after assessing clinical plausibility of their predictions for non-LTS and ensuring the cure fractions estimated from the OS data to be reasonably higher than the cure fractions estimated from PFS data. In the base-case analysis:
  - Log-normal MCM provided the best fit to the observed PFS data with an estimated proportion of LTS as 17.0% [95% CI: 10.0% - 25.5%]
  - Exponential MCM provided the best fit to the observed OS data with an estimated proportion of LTS as 25.7% [95% CI: 16.7% - 35.7%]
  - In the sensitivity analysis, using an SMR of 1.57 in the MCMs for the survival of LTS yielded similar estimates for the proportion of LTS from PFS (17.5% [95% CI: 10.4% - 26.2%]) and OS (26.4% [95% CI: 17.2% - 36.5%]) with no effect on the structural form of the best-fitting MCMs.
- Across clinically plausible models that maintain the hierarchy between cure fractions estimated from the two endpoints, in the base-case, the range for the estimated proportion of LTS was 16.7%-19.1% from the PFS data and 23.5%-26.1% from the OS data.
- In the sensitivity analysis, using SMR = 1.57 for the survival of LTS, while maintaining hierarchy between the cure fractions estimated from the two endpoints, clinically plausible models generated consistent results estimates for the proportion of LTS from PFS (17.2%-19.7%) and OS (24.2%-26.8%)
- The survival curves derived from the selected MCMs for the cured, uncured and combined populations in the base case (i.e., SMR = 1) are compared against the reported Kaplan-Meier curves for the combined population in **Figure 2** (for PFS) and in **Figure 3** (for OS).
- Smoothed hazard rates (event/year) observed in the trial, and age- and sex-adjusted mortality rates for general population are compared against the hazards predicted from the selected MCMs for the base-case in **Figure 4** (for PFS) and in **Figure 5** (for OS).
  - Smoothed hazard rates observed in the trial showed convergence towards age- and sex-adjusted general population mortality rates by the end of follow-up for both PFS and OS indicating maturity of data and its suitability for modeling with MCMs.
  - For both endpoints, smoothed hazard trends indicated minimal-to-no excess hazard from the disease beyond year 4 and were well-captured by the predicted hazards from MCMs
- In the base-case, estimated mean PFS and OS over a 10-year time horizon (i.e.,10-year restricted mean PFS and OS) for the combined population was 24.5 months and 39.6 months, respectively **(Table 1)** from the selected MCMs.
- **Table 2** displays the 5-, 10- and 20-year PFS and OS rates, along with corresponding mean and median durations for the cured, uncured and combined populations estimated from the selected best-fitting MCMs. Median baseline age in the study population analyzed by MCMs was 55. Therefore, a lifetime horizon of 45 years was used for survival extrapolations and lifetime mean PFS and OS calculations to capture long-term health benefits of lifileucel on the cured subgroup.
- The discordance between the cure fractions estimated from PFS and OS data indicate the likelihood of a subgroup of patients achieving statistical cure despite developing progression and should be approached with caution. Clinically, this discordance may be a consequence of subsequent systemic and locoregional therapies, speed of progression, sustained effects of prior ICIs, treatability of tumor with radiation therapy, and other prognostic variables such as LDH levels and liver metastases of progressive disease patients.

Figure 2. Kaplan-Meier curve for PFS overlaid with best estimations via MCM for SMR = 1

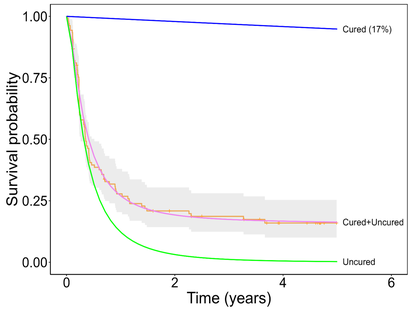
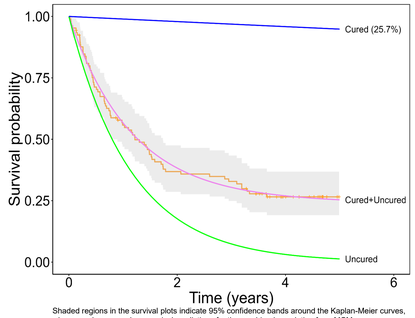


Figure 3. Kaplan-Meier curve for OS overlaid with best estimations via MCM for SMR = 1



Shaded regions in the survival plots indicate 95% confidence bands around the Kaplan-Meier curves, where purple curves show survival predictions for the combined population from MCMs

Figure 4. Observed and predicted PFS hazards from best-fitting MCM alongside general population mortality rates for SMR = 1

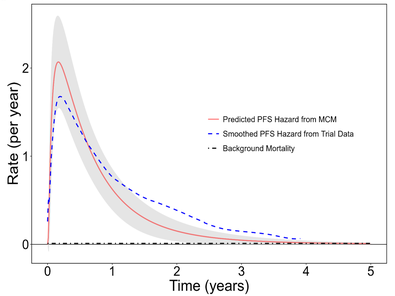
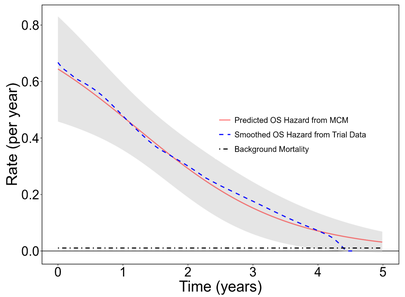


Figure 5. Observed and predicted mortality rates from best-fitting MCM alongside general population mortality rates for SMR = 1



Shaded regions in the hazard plots indicate 95% confidence bands around hazards predicted by MCMs

Table 1. 10-year restricted mean PFS and OS from best-fitting MCMs for cured, uncured and combined populations

10-year restricted mean (months)	Uncured population	Cured population	Combined population
SMR = 1			
PFS	6.2	113.9	24.5
OS	13.8	113.9	39.6
SMR = 1.57			
PFS	6.1	110.5	24.4
OS	13.8	110.5	39.3

MCM: Mixture cure model, SMR: Standardized morality ratio, PFS: Progression-free survival, OS: Overall survival

Table 2. Landmark survival rates along with lifetime mean and median survival durations from best-fitting MCMs for cured, uncured and combined populations assuming SMR = 1

Survival	5-years	10-years	20-years	Median (months)	Lifetime Mean (months)
Uncured population					
PFS	0.3%	0.0%	0.0%	3.7	6.3
OS	1.3%	0.0%	0.0%	9.4	13.9
Cured population					
PFS	95.3%	89.0%	70.7%	325.4	307.8
OS	95.3%	89.0%	70.7%	325.4	307.8
Combined population					
PFS	16.4%	15.1%	12.0%	4.8	57.5
OS	25.5%	22.9%	18.2%	15.2	89.5

MCM: Mixture cure model, SMR: Standardized morality ratio, PFS: Progression-free survival, OS: Overall survival

- Selected MCMs estimated 10-year PFS and OS rates as >15% and lifetime mean PFS and OS as 57.5 and 89.5 months, respectively.
- Uncured patients were estimated to have negligibly small PFS and OS rates beyond year 5 implying long-term clinical benefit of lifileucel can be attributable to its curative potential. As patients were not classified as cured and uncured by the MCMs at the individual level, an internal validation of estimates for the uncured subgroup using the study data was not possible without restrictive assumptions.
- 10-year mean PFS and OS estimates for cured, uncured and combined populations were all minimally sensitive to SMR assumed for the survival of LTS

Conclusions & Limitations

- Emerging survival plateaus and underlying hazard trends in C-144-01 trial can be adequately captured by MCMs, providing insights into survival trends of cured and uncured subgroups which may be otherwise not inferable from reported Kaplan-Meier curves .
- Modest variation in the estimated cure fractions with respect to model choice and changes in the incorporation of background mortality rates into the MCMs emphasize the robustness of the results
- The convergence of hazard rates observed in the trial to the mortality rates of the general population emphasize maturity of the data and offer practical insights for the design of future clinical trials investigating tumor infiltrating lymphocyte therapies in advanced melanoma
- Estimated fractions of LTS in the trial were clinically meaningful and highlight lifileucel's curative potential in addressing the unmet need in previously treated advanced melanoma. In particular, proportion of LTS derived from the PFS data may offer insights into the long-term quality of life and reduced burden of subsequent treatment for patients treated with lifileucel.
- This analysis has the following limitations arising from the methodological nature of MCMs and limited availability of data
  - Likelihood of "statistical cure" was estimated only at the population rather than on an individual level and separately from PFS and OS data, while conceptually and clinically, there is likely a single "clinical cure" fraction for the study population
  - Patients were classified as cured or uncured at the time of lifileucel infusion implying an association with the propensity for cure and baseline characteristics
  - Estimated background mortality rates included the excess mortality associated with melanoma but did not account for the exclusion of patients' melanoma and treatment history.

References

1. Sarnaik AA, et al. J Clin Oncol 2021;39:2656–2666. **2.** Chesney J, et al. J Immunother Cancer 2022;10:e005755. **3.** Iovance Biotherapeutics, Inc. "Iovance's Amtagvi (lifileucel) Receives Health Canada Approval for Advanced Melanoma". Available from https://ir.iovance.com/node/15331/pdf. Accessed on October 1, 2025. **4.** Phillips, C. "First Cancer TIL Therapy Gets FDA Approval for Advanced Melanoma". Available from https://www.cancer.gov/news-events/cancer-currents-blog/2024/fda-amtagvi-til-therapy-melanoma. Accessed on October 1, 2025. **5.** Rutherford MJ, et al. NICE DSU Technical Support Document 21: Flexible Methods for Survival Analysis. Available from https://sheffield.ac.uk/nice-dsu/tsds/full-list. January 2020. Accessed on September 4, 2025. **6.** Hauschild A, et al. J Clin Oncol 2018;36:3441–3449. **7.** Weber J, et al. J Clin Oncol 2025;43:929-937 **8.** Othus M, et al. Value Health 2017;20:705-709. **9.** Mohr P, et al. Ann Oncol 2020; 31:S747. **10.** Green N, et al. Stats in Med 2025; 44:e70132 **11.** Human Mortality Database. USA Total population. Available from https://www.mortality.org/Country/Country?cntr=USA. Accessed on November 8, 2024. **12.** Sadeq MA, et al. Sci Rep 2023;13:10257. **13.** Seitter SJ, et al. Clin Cancer Res 2021;27:5289–5299. **14.** Wolchok JD, et al. N Engl J Med 2025;392:11–22. **15.** Moke DJ, et al. Cancers (Basel) 2021;13:3956. **16.** Latimer N. NICE DSU Technical Support Document 14: Survival Analysis For Economic Evaluations Alongside Clinical Trials - Extrapolation With Patient-Level Data. Available from: https://sheffield.ac.uk/nice-dsu/tsds/full-list. March 2013. Accessed on September 4, 2025.

Disclosures

J. Larkin reports grants from Achilles, BMS, MSD, Nektar, Novartis, Pfizer, Roche, Immunocore, Aveo, Pharmacyclics, NIHR Royals Marsden-Institute of Cancer Biomedical Research Center; consultancy with iOnctura, Apple Tree, Merck, BMS, Eisai, GSK, Incyte, Pfizer, Novartis, MSD, Iovance, Boston Biomedical, YKT Global, Immunocore; payment or honoraria for expert testimony and presentations from Eisai, Novartis, Incyte, Merck, TouchIME, TouchEXPERTS, Pfizer, Roche, iOnctura, CRUK, GSK, Dynavax; P. Lorigan reports grants from BMS and Pierre Fabre; consultancy with BMS, Ultimovacs, MLA Diagnostics and Pierre Fabre; payment or honoraria for expert testimony and presentations from BMS and MSD; P. Mohr reports grants from MSD, Novartis and BMS, payment or honoraria for expert testimony and presentations from MSD, Novartis, Pierre Fabre, Sanofi, Roche, Beiersdorf, Amgen, Almirall Hermal, SUN Pharma, BMS, Regeneron, Delcath, Immunocore; M. Kurt, J. Wang, J. Jiang and X.Wu report employment and stock options with Iovance, E. Dlotko, L. Cox and D. Freigofaite report employment with Fiecon limited and funding from Iovance.

Acknowledgments

- This study was sponsored by Iovance Biotherapeutics, Inc. (San Carlos, California, United States of America)
- All authors contributed to and approved the presentation. Medical writing and editorial support was provided by FIECON limited