Abstract 9592

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Long-term survivorship rates among previously treated advanced melanoma patients achieving objective response (OR) with lifileucel

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Introduction

- Treatment options are limited for anti-PD-1 resistant advanced melanoma and have historically been associated with poor survival outcomes.
- Lifileucel - an FDA- and Health Canada-approved autologous tumor-infiltrating lymphocyte cell therapy – showed durable response benefits for anti-PD-1 resistant advanced melanoma patients in the single arm, global, Phase 2, C-144-01 (NCT02360579) trial.[1,2,3,4]
- In the C-144-01 trial, "Commercially Compliant Set" comprised patients in Cohorts 2 and 4 (n=106) who received lifileucel that is manufactured at commercially approved sites and meeting commercial specifications.
- In-line with broader analysis in Medina et al[5], at a median follow-up of 47.4 months, objective response rate (ORR) in CCS was 35.8%. The breakdown of best overall response among complete and partial responses in CCS was 7.5% and 28.3%, respectively.
- Durability of response with lifileucel was manifested as plateaus in duration of response (DoR) and overall survival (OS) curves for responders in CCS and signify the possibility of long-term survivors (LTS) among responders.
- Mixture cure models (MCMs) are flexible survival modeling frameworks capturing latent survival heterogeneity between LTS and non-LTS at the population level, and previously reported corresponding fractions of LTS and non-LTS using patient-level progression-free survival (PFS) and OS data from CCS.[6,7]
- The objective of this study was to investigate the association between achieving objective response (OR) with lifileucel and being a long-term survivor using DoR and OS data from the responder subgroup in CCS with 4-year follow-up (data cut-off: 06/30/23) using MCMs.
- Due to limited sample size of responders in CCS (n=38), maturity of DoR and OS data were also investigated for the applicability of MCMs.

Methods

- In MCMs[8-12] (**Figure 1**), DoR and OS of responders were assumed to be distinct between LTS and non-LTS, where the fraction of LTS represented the underlying "*statistical cure*" rate.
- In the context of MCMs and this study, "*statistical cure*" differs from the notion of "*clinical cure*". While statistical cure represents the fraction of patients whose mortality risk returns to the same level as general population, clinical cure refers to complete eradication of tumor cells with no signs and symptoms of disease without a further need for treatment, specifically.
- In both DoR and OS analyses, LTS (i.e. cured subgroup) were free of melanoma-related mortality risk, whereas non-LTS (i.e. uncured subgroup) were subject to both melanoma- and non-melanoma-related mortality risk.
- In DoR analysis, LTS were required to maintain response until death, whereas non-LTS could lose response through resistance to lifileucel.
- MCMs were performed on patient-level DoR and OS data from the responder subgroup within CCS (**Table 1**).
- Base case survival trend of LTS was assumed identical to survival trend of age- and sex-adjusted United States (US) general population derived from US lifetables.[13] Standardized mortality ratio (SMR) represented the amount of excess mortality for LTS compared to general population. Base case assumed SMR=1 and in sensitivity analyses SMR of 1.57 was used.[14-17]

Figure 1. Schematic overview of an MCM in OS analysis

Responder to Lifileucel → Cured → Survival trend of patients follows that of general population, with no excess mortality due to melanoma (*)

Responder to Lifileucel → Uncured → Survival trend of patients are affected by background mortality & melanoma-related mortality (**)

*: In DoR analysis, cured subgroup also maintains response until death, **: In DoR analysis, uncured subgroup can also lose response due to resistance to lifileucel

- DoR and OS outcomes for non-LTS were modelled using standard parametric distributions[18] which enable long-term projections with easily interpretable and clinically intuitive hazard functions. Fractions of LTS were derived alongside the outcomes of non-LTS via maximum likelihood methods.
- Candidate MCMs were assessed on statistical goodness-of-fit criteria, visual comparison to survival and underlying hazard trends.

Table 1. Key clinical characteristics of responders within CCS

Characteristics	Responders (n=38)
Age, mean	54
Male, %	57.9
DoR, median (range), years	3.04 (0.51, NR)
BRAF mutation status, %	Mutant: 18; Wildtype: 77; Unknown/Other: 5
ECOG PS, %	0: 63; 1: 37
Prior systemic therapies, %	Anti-PD-1: 100
	Anti-CTLA-4: 84
	Anti-PD-1 & anti-CTLA-4: 45
	BRAF+/-MEK inhibitors: 18
	Anti-PD-1 therapy in metastatic setting: 79
	Anti-PD-1 therapy in adjuvant setting: 5
	Anti-PD-1 therapy in adjuvant & metastatic settings: 16
Prior LoT, %	1: 11; 2: 26; >2: 63 (median: 3)
LDH, %	≤ULN: 63; >ULN: 37

CCS: Commercially Compliant Set; CTLA-4, Cytotoxic T-lymphocyte antigen-4; DoR, Duration of response; ECOG PS, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; LoT, Lines of therapy; NR, Not reported; PS, Performance Status; ULN, upper limit of normal.

Results

- In the base case setting (i.e. SMR = 1), Weibull MCM provided the best fit to the OS data with an estimated fraction of LTS as 52.9% (95% CI: 35.7%–69.5%) and exponential MCM provided the best fit to the DoR with an estimated fraction of LTS as 50.4% (95% CI: 31.3%-66.7%).
- Using an SMR of 1.57 in MCMs (i.e. 57% higher mortality rate than age- and sex-adjusted US general population mortality rate for the cured subgroup) yielded similar estimates for the fraction of LTS from OS (54.1% [95% CI : 36.4% -70.9%]) and DoR (51.7% [95% CI: 32.4%-68.0%]) with no effect on the structural form of the best-fitting MCMs.
- Ranges for estimated fraction of LTS across clinically plausible MCMs in the base case were 48.4%-52.9% from OS and 50.4%-51.1% from DoR.
- In the base-case, estimated mean DoR and OS for responders over a 10-year time horizon (i.e. restricted mean survival time [RMST]) were 5.18 and 5.94 years, respectively (**Table 2**) from the selected MCMs.
- The DoR and OS curves derived from the selected MCMs in the base case (i.e., SMR = 1) are compared against the reported Kaplan-Meier curves for the combined population in **Figure 2**. Estimated DoR and OS trends for LTS and non-LTS from the selected MCMs are also displayed in **Figure 2**.
- Smoothed hazard rates observed in the trial showed convergence towards age- and sex-adjusted US general population mortality rates by the end of follow-up for both DoR and OS indicating maturity of data and its suitability for modeling with MCMs (**Figure 3**).

Conclusions and Limitations

- Estimated fractions of LTS from DoR and OS were clinically meaningful, robust to model choice and consistent with each other. Consistent with clinical intuition, fraction of LTS was higher among responders than within the overall cohort (CCS), underscoring importance of achieving OR with lifileucel for its long-term survival benefit.
- Results reinforce clinical potential of lifileucel for addressing unmet need in anti-PD-1 resistant advanced melanoma by demonstrating how durable responses translate to long-term survival benefits with the potential of cure.
- Despite more stringent requirements imposed on the definition of LTS in DoR and OS analysis of responders compared to analysis of OS and PFS data by MCMs for the overall cohort (CCS), the alignment among the estimated fractions of LTS indicates the strength and stability of curative potential for lifileucel.
- Similar 10-year and lifetime mean DoR and OS estimates from the MCMs indicate that responses are maintained for most of patients' survival while implying improved quality of life and reduced disease burden among responders to lifileucel.

- For both DoR and OS, smoothed hazard trends indicated minimal-to-no excess hazard from the disease beyond year 4 and were consistent with the predicted hazard trends from MCMs.
- **Tables 2** and **Table 3** display 5-, 10- and 20-year DoR and OS rates as well as median and mean durations of DoR and OS over a 10-year and lifetime horizon.
- When the fractions of LTS among responders estimated from DoR and OS data were scaled by the ORR to obtain an indirect estimate for the fraction of LTS in CCS, they (~17.4% - 18%) showed alignment with the fractions of LTS previously estimated from PFS (17%) and OS (25.7%).

Figure 2. Kaplan-Meier curve overlaid with best estimations via MCMs for SMR = 1; **A)** DoR and **B)** OS

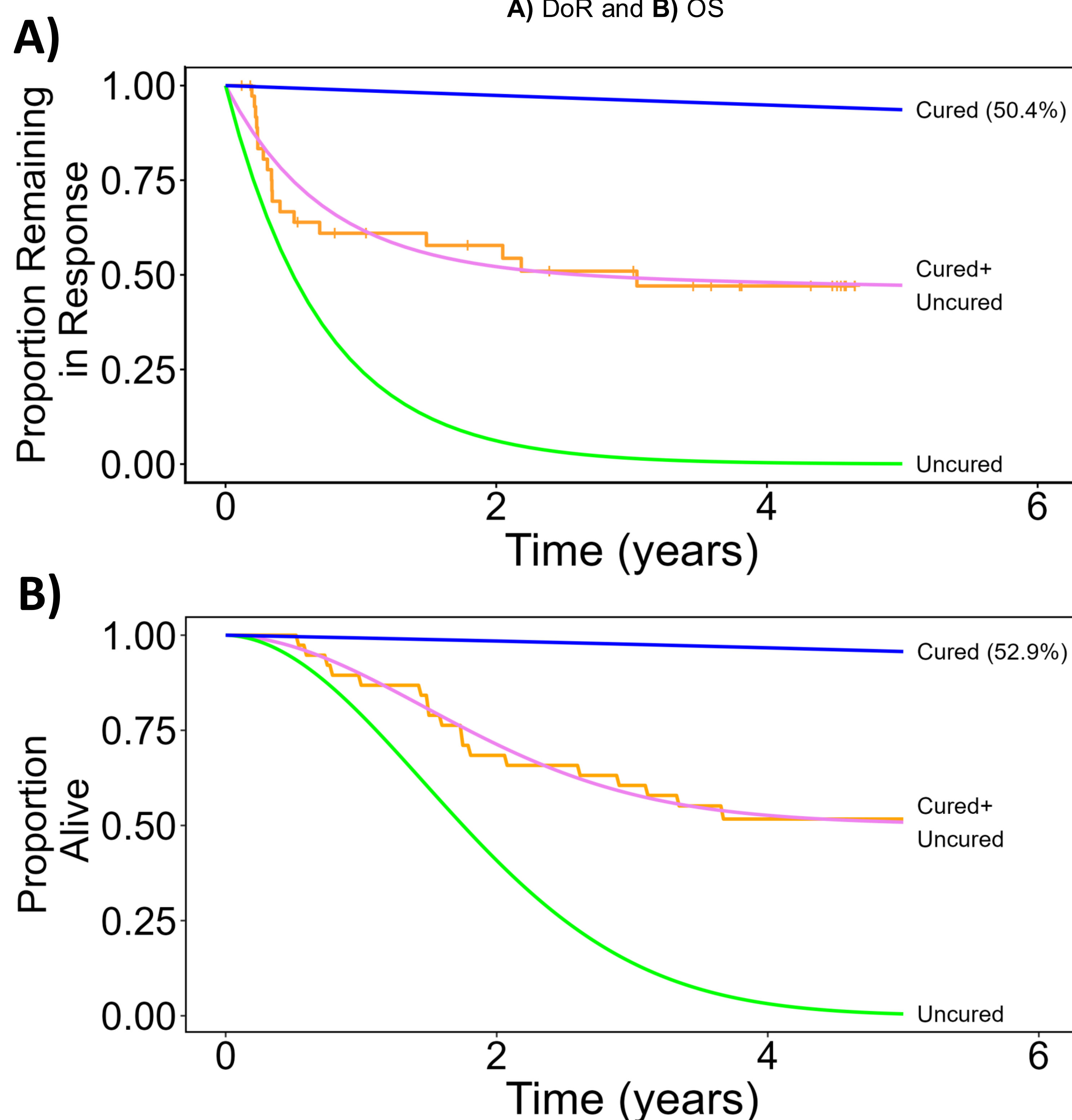
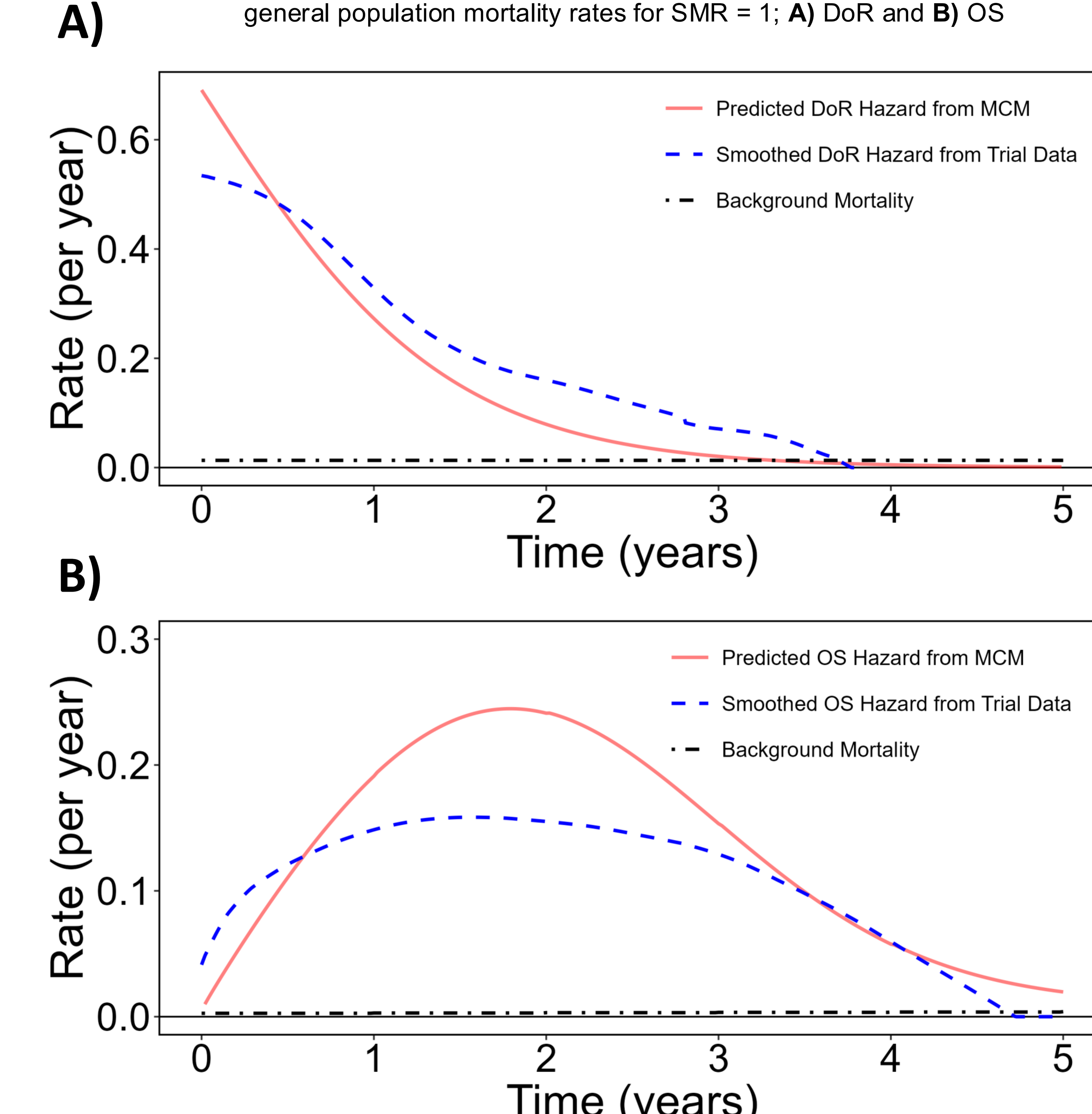


Figure 3. Observed and predicted hazard trends from best-fitting MCMs alongside general population mortality rates for SMR = 1; **A)** DoR and **B)** OS



DoR, Duration of response; MCM, Mixture cure model; OS, Overall survival; SMR, Standardized mortality ratio.

Table 2. Landmark survival rates, 10-year RMSTs and lifetime mean survival (SMR = 1)

Outcome	5-years	10-years	20-years	10-year RMST (years)	Median (years)	Lifetime mean* (years)
DoR	48.3%	45.3%	36.6%	5.18	2.95	13.74
OS	50.9%	47.5%	38.4%	5.94	6.19	14.93

Table 3. Landmark survival rates, 10-year RMSTs and lifetime mean survival (SMR = 1.57)

Outcome	5-years	10-years	20-years	10-year RMST (years)	Median (years)	Lifetime mean* (years)
DoR	48.3%	43.6%	31.3%	5.15	3.24	11.90
OS	50.7%	45.7%	32.7%	5.88	5.67	12.97

*Lifetime horizon of 46 years (based on mean age of 54 years for responders) was used for long-term DoR and OS extrapolations to capture long-term health benefits of lifileucel on the cured subgroup. The lifetime mean survival for the cured subgroup was 26.54 years under SMR =1 and 22.38 years under SMR = 1.57. DoR, Duration of response; OS, Overall survival; RMST, Restricted mean survival time; SMR, Standardized mortality ratio.

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