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Analysis of long-term survivorship (LTS) rates for stage IIB/IIC melanoma using published data from real-world and randomized controlled trials (RCTs)

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Objectives

- Recurrence-free survival (RFS) is a potential surrogate endpoint for overall survival (OS) in stage II-III melanoma (Suciu *et al*. 2018)
- Several randomized controlled trials (RCTs) and observational studies in stage II melanoma report RFS with plateauing behavior, indicating the possibility of long-term survivors, i.e., patients with low risk of recurrence (Winge-Main *et al*. 2023, Sondak *et al*. 2002)
- However, there is uncertainty regarding the long-term survivorship (LTS) rates among patients with stage IIB/IIC melanoma
- This study estimated the proportion of the long-term survivors among stage IIB/IIC melanoma patients via mixture cure models (MCMs) using published RCTs and real-world data (RWD) sources

Methods

- Published RFS data for stage IIB/IIC melanoma patients from several RCTs as well as three real-world data (RWD) studies were analyzed to estimate the proportion of patients who are long-term survivors (**Table 1** and **Table 2**)
- Two RWD studies from the USA that were used to validate long-term RFS extrapolations in a recent National Institute for Care Health Excellence (NICE) technical appraisal guidance document (NICE 2022), and a RWD set from Norway with a large sample size and long follow-up were included in the analyses
- RFS curves of each included study were digitized and the algorithm by Guyot et al. (2012) was used to generate synthetic individual patient-level time-to-event data
- Reconstructed time-to-event data across 10 RCTs in stage II melanoma, identified by a targeted literature review and a subset of it restricted to the surgery alone arms of the RCTs published after year 2000 were pooled
- MCMs were fit to each reported or pooled RFS curve separately while accounting for the non-disease-related mortality for each cohort under consideration
- A MCM probabilistically classifies patients in mutually exclusive subgroups as long-term survivors (cured) or uncured
- Cured patients are assumed to be free of risk of recurrence or disease-related mortality
- The analytical form for the survival function of a cohort in an MCM is given below:

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

  Where
  - $S(t)$ represents the survival at time t for the overall population
  - $S^*(t)$ is the general population survival at time t, i.e. (i.e., $S^*(t)$= 1 – background mortality)
  - π represents the probability of being statistically "cured," (i.e., the proportion of long-term survivors)
  - $S_u(t)$ represents the RFS of the statistically "uncured" subgroup relative to general population (i.e., $S_u(t)$ represents the time to recurrence or disease-related death, whichever occurs sooner, for the uncured subgroup)

Table 1. List of RCTs included in the pooled data

No	Author year (trial name)	Control	Treatment	Number of patients
Articles published before 2000				
1	Gonzalez et al. 1978	Placebo	Levamisole	90
2	Miller et al. 1988	Placebo	Transfer factor	99
3	Oratz et al. 1991	Placebo	Melanoma antigen vaccine	45
4	Creagan et al. 1995	Observation	Interferon Alfa-2a	160
5	Wallack et al. 1995	Vaccinia Vaccine Virus - Placebo	Vaccinia Melanoma Oncolysate	217
Articles published after 2000				
6	Sondak et al. 2002 (SWOG-9035)	Observation	DETOX vaccine	600
7	Agarwala et al. 2017 (EORTC E1697)	Observation	Interferon	1150*
8	Corrie et al. 2018 (AVAST-M)	Observation	Bevacizumab	1343*
9	Eggermont et al. 2020 (EORTC 18081)	Observation	Interferon	112
10	Slingluff et al. 2021 (MAVIS)	Placebo	Seviprotimut-L	111

* These two RCTs included both stage II and stage III patients but did not report the sample sizes of patients in each stage separately. Therefore, the reported sample sizes include stage III patients as well.
Notes. The control arms (surgery alone) of RCTs published after 2000 were pooled and analyzed separately in a subgroup analysis.

- Background mortality rates [i.e. 1-S*(t)] for each cohort was estimated by using age- and sex-adjusted background mortality rates reported by the World Health Organization and adjusted for the enrollment distribution of the patients in the cohort across countries participating in the associated study or pooled data set (World Health Organization 2023)
- The time-to-event outcomes for uncured patients [i.e. $S_u(t)$] were estimated using five parametric distributions (Exponential, Weibull, Loglogistic, Gamma, Lognormal) using maximum likelihood methods
- The best parametric distribution was selected based on statistical goodness-of-fit criteria including Akaike information criterion (AIC) and Bayesian information criterion (BIC), and visual fit to the reported data
- The proportion of cured patients and the corresponding 95% confidence intervals (CIs) were calculated for each candidate MCM
- RFS rates for the uncured population by years 2,5, and 10 were calculated based on the best-fitting MCM
- The proportions of the long-term survivors estimated from each study were compared
- All analyses were conducted in R programming language

Table 2. Included studies in the analyses and key baseline characteristics driving the background population mortality estimation

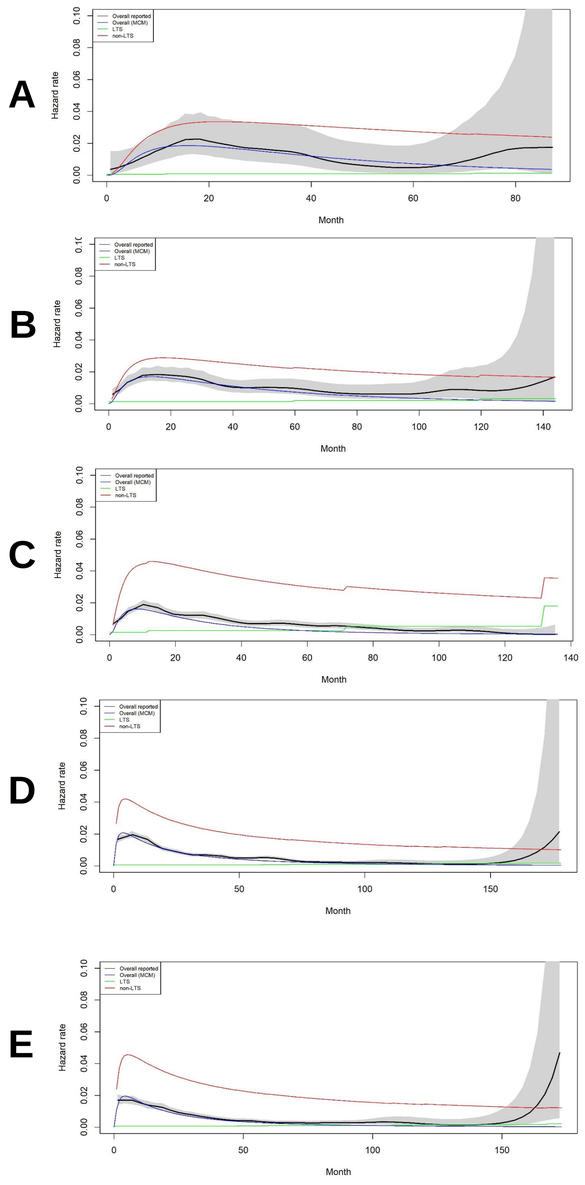
Study	Type	Country	Number of patients (Stage IIB)	Number of patients (Stage IIC)	Baseline age	Proportion of male patients	Years of enrollment
Bajaj et al. (2020)	Prospective cohort database	USA	63	27	59	56%	2010-2016
Samlowski et al. (2022)	Oncology network data	USA	375	192	65	62%	2008-2017
Winge-Main et al. (2023)	Cancer registry	Norway	1,551	766	74*	54%	2008-2018
Pooled data from published RCTs	RCTs (Table 1)	Multiple	3,927**		54	58%	1976-2017
Pooled data from surgery alone arm of the published RCTs after 2000	RCTs (Table 1)	Multiple	1,635**		54	57%	1992-2017

* Calculated using the mean ages published in Winge-Main et al. (2020)
** Number of patients was not reported separately for stage IIB and stage IIC, some of the RCTs included stage III patients as well (please see **Table 2** for the details)

Results

- MCMs with lognormal distribution provided the best fit according to goodness-of-fit criteria in all instances, and relatively more conservative LTS rates than other candidate models
- Best-fitting MCMs provided an accurate fit to the reported RFS curves in all instances capturing emerging plateaus (**Figure 1**)
- Comparison of model-predicted and observed (smoothed) hazard rates also verified the quality of the visual fit to the reported data by log-normal MCMs (**Figure 2**)
- The estimated LTS rates (95% CI) were (**Table 3**)
  - 34% (14%-61%) and 31% (21%-44%) for the US RWD sets
  - 56% (52%-60%) for the Norwegian RWD
  - 46% (43%-50%) for the pooled RCT data
  - 52% (48%-56%) for the restricted subset of the pooled RCT data
- 95% CIs of the LTS rates indicate that the MCMs fit to pooled datasets from published RCTs and RWD from Norway were more robust than those fit to the RWD from the USA (**Table 3**). The robustness of the LTS rates and the fit by the MCMs to the pooled datasets from published RCTs and RWD from Norway was mostly due to relatively larger sample sizes of these datasets
- The range for the RFS rates for uncured stage IIB/IIC patients were estimated as 41%-59%, 13%-25%, 3%-9%, in years 2,5, and 10, respectively (**Table 3**)

Figure 2. Comparison of observed and model-predicted RFS hazard rates. A) Bajaj et al. (2020); B) Samlowski et al. (2022); C) Winge-Main et al. (2023); D) Pooled data from published RCTs; E) Pooled data from surgery alone arm of the published RCTs after 2000.

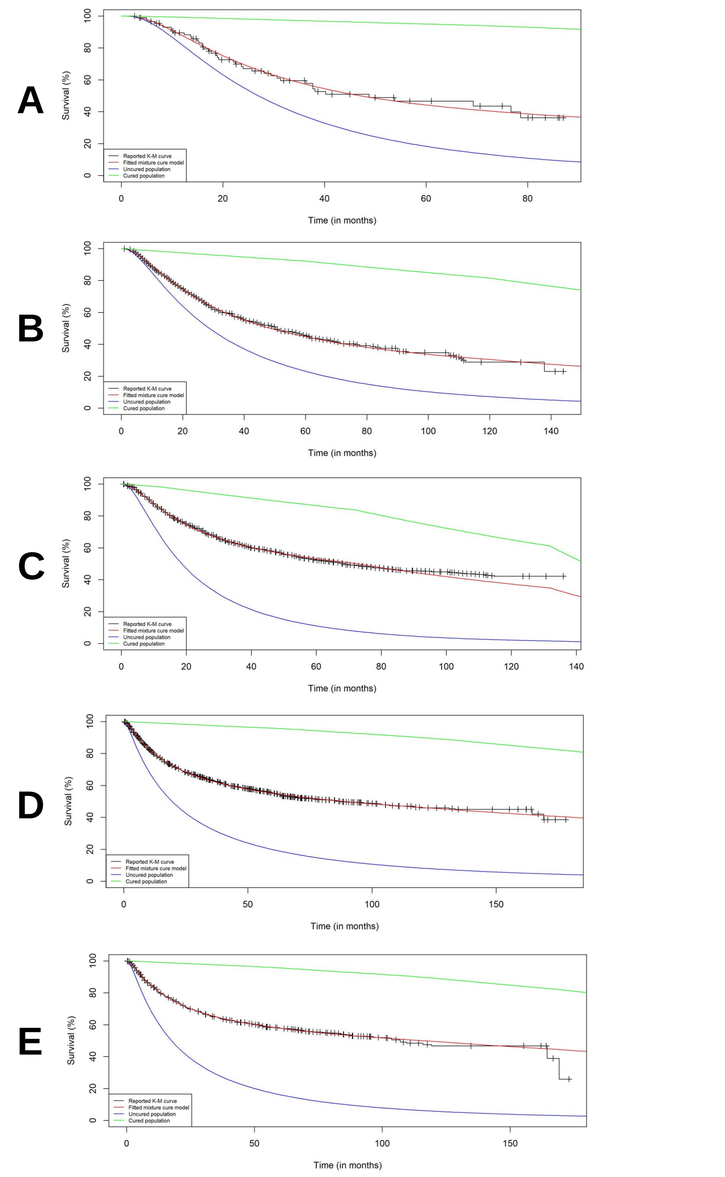


Notes. Shaded areas represent the 95% CIs of the hazards corresponding to the reported RFS data

Table 3. Summary of the results from the best-fitting MCMs

Outcome		Bajaj et al. (2020)	Samlowski et al. (2022)	Winge-Main et al. (2023)	Pooled data from published RCTs	Pooled data from the surgery arm of the RCTs published after 2000
RFS rate for the overall population in year 5 (in %)		46.68	45.39	52.38	55.15	57.77
Estimated cure fraction from the best-fitting MCM, in % (95% CI)		34 (14-61)	31 (21-44)	56 (52-60)	46 (43-50)	52 (48-56)
RFS rate for uncured population (in %)	2 years	55.27	57.06	39.61	43.78	40.13
	5 years	18.33	23.15	11.08	19.88	16.14
	10 years	4.43	7.22	2.17	8.29	5.86
Median RFS for the uncured population, in months (range based on MCMs)		27.0 (25.1-38.0)	28.7 (26.1-33.5)	18.6 (17.9-19.5)	19.5 (17.4-19.5)	17.6 (16.1-17.6)

Figure 1. Best-fitting MCMs to the RFS curves. A) Bajaj et al. (2020); B) Samlowski et al. (2022); C) Winge-Main et al. (2023); D) Pooled data from published RCTs; E) Pooled data from surgery alone arm of the published RCTs after 2000



Discussion

- Our analyses showed that the LTS rates among patients with stage IIB/IIC melanoma ranged between 31% and 52%
- These estimates are consistent with the rates reported by a recent study based on RWD from Sweden (Eriksson et al. 2021)
  - Stage IIB: 62% (95% CI 59%-66%)
  - Stage IIC; 42% (95% CI 37%-46%)
- Narrower 95% CIs of the LTS rates from the best-fitting MCMs to the pooled data from published RCTs and RWD from Norway indicate the maturity of the follow-up in these datasets and stability of the LTS rates
- Median RFS and RFS rates of the uncured subgroup in the datasets with relatively higher cure fractions (e.g., Winge-Main et al. 2023) are still poorer than those from other data sources, indicating the unmet need even in these settings
- A limitation of this study is that the definition and recording of RFS may differ between the RCTs and RWD sources
- Another limitation is that pooled data from the RCTs are relatively older whereas RWD sources utilize more recent data reflecting the changes in the resection technology as well. Therefore, a head-to-head comparison of estimated LTS rates between these sources may not be comparable as the LTS rates are subject to change over time

Conclusion

The wide range of estimated LTS rates across different cohorts and settings highlights an unmet need for adjuvant treatments for patients with completely resected stage IIB/IIC melanoma.

Acknowledgments

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- All authors contributed to and approved the presentation

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