MSR21

Do Lifetables Overestimate Non-Cancer-Specific Survival in Oncology? A Case Study From Treatment-Naïve Advanced Melanoma

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Background

- In oncology, adjusting long-term survival extrapolations and exploring survival heterogeneity borne by long-term survivors (in excess hazard and mixture cure models) often require accounting for non-cancer-specific survival (NCSS).
- NCSS can be used to reduce uncertainty in long-term survival predictions and assess the severity of an indication in health technology assessments by calculating the shortfall of quality-adjusted life-years for the disease population compared to general population[1]
- In economic evaluations of oncology drugs, NCSS is commonly estimated using general population life tables; however, this approach is often unable to account for the differences in disease history and prognostic characteristics between the trial population and general population.

Objective

- This study compared NCSS trends that are derived from local lifetables and aggregate-level clinical data in treatment-naïve advanced melanoma.

Methods

Input Data

- Publicly available Kaplan-Meier curves for overall-survival (OS) and melanoma-specific survival (MSS) from the Phase III CheckMate-067 study[2] were digitized to reconstruct pseudo individual-patient level data (IPD) for each arm.
- Minimum follow-up in the study was 10 years, with 127-month-long Kaplan-Meier curves for both OS and MSS

Modelling

- In the CheckMate-067 study, there were 173, 192, and 243 deaths in the nivolumab plus ipilimumab, nivolumab and ipilimumab arms, respectively. Of these deaths, 139, 163 and 221 are melanoma-related in nivolumab plus ipilimumab, nivolumab and ipilimumab arms, respectively.
- Due to randomized nature of the trial, NCSS distributions were assumed to be identical across the arms. Therefore, pseudo-IPD for OS and MSS were pooled separately across arms to generate a non-parametric NCSS curve which was smoothed to ensure monotonicity over time using isotonic regression.
- As a benchmark, age- and sex-adjusted lifetables published by World Health Organization[3] (WHO) were used to generate NCSS curves for each participating country in the trial, which were weighted uniformly across all countries to derive an aggregate NCSS curve for the trial cohort.
- Weekly NCSS rates and restricted mean survival times (RMSTs) estimated from the trial- and lifetable-based NCSS distributions were compared.
- The NCSS curves derived from each source (e.g. aggregate-level trial data and lifetables) were also modeled with standard parametric distributions and splines suggested by NICE for comparison of their visual trends.[4]

Results

Mathematical Formulation of the Optimization Model used to Smoothen the NCSS elicited from the trial

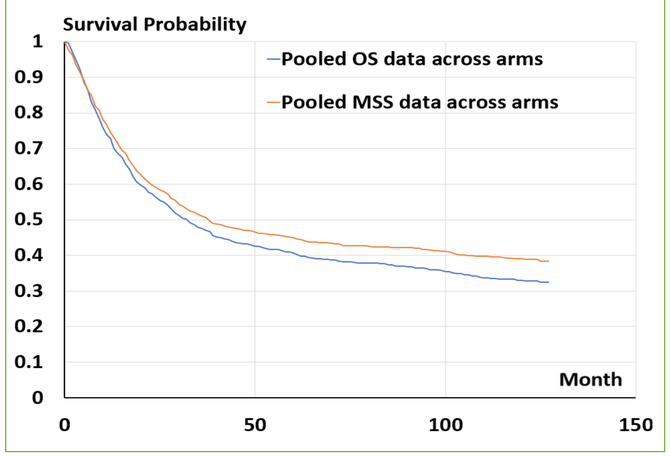
Decision Variables	$S(t)$: Smoothed NCSS distribution
Parameters	$Q(t)$: NCSS distribution elicited from trial-reported OS and MSS T: Number of months in the time horizon, t: Index of each month
Constraints	$S(t) \geq S(t+1)$ for $t = 0,1,..\mathrm{T}-1; S(0) = 1; S(T) \geq 0$
Objective Function	Minimize: $\sum_{t=0}^{T}\left(S(t) - Q(t)\right)^2$ (sum of squared errors)

Table 1: Summary of statistical goodness of fit criteria

Source	Family of Model	Distribution	AIC	BIC	AIC - $\min_{AIC}$	BIC - $\min_{BIC}$
Lifetable-Based NCSS	Standard Parametric Distributions	Exponential	8.93	4.93	0.00	0.17
		Gamma	10.81	4.81	1.88	0.05
		Generalized Gamma	12.77	4.77	3.84	0.01
		Gompertz	10.76	4.76	1.82	<0.01
		Loglogistic	10.82	4.82	1.89	0.06
		Lognormal	10.91	4.91	1.98	0.15
		Weibull	10.79	4.79	1.86	0.03
	Splines	Spline 1-knot Hazards	12.76	6.76	3.83	2.00
		Spline 2-knot Hazards	14.76	6.76	5.82	2.00
		Spline 1-knot Normal	N/A	N/A	N/A	N/A
		Spline 2-knot Normal	14.76	6.76	5.83	2.00
		Spline 1-knot Odds	12.78	6.78	3.84	2.02
		Spline 2-knot Odds	14.76	6.76	5.82	2.00
Trial-Based NCSS	Standard Parametric Distributions	Exponential	4.34	0.34	0.00	0.02
		Gamma	6.33	0.33	1.98	<0.01
		Generalized Gamma	N/A	N/A	N/A	N/A
		Gompertz	N/A	N/A	N/A	N/A
		Loglogistic	6.32	0.32	1.98	<0.01
		Lognormal	6.32	0.32	1.97	<0.01
		Weibull	6.33	0.33	1.98	<0.01
	Splines	Spline 1-knot Hazards	8.32	2.32	3.97	2.00
		Spline 2-knot Hazards	10.32	2.32	5.97	2.00
		Spline 1-knot Normal	N/A	N/A	N/A	N/A
		Spline 2-knot Normal	10.32	2.32	5.97	1.99
		Spline 1-knot Odds	8.32	2.32	3.97	2.00
		Spline 2-knot Odds	10.32	2.32	5.97	2.00

N/A: Not available due to non-convergence of the model, AIC: Akaike Information criteria, BIC: Bayesian Information criteria. Rows shaded in orange indicate selected top 4 distributions according to non-dominance of AIC and BIC, and rows shaded in yellow indicate distributions for which maximum likelihood estimation did not generate a convergent solution. The model distributions in **bold** indicate the best-fitting model based on goodness of fit and visual alignment to either nonparametric lifetable or elicited trial-data

Figure 1: Observed MSS and OS data pooled across the arms of the study



Results (continued)

Figure 2: Raw and smoothed NCSS distributions elicited from the trial-reported data

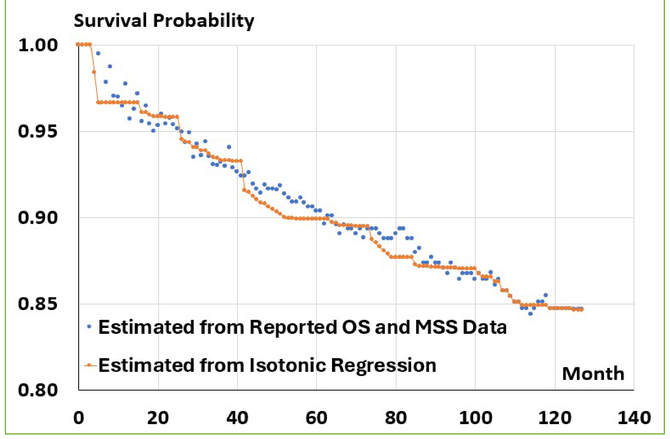


Figure 3: Selected standard parametric distributions used to model NCSS distribution derived from WHO lifetable data

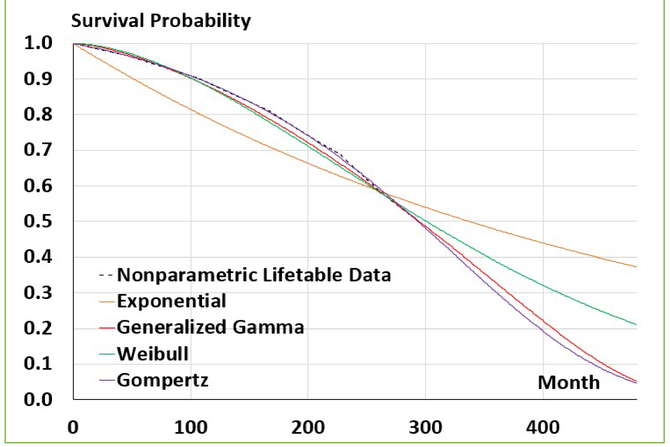
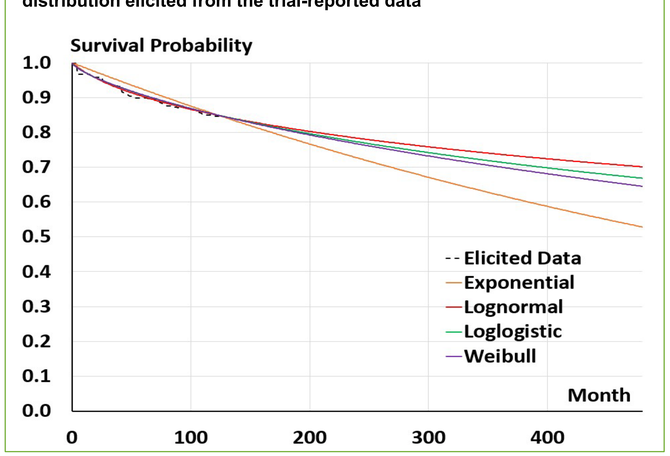
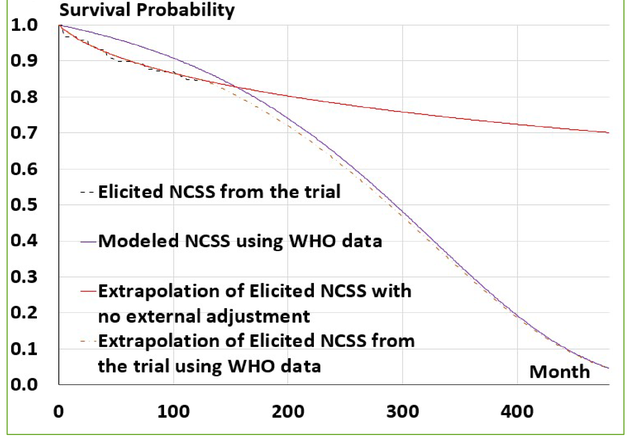


Figure 4: Selected standard parametric distributions used to model NCSS distribution elicited from the trial-reported data



Results (continued)

Figure 5: Comparison of extrapolated NCSS derived from trial-reported data and lifetable data



- NCSS elicited from trial-reported OS and MSS was non-monotone emphasizing the need for isotonic regression. In the smoothening process, the optimized sum of square of errors between the elicited and modeled NCSS distributions was <0.01.
- Lifetable-based NCSS exhibited a more favorable trend than trial-based NCSS with an average overestimation margin of 4% across 10-years after randomization.
- Estimated 10-year RMSTs from the trial- and lifetable-based NCSS were 9.09 and 9.53 years, respectively. Estimated 30-year RMSTs from the trial- and lifetable-based NCSS were 24.9 and 22.1 years, respectively.
- Best-fitting models to lifetable-based NCSS (Gompertz) and trial-based NCSS (lognormal) displayed considerably different visual trends and crossed each other at year 12.75.
- Based on a log-rank test, the two NCSS curves derived from trial-reported data and WHO lifetables were statistically indistinguishable from each other (corresponding p-value = 0.958).
- Long-term extrapolations in **Figure 5** illustrate the overestimation of the lifetable-based NCSS by the NCSS elicited from trial-reported data and emphasize the need for the adjustment of long-term NCSS obtained from trial-reported data with lifetable-based NCSS despite its limitations.

Conclusions

- Local lifetables may slightly overestimate medium-term NCSS compared to trial-derived estimates but tend to be more conservative when projecting long-term survival in treatment-naïve advanced melanoma, consistent with past work in muscle invasive urothelial carcinoma.[5]
- Further analyses across different tumor types are necessary to assess broader applicability of these results.

References

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5. Srinivasan et al. Modeling and Comparison of Non-Disease-Related Survival Using Local Lifetables and Reported Trial Data: A Case Study From Adjuvant Treatment of Muscle-Invasive Urothelial Carcinoma. Value in Health (2022): 25(12): S353

Acknowledgments

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