Lumanity

Methods for Incorporating External Evidence: A Comparison of Their Impact on Extrapolations and Uncertainty Estimates Using a Melanoma Case-Study

Authors: Kearns B[1], Wolff H[2], Kilvert H[3]

Affiliations: [1]Lumanity, Sheffield, UK; [2]Lumanity, Utrecht, The Netherlands; [3]Lumanity, Manchester, UK

INTRODUCTION

- To fully quantify the benefit of a treatment, many cost-effectiveness analyses require extrapolation of survival data[1]
- For oncology treatments, the effect of treatment on overall survival is often a key driver of cost-effectiveness, but the available evidence is typically immature, with less than 50% of deaths observed.[2] Extrapolations from immature data will be uncertain and potentially biased. Hence there is the potential to improve extrapolations by incorporating relevant external evidence
- Several methods have been proposed for the incorporation of external evidence.[3-6] However, it is unclear how the results of these methods differ, and which ones should be used

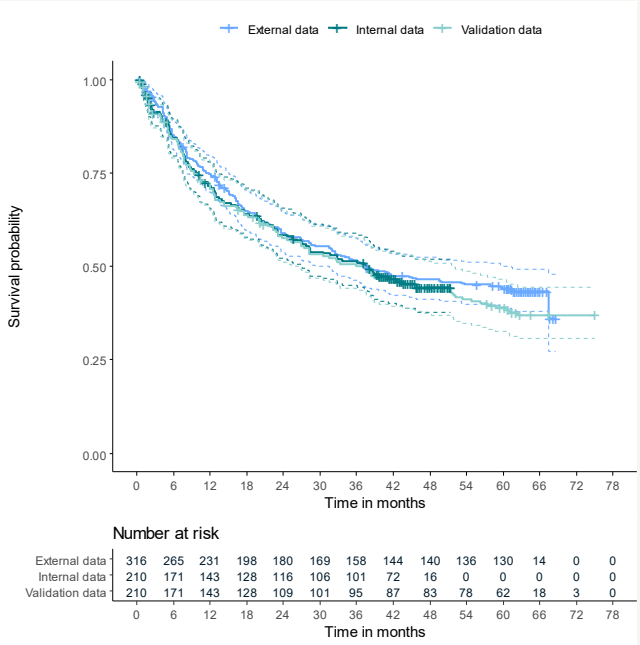
OBJECTIVES

- The primary objective of this study was to use an oncology case-study to compare the impact of different methods for incorporating external evidence on survival extrapolations. This included investigating both the accuracy of, and uncertainty in, extrapolations
- As a secondary objective, the impact of the different methods on within-sample fit was explored

METHODS

- The Phase III randomized controlled trials CheckMate 066[7] and CheckMate 067[8] evaluated nivolumab in previously untreated advanced melanoma. Results from both trials were published at similar times, with maximum follow-up of 51 months for CheckMate 066 and 66 months for CheckMate 067
- CheckMate 066 was treated as the internal evidence (i.e., the study that we aim to predict the survival outcomes for, due to having shorter follow-up), while CheckMate 067 provides the contemporaneous external evidence
- A subsequent CheckMate 066 publication, with a maximum follow-up of 72 months, was used to validate the extrapolation results[9]

Figure 1. Data used in case-study



- We considered five methodological approaches to extrapolate the internal data:

1. No use of external evidence.
2. Piecewise: swapping the model fitting to the external data at 48 months, when the numbers at risk for CheckMate 066 were between 20% to 10%, based on published recommendations.[10]
3. Bias adjusted: applying a hazard ratio, estimated from a Cox proportional hazards model fit to both datasets with study as the covariate. The internal data were extrapolated by using a hazard ratio applied to the log-normal curve that was fitted to the external data.
4. Informative prior: where a survival model was fitted to the external evidence using RStan and the resulting posterior distributions (for all parameters) were used as prior distributions when fitting the same survival model to the internal evidence.[11]
5. Flexible M-spline: pooling the two datasets and generating survival estimates via a flexible M-spline model.[12] To reflect the piecewise approach, external evidence was only used from Month 48 onwards.

- The first four approaches used a log-normal model for baseline survival as this provided the best fit to the internal data, based on the Akaike information criterion of the models
- To validate the extrapolations arising from each method, point-estimates and 95% confidence intervals (or credible intervals, depending on the method) for 72-month predictions were compared. To assess the impact on within-trial fit, 12-month point-estimates were also compared

RESULTS

Figure 2. Impact of incorporating external evidence on survival estimates

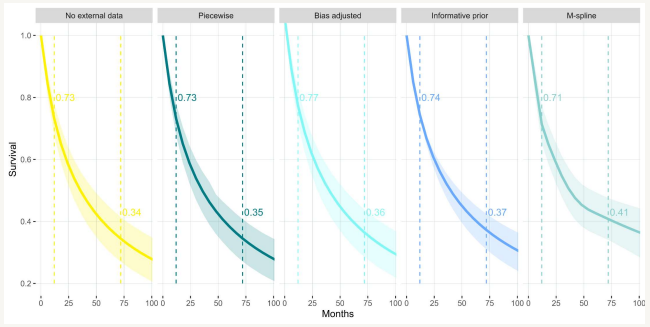


Table 1. Survival estimates with 95% prediction intervals

Method	Time (months)				
	12	36	72	108	144
Validation data	0.707	0.501	0.370	n/a	n/a
No external data	0.732 (0.677-0.779)	0.497 (0.426-0.560)	0.345 (0.270-0.415)	0.264 (0.194-0.334)	0.214 (0.148-0.282)
Piecewise	0.732 (0.677-0.780)	0.497 (0.426-0.560)	0.345 (0.271-0.408)	0.265 (0.195-0.330)	0.214 (0.149-0.278)
Bias adjusted	0.773 (0.716-0.824)	0.526 (0.451-0.592)	0.364 (0.286-0.438)	0.279 (0.205-0.354)	0.226 (0.157-0.298)
Informative prior	0.744 (0.736-0.745)	0.522 (0.476-0.555)	0.373 (0.310-0.425)	0.292 (0.226-0.351)	0.241 (0.176-0.302)
M-spline	0.714 (0.653-0.773)	0.507 (0.438-0.574)	0.408 (0.341-0.456)	0.354 (0.270-0.436)	0.308 (0.205-0.407)

- For the 72-month extrapolations, extrapolation without external evidence led to survival estimates that were too low (72-month predicted survival of 34% compared with observed 38%). The incorporation of external evidence led to increased and more accurate estimates for all four methods (range 35% to 41%). Based on 72-month prediction, the most accurate method was the informative prior followed by the bias adjusted method
- Confidence intervals are the widest (15.2%) at 6 years for the bias adjusted method, which is the only method that led to more uncertainty than no external data (14.4%). The smallest confidence interval width is for the informative prior method (11.5%)
- Based on 1-year and 3-year within-trial outcomes, the most accurate estimates were from the M-spline method, followed by no external data/piecewise method (the two give identical estimates for the within-trial period)

CONCLUSIONS

- Incorporating external evidence can increase the accuracy of survival extrapolations
- For this case-study, the informative prior method led to the most accurate 72-month predictions, with the smallest uncertainty. The use of informative priors did lead to worse within-sample estimates compared with using no external data (or only using external data for the extrapolated phase)
- Other methods for incorporating external evidence, such as hierarchical models[13], could be explored as well as incorporating additional external evidence such as general population mortality[14]

REFERENCES

1. Kearns et al. BMC medical research methodology. 2021; 21: 1-11.
2. Tai et al. Value in Health. 2021; 24: 505-12.
3. Bullement and Kearns. Health Services and Outcomes Research Methodology. 2022; 22: 317-31.
4. Bullement et al. Med Decis Making. 2023; 43: 610-20.
5. Guyot et al. Med Decis Making. 2017; 37: 353-66.
6. Jackson et al. Med Decis Making. 2017; 37: 377-90.
7. Ascierto et al. JAMA oncology. 2019; 5: 187-94.
8. Larkin et al. New England Journal of Medicine. 2019; 381: 1535-46.
9. Robert et al. Journal of Clinical Oncology. 2020; 38: 3937.
10. Palmer et al. Value in Health. 2023; 26: 185-92.
11. Soikkeli et al. Value in Health. 2019; 22: 1012-7.
12. Jackson C. arXiv. 2023; arXiv:230603957.
13. Dron et al. Contemp Clin Trials Commun. 2019; 16: 100446.
14. van Oostrum et al. Value in Health. 2021; 24: 1294-301.

An electronic version of the poster can be viewed by scanning the QR code.

Poster presented at ISPOR EU 2023; 12–15 November 2023; Copenhagen, Denmark.