Comparison of in Network Meta-analyses using Standard, Mixture Cure and Spline Models

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BACKGROUND AND OBJECTIVES

Novel immune therapies are potentially curative options in oncology. The need to capture the cure fraction or the plateau of long-term survival in patients treated with novel therapies call for more flexible approaches for survival extrapolations, such as spline or mixture cure model. The aim of this research is to examine how these techniques can be incorporated into the network meta-analysis (NMA), that is commonly used for health technology assessment (HTA) purposes in the absence of head-to-head comparisons. Previously, we have compared a traditional parametric network meta-analysis (PNMA) and a novel mixture-cure PNMA (MCPNMA) methodology for extrapolating overall survival (OS): (van Oostrum, 2019, #pcn441). In this study, we explore another method capturing time-varying hazards: a novel spline NMA.

METHODS

To test the three NMA methodologies, two melanoma trials comparing potentially curative treatments with a standard of care therapy were used. Trial 1 (Ascierto, 2018) compared nivolumab versus dacarbazine (Figure 1)[1], and trial 2 (Robert, 2011) compared ipilumumab+dacarbazine versus dacarbazine (Figure 2)[2]

Figure 1. OS KM of trial 1 (Ascierto, 2018)

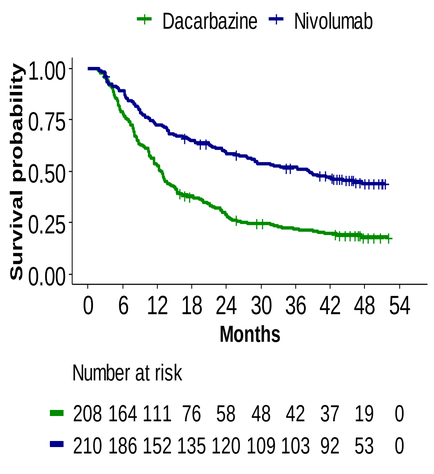
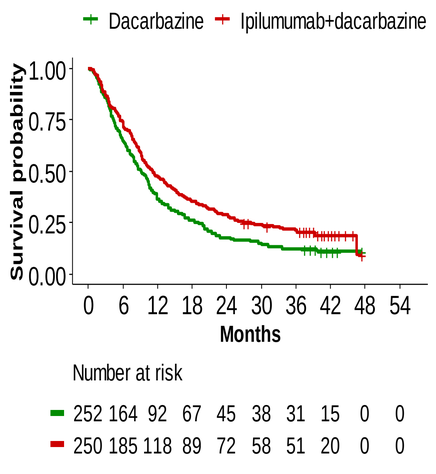


Figure 2. OS KM of trial 2 (Robert, 2011)



Patient-level data were simulated by using the Guyot algorithm[3] on the extracted Kaplan-Meier (KM) curves from the publications.

Two types of spline models were fitted on the trial data. First, three parametric distributions (Weibull, lognormal, loglogistic) were fitted using the Royston-Parmer model.[4] The knot placement was estimated within the log-likelihood function, as described in Royston, 2002.[4] Secondly, a model was fitted directly on the log hazard, using the same underlining spline function as in the first model type. Trial 1 was used as a reference. Best fitting distributions using the standard PNMA and MCPNMA methodologies are also presented in Table 1 and described in detail in van Oostrum, 2019 (#pcn441).

All the models incorporated general population mortality (GPM) to ensure that the predicted mortality hazards cannot go lower than GPM over time.

The survival extrapolations were compared in terms of visual and statistical fit (LOO Information Criterion [LOOIC]), mean (incremental) survival, and corresponding uncertainty.

RESULTS

Spline NMA and MCPNMA had a better statistical fit (LOOIC) over the trial data compared to PNMA. Table 1 presents LOOIC scores, mean and incremental mean survival (in years) for spline NMA models and best fitting PNMA and MCPNMA distributions. Figures 3-4 present the plots of the log-hazard spline NMA and Royston-Parmer spline NMA models.

Figure 3. Survival fit using Log hazard Spline NMA

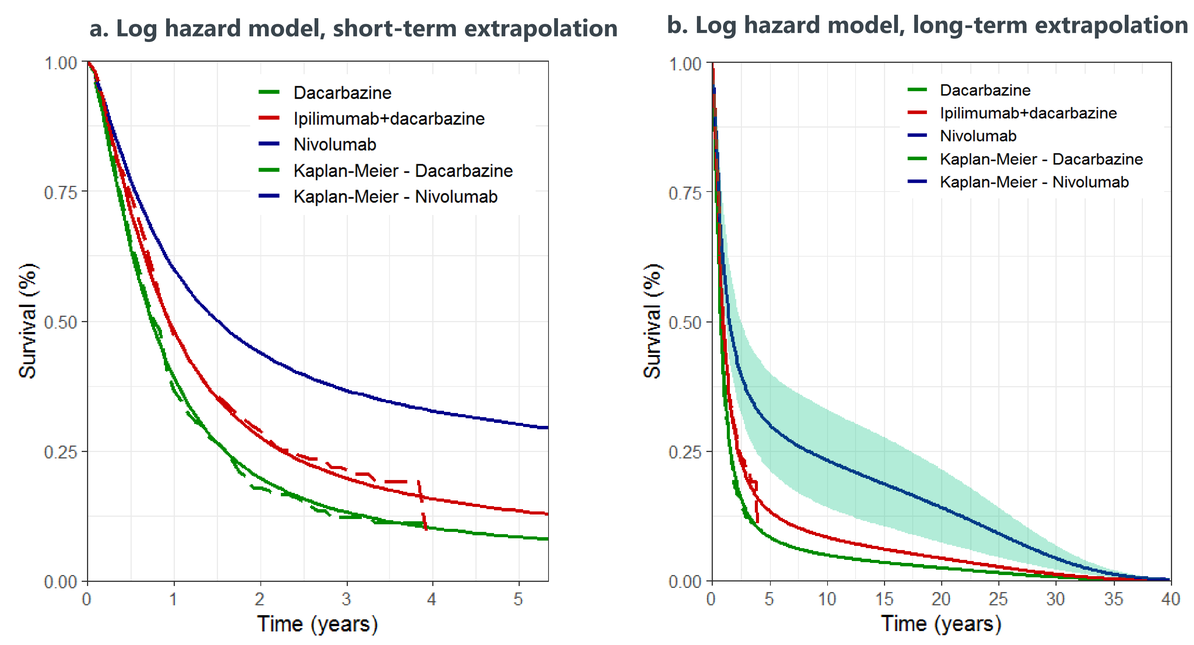


Figure 4. Survival fit using Royston-Parmer Spline NMA

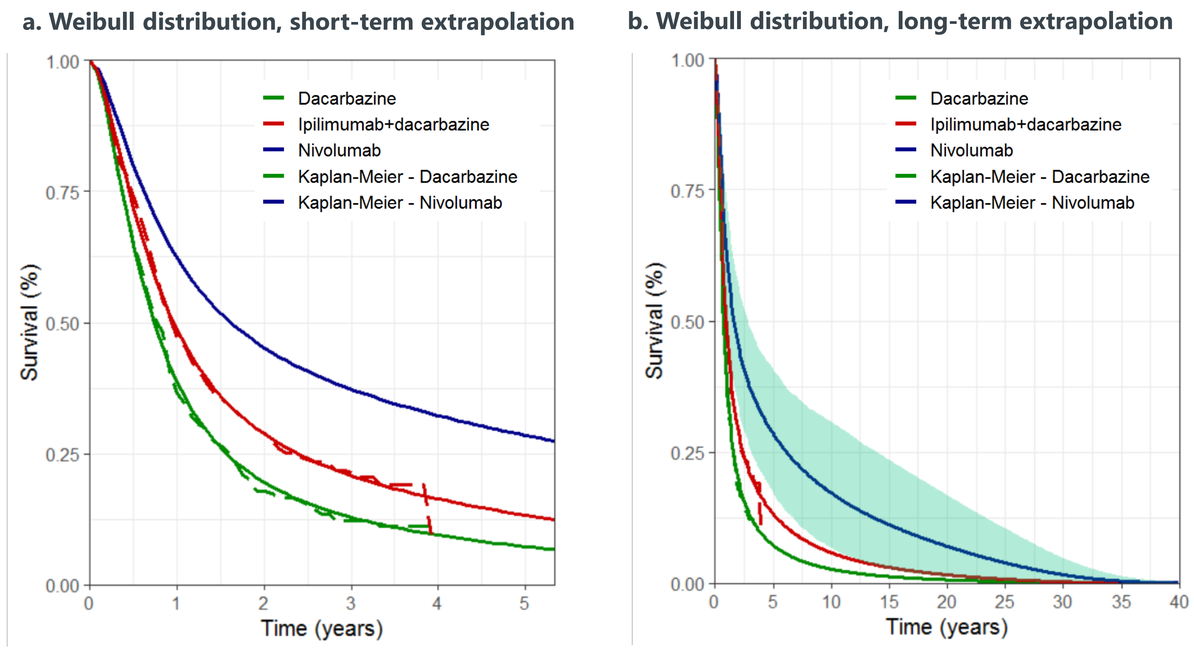


Table 1. Statistic fit and mean survival in years by methodology

Methodology	LOOIC	Mean life years [95% CrI]			Incremental life years [95% CrI]	
		Dacarbazine	Ipilimumab+ dacarbazine	Nivolumab	Ipilimumab+ dacarbazine vs Dacarbazine	Nivolumab vs Dacarbazine
Spline NMA						
Log-hazard model	5,718	2.1 [1.4 - 2.9]	3 [2.1 - 4.3]	6.6 [4.4 - 9]	0.9 [0.2 - 2.3]	4.4 [2.6 - 6.7]
Royston-Parmer model						
Weibull	5,713	1.7 [1.2 - 2.5]	2.5 [1.7 - 3.7]	5.2 [2.8 - 8.2]	0.8 [-0.1 - 1.9]	3.5 [1.4 - 6.1]
Loglogistic	5,726	1.8 [1.5 - 2.4]	2.4 [1.9 - 3.1]	3.7 [2.6 - 5.2]	0.6 [0.1 - 1]	1.9 [1.0 – 3.0]
Lognormal	5,714	1.6 [1.2 - 2.1]	2.4 [1.8 - 3.2]	3.4 [2 - 5.8]	0.8 [0.1 - 1.6]	1.8 [0.6 - 3.8]
PNMA						
Lognormal (best fit)	5,743	2.1 [1.7-2.6]	3.2 [2.2-4.5]	6.1 [4.8-7.5]	1.1 [0.2-2.2]	4.0 [2.6-5.5]
MCPNMA						
Lognormal (best fit)	5,681	4.6 [3.3-5.9]	5.9 [1.6-16.6]	9.0 [5.8-11.3]	1.3 [-3.3-11.9]	4.4 [1.0-7.1]

CONCLUSION

NMA based on spline models can be seen as alternative to PNMA. The choice between the models should be informed by fit statistics, long-term survival observational data and expert opinion on clinical plausibility of long-term survival extrapolations.

REFERENCES

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KEYWORDS

Oncology, health technology assessment, indirect treatment comparison, mixture cure models, spline models, network meta-analysis