Synthesis of survival outcomes in economic evaluation: does the NMA model matter?

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Background

HTA submissions with survival outcomes often rely on the proportional hazards assumption. However, network meta-analysis (NMA) methods of time-to-event data have been developed to relax this assumption for a range of different parametric and non-parametric survival models. These models can lead to differences in survival estimates, which could translate into different cost-effectiveness results and thereby influence the decision-making process. This research aims to assess the impact of different NMA methods for time-to-event outcomes on cost-effectiveness results in the recent NICE melanoma guideline update.

What we did and why

The recent NICE melanoma guideline update (1) included a review of therapies for advanced melanoma to determine the most effective and cost-effective treatment. There is no head-to-head trial comparing all treatments, so an NMA was conducted to combine the available evidence to best inform the survival estimates to be used in the economic model.

Using a network of 9 treatments, we fit NMA survival models for progression-free (PFS) and overall survival (OS) for: Cox proportional hazards (PH), generalised gamma with one and two treatment effects, fractional polynomial (FP), and piecewise exponential with one, two, and three cut points (Table 1). The survival estimates from the NMA models were incorporated into an economic model, to compare the impact on total costs, QALYs, and net monetary benefit (NMB). The economic model was a partitioned survival analysis, based on drug costs used in decision making.

Model fit statistics and visual inspection by clinical experts were used to determine goodness of fit and appropriate extrapolation of the survival estimates generated by each NMA method. None of the NMA models aligned with clinical expectations of long-term survival and we were advised that after 10 years, overall survival would be consistent with general population mortality, and so we applied rates from UK life tables after this time point.

Outcomes and impact

The type of NMA model used led to substantially different survival estimates, and thus cost-effectiveness results. The magnitude of the difference varied by treatment. Figures 1 and 2 show the difference between the survival curves generated in the FP model and the generalised gamma with one treatment effect model for PFS and OS, respectively.

The FP model better captured differences in the shapes of the survival curves for different treatments than other models that we fitted. Figures 1 and 2 demonstrate the difference in speed of response between targeted therapies (dabrafenib plus trametinib and encorafenib plus binimetinib) and immunotherapies (nivolumab, pembrolizumab and ipilimumab), which aligns with clinical expectation.

The model assuming proportional hazards gave a poor fit and overestimated survival relative to all other models: for example, pembrolizumab had 26% fewer QALYs with the FP model.

All models except the generalised gamma models indicated nivolumab plus ipilimumab as the most cost-effective treatment, and all models predicted dabrafenib plus trametinib to be the least cost-effective.

Figure 1: PFS curves; fractional polynomial (left), generalised gamma with 1 treatment effect (right)

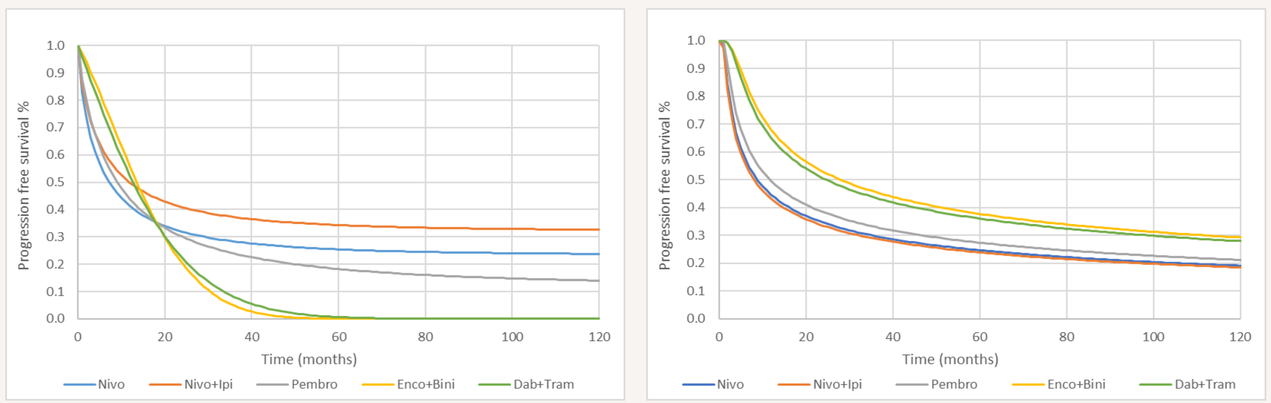

Figure 2: OS curves; fractional polynomial (left), generalised gamma with 1 treatment effect (right)

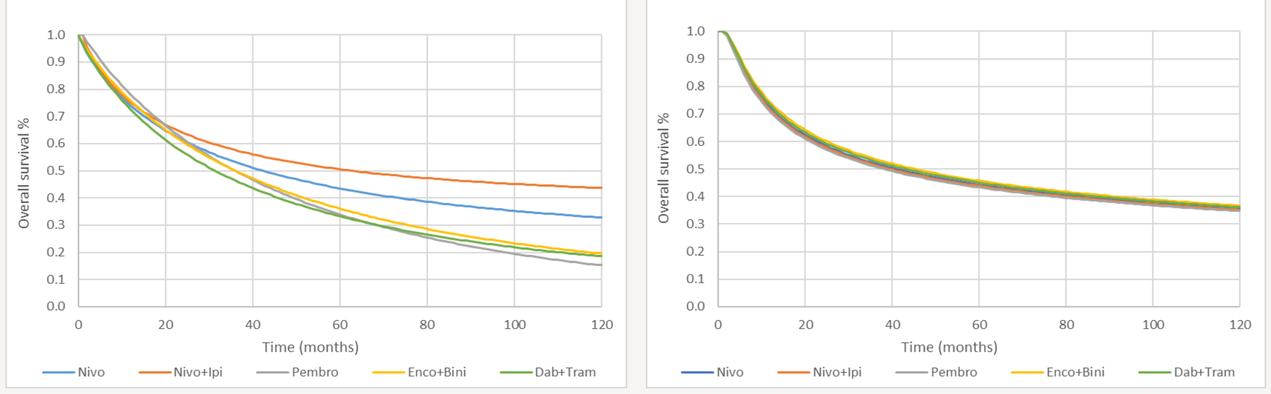

Table 1: Percentage change in NMB between NMA methods compared with the Cox PH model.

	Pembro	Nivo	Nivo+Ipi	Enco+Bini	Dab+Tram
Cox proportional hazards	-	-	-	-	-
Fractional polynomial	47%	-8%	2%	59%	41%
Generalised Gamma 1 treatment effect	2%	0%	50%	23%	9%
Generalised Gamma 2 treatment effects	1%	0%	26%	50%	37%
Piecewise exponential, 1 cut point at 6 months	55%	23%	54%	28%	8%
Piecewise exponential, 1 cut point at 15 months	69%	19%	33%	48%	27%
Piecewise exponential, 2 cut points at 12 and 18 months	64%	14%	29%	50%	28%
Piecewise exponential, 3 cut points at 6, 12 and 18 months	63%	10%	28%	36%	19%

Table 1 shows the percentage change in NMB for each treatment between the 8 NMA methods explored. The large differences between outcomes from each model indicate that the NMA method selected can have a substantial impact on the absolute cost-effectiveness results, despite the overall conclusions being stable in this case study. A limitation of this analysis was that time on treatment was not estimated using these methods but is likely to be a driver of costs in the economic analysis, which could explain why the NMA method selected did not change the overall conclusions.

What we learnt

Although the different NMA methods did not lead to different conclusions in terms of the rank order of cost-effectiveness in this case study, this may not be the case in other economic evaluations. For example, where differences in OS between treatments are smaller, or where the economic model is more sensitive to OS. This is a single case study, and further work is required to understand situations where decision-making is sensitive to the choice of NMA models.
The stability in rank order across NMA methods indicates confidence in the cost-effectiveness outcomes.

References:
1. National Institute for Health and Care Excellence (2022) Melanoma: assessment and management, NG14

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