The Impact of Treatment Effect Parametrization in Mixture Cure Models on (Incremental) Survival Estimates and Uncertainty

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Introduction

NICE decision unit (DSU) 21 discusses mixture cure models (MCM) considering one trial arm and hence do not discuss treatment effects (TE) [1]. As indirect treatment comparisons (ITCs) are becoming more common, we argue that these models need to be explored for multiple treatment arms. Therefore, we explored a MCM network meta-analysis (NMA), focussing on TE applied to MCM parameters.

Methods and materials

We conducted a MCM network meta-analysis (NMA) in melanoma for two randomized control trials (RCTs), Checkmate 067 [2] and Keynote 006 [3].

The Checkmate 067 trial was chosen as the reference trial, and ipilimumab was chosen as the reference treatment.

The following MCMs were tested; exponential, Gompertz, loglogistic, lognormal and Weibull. The base model applies TE on all MCM parameters (cure, scale and shape) (model1). The Leave-One-Out-Information-Criteria (LOOIC) is used to determine the goodness-of-fit. The MCM with lowest LOOIC is further optimized by only keeping the TEs for parameters for which the value of the SD smaller than the (absolute) value of the TE (model 3). We also explore a model with applying TE to the cure parameter only (model 2), which is the standard/base case setting in flexsurvcure.

Results

Finding the best fitting MCM

We conducted a MCM network meta-analysis (NMA) in melanoma for two trials (Keynote 006 (comparing pembrolizumab versus ipilimumab) and Checkmate 067 (comparing nivolumab versus ipilimumab). We aim to estimate the relative treatment effect of the three treatments for which the Kaplan Meiers (KMs) are depicted in *figure 1.* This results in the network of evidence as shown in *figure 2.* The Weibull, lognormal, loglogistic and Gompertz MCMs were tested for the best fit while applying treatment effects on all parameters (shape, scale and cure). The lognormal MCM rendered the best fit considering the LOOIC, and therefore is used for all further analyses (model 1 in *table 2*).

Figure 1a. Kaplan Meier Keynote 006

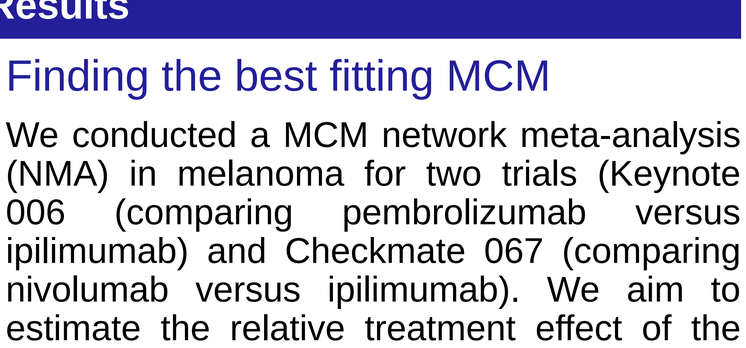


Figure 1b. Kaplan Meier Checkmate 067

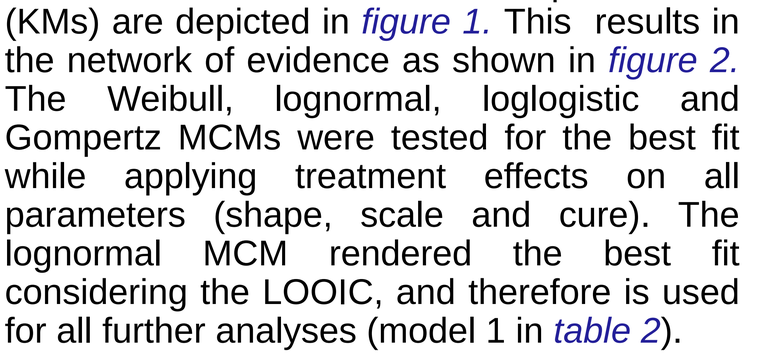
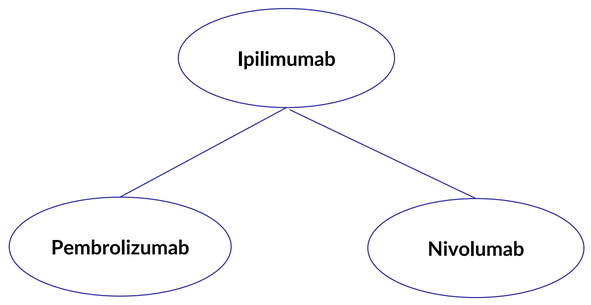


Figure 2. Network of evidence



Finding the optimal MCM with regards to TEs applied to parameters

We aimed to optimize the lognormal MCM by only including TEs for which the SD was smaller than the treatment effect itself. *Table 1* shows the TE for each of the parameters. None of the TEs applied to the cure parameter had a SD < the TE. For the scale parameters, the SD for both treatments was smaller than the TE. For the shape parameters, only the TE for nivolumab had a SD < (the absolute) TE. Based on this we find that the lognormal MCM with TEs applied to the scale and shape parameters renders the best fitting model (model 3).

Table 1. Treatment effects per MCM parameter

Parameter	Treatment	Tx effect	SD	SD < Tx effect
Cure	Ipilimumab	NA	NA	NA
	Nivolumab	1.48	3.33	No
	Pembrolizumab	-0.10	0.31	No
Scale	Ipilimumab	NA	NA	NA
	Nivolumab	0.68	0.37	Yes
	Pembrolizumab	0.51	0.18	Yes
Shape	Ipilimumab	NA	NA	NA
	Nivolumab	0.36	0.14	Yes
	Pembrolizumab	0.10	0.11	No

Survival and cure results

The incremental survival and cure fractions of respectively ipilimumab and pembrolizumab versus nivolumab for model 1 (TE applied to cure, scale and shape parameters) , model 2 (TE applied to the cure parameter only) and model 3 are displayed in *table 2*. For model 3 no TE was applied to the cure parameter, hence the cure rate amongst all treatments is equal. In this scenario it is assumed that nivolumab and pembrolizumab impact uncured survival only. The survival curves for each of these models are shown in *figure 3*.

Table 2. Cure and survival estimates for each model

Treatment effect applied to which parameters?		Model fit	Ranking		Cure		Survival		
		LOOIC	Best to worst	Tx	Cure fraction	Lower- and upper bound	Mean	Incremental	Lower- and upper bound
Model 1	cure scale and shape	8465.35	2	Ipilimumab	0.12	0.065 to 0.128	5.16	NA	NA
				Nivolumab	0.11	0.0004 to 0.344	7.88	2.89	0.58 to 5.24
				Pembrolizumab	0.13	0.193 to 0.287	6.99	1.81	0.38 to 3.55
Model 2	Cure ()	8471.28	3 (Worst)	Ipilimumab	0.071	0.0005 to 0.178	4.66	NA	NA
				Nivolumab	0.305	0.198 to 0.402	9.09	4.35	2.54 to 6.08
				Pembrolizumab	0.113	0.0008 to 0.290	5.35	0.62	0.00 to 2.63
Model 3	Scale and shape	8461.09	1 (best)	Ipilimumab	0.148	0.007 to 0.238	5.50	NA	NA
				Nivolumab	0.148	0.007 to 0.238	8.13	2.63	1.33 to 4.22
				Pembrolizumab	0.148	0.007 to 0.238	7.09	1.56	0.51 to 3.07

Figure 3a. Model 1 (TE applied to all parameters)

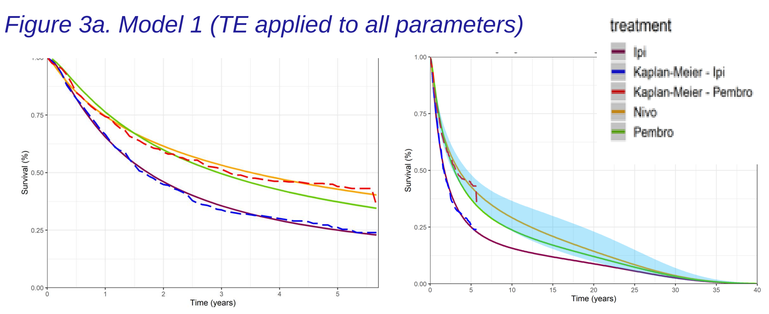


Figure 3b. Model 2 (TE applied to cure parameter only)

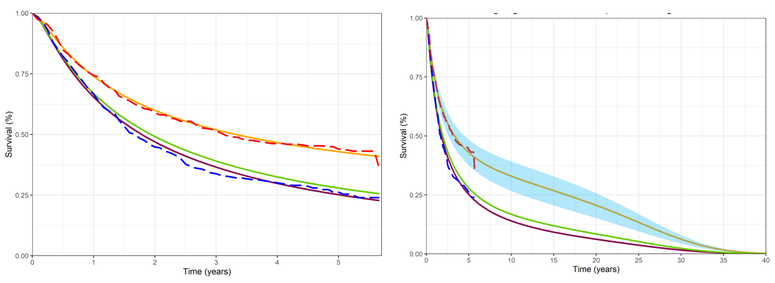
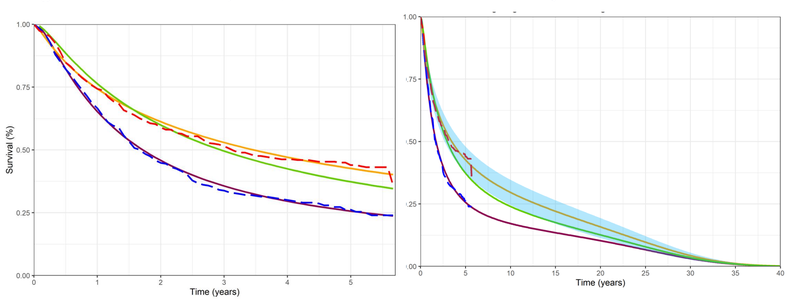


Figure 3c. Model 3 (TE applied to scale and shape)



Conclusions

We aimed to explore the optimal MCM with regards to TE for a NMA of the checkmate 067 and KEYNOTE 006 trials in metastatic melanoma. For this network of evidence, our results show that MCMs with TE applied to different model parameters results in different cure estimates per treatment in the evidence network and different (incremental) mean survival and corresponding uncertainty. This will impact the incremental cost-effectiveness ratio and corresponding uncertainty and therefore HTA reimbursement decisions.

References

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