Poster #: MSR50

Comparing Survival Extrapolation Outcomes Using Different Network Meta-analyses (NMA) Methods: An Application in Patients with Metastatic Renal Cell Carcinoma (mRCC) Treated with Immunotherapy (IO) Renal-based Combinations

F. Kroi, S. Depalma, H. El Alili, A. Verhoek, S. van Beekhuizen, B. Heeg
Cytel, Rotterdam, Netherlands

Background

- Due to limited follow-up in randomised controlled trials (RCT), survival extrapolation beyond the follow-up period is essential to inform reimbursement decisions.[1] Depending on the hazard rates, more advanced extrapolation survival models might be justified. Network meta-analyses (NMA) are used to compare studies in the absence of direct evidence.[2]

Objective

- This study aimed to compare survival extrapolation outcomes from different NMA methods.

Key Results

- Due to proportional hazard assumption (PHA) violation, hazard ratio NMA outcomes significantly differed compared to parametric and piecewise NMA methods. The outcomes from the hazard ratio NMA should not be considered valid.
- The piecewise NMA outcomes had wider credible intervals (CrI) compared to the parametric NMA due to less data for the extrapolation of the tail.
- The parametric NMA fitted the data best compared to the other two NMA methods and showed less wide CrIs in the outcomes.

Conclusions

- Parametric NMA is considered the method with the most robust outcomes compared to the other tested NMA methods.
- The appropriate NMA method should be selected carefully to avoid biased estimates in health economic models used for reimbursement decision-making.

Limitations

- Alternative NMA methods (i.e., fractional polynomials, splines) were not investigated.

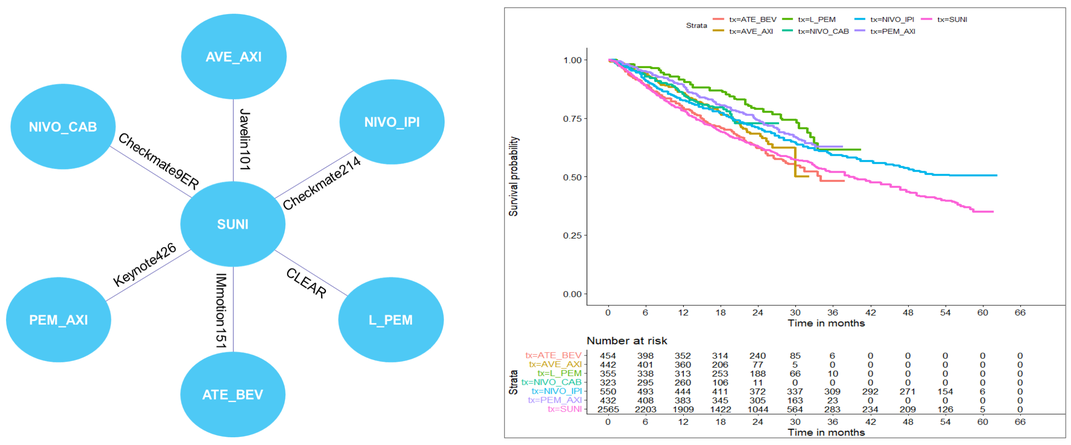
Methods

- The network from a recently published hazard ratio NMA in first-line systemic therapies for metastatic renal cell carcinoma was used as an example.[3]
- Six different RCTs, including seven different immunotherapy treatments (i.e., sunitinib, nivolumab + ipilimumab, avelumab + axitinib, nivolumab + cabozantinib, pembrolizumab + axitinib, atezolizumab + bevacizumab, pembrolizumab + lenvatinib), were included in the analyses.
- The Kaplan-Meier (KM) graphs from the RCTs were used to reconstruct pseudo-individual patient-level data using the Guyot method.[4] The PHA was assessed statistically with a Schoenfeld test.
- The outcomes (i.e., mean survival and incremental mean survival) from three different NMA methods (hazard ratio NMA, parametric NMA and piecewise NMA) were compared.
- For the piecewise NMA, a data cut at 12 months was assumed based on KM observation.
- Uncertainty was estimated with the use of a Markov chain Monte Carlo simulation in the hazard ratio NMA and a Bayesian model for the parametric and piecewise NMA. Five different distributions (i.e., exponential, Weibull, log-logistic, log-normal and Gompertz) were fitted to the data.
- The statistical fit of the models was assessed using the leave-one-out information criterion (LOOIC). Outcomes with a p-value <0.05 were considered statistically significant.

Results

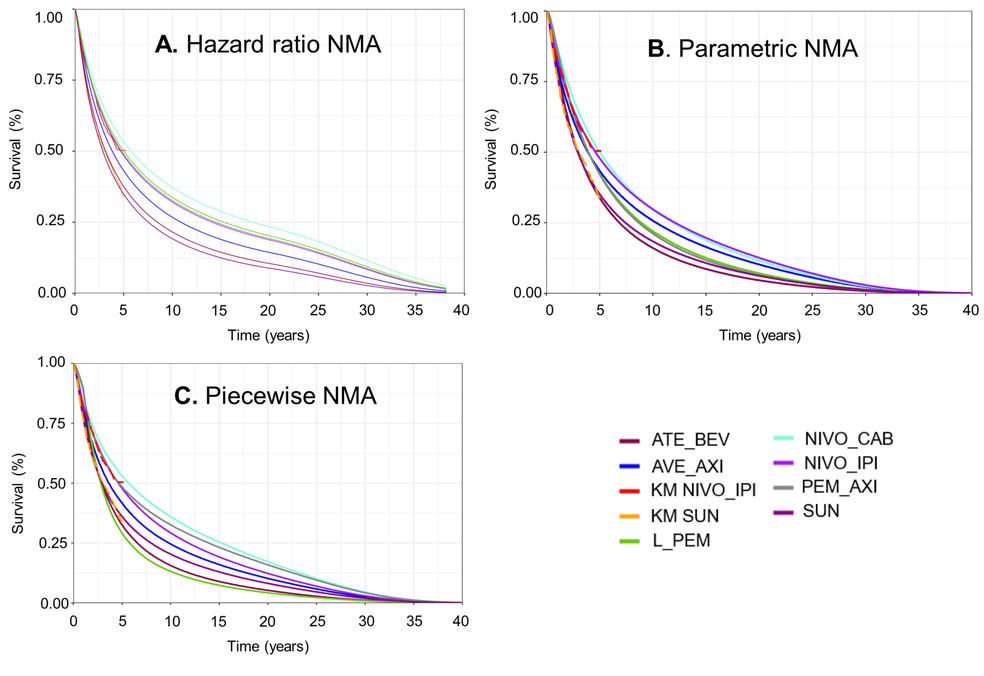
- The PHA was violated in the pembrolizumab + lenvatinib vs. sunitinib trial. A delayed treatment effect was identified in the nivolumab + ipilimumab vs. sunitinib and the avelumab + axitinib vs. sunitinib trials.
- The PHA violation (i.e., no constant hazard rates) and delayed treatment effect (i.e., hazard rates change after a timepoint) justified the use of parametric and piecewise NMA methods, respectively.[5]
- Figure 1 presents the network of evidence and the reconstructed KM curves.

Figure 1. Network of evidence and reconstructed KM curves



- Based on the LOOIC, log-normal and log-logistic were the best-fitting distributions for the parametric NMA and the piecewise NMA, respectively. For the hazard ratio NMA, the log-normal distribution outcomes were used (Figure 2).

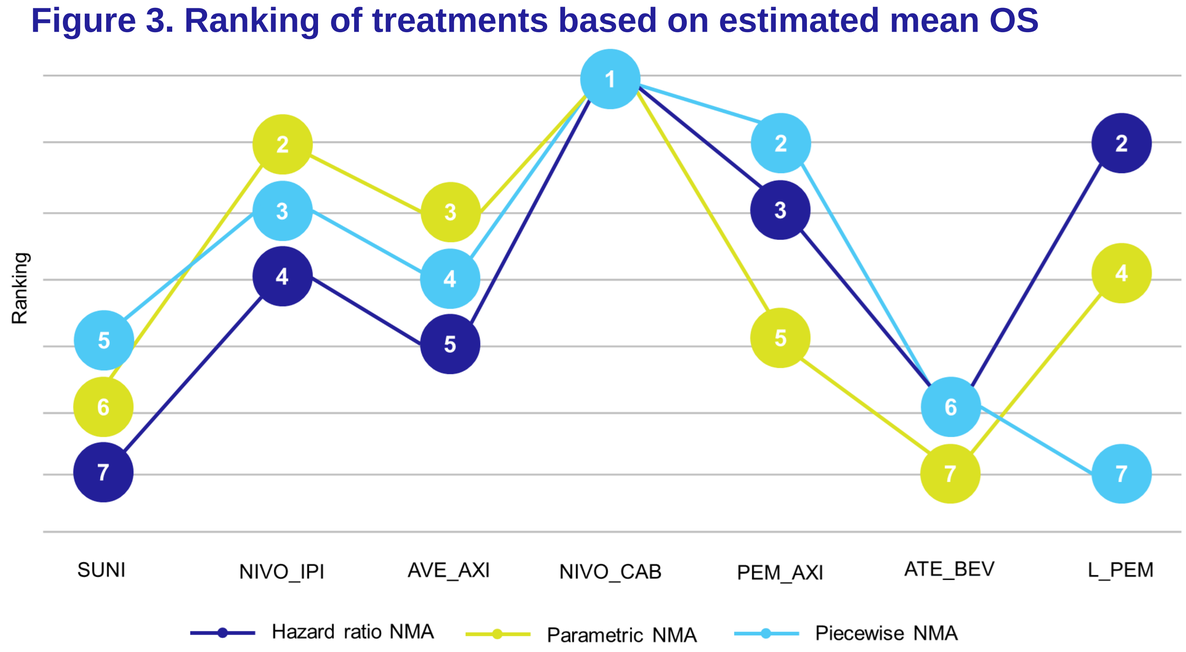
Figure 2. Extrapolated curves per treatment and NMA method



Results (cont.)

- Data fit was slightly better in the log-normal parametric NMA compared to the log-logistic piecewise NMA (i.e., LOOIC: 19,356 vs. 19,375). The fit from the hazard ratio NMA could not be compared with the other NMA methods.
- Nivolumab + cabozantinib was ranked first based on the estimated mean overall survival (OS) in all three NMA methods (Figure 3).

Figure 3. Ranking of treatments based on estimated mean OS



- The estimated incremental mean survival outcomes (Table 1) showed that hazard ratio NMA outcomes significantly differed compared to the other NMA methods.
- Atezolizumab + bevacizumab was estimated to be better than sunitinib in the hazard ratio NMA but not in the other two NMA methods.
- Nivolumab + cabozantinib crosses with nivolumab + ipilimumab only in the parametric NMA.
- Due to violation of the PHA, the outcomes from the hazard ratio NMA should not be considered as valid.

Table 1. Incremental mean OS compared to sunitinib

NMA methods	Hazard ratio NMA (95% CrI)	Parametric NMA (95% CrI)	Piecewise NMA (95% CrI)
Treatments	**Incremental OS (years)**		
Sunitinib	-	-	-
Nivolumab + ipilimumab	**3.38 (1.40, 5.33)**	**2.40 (1.16, 3.63)**	**1.90 (0.51, 3.27)**
Avelumab + axitinib	1.92 (0.03, 3.79)	1.56 (-0.70, 3.80)	0.94 (-1.89, 3.84)
Nivolumab + cabozantinib	**4.86 (2.81, 6.88)**	2.45 (-0.59, 5.78)	3.34 (-2.96, 8.73)
Pembrolizumab + axitinib	**3.53 (1.54, 5.49)**	0.75 (-1.00, 2.88)	2.72 (0.49, 4.78)
Atezolizumab + bevacizumab	0.59 (-1.19, 2.36)	-0.40 (-1.93, 1.55)	-0.86 (-2.75, 1.18)
Pembrolizumab + lenvatinib	**3.84 (1.83, 5.82)**	0.89 (-1.47, 3.59)	-1.16 (-4.18, 2.50)

Abbreviations: CrI, credible interval; NMA, network meta-analysis; OS, overall survival

- Piecewise NMA showed better survival compared to parametric NMA. This was expected since piecewise NMA can represent flexible hazards; something that parametric NMA cannot do so well.
- Piecewise NMA had little data to extrapolate the tail on and, as a result, the incremental mean survival outcomes included broader CrIs.
- Due to a better fit of the data and less wide CrIs, the outcomes from the parametric NMA were considered the most robust in this case.

References

1. Rutherford, MJ., et al. NICE DSU Technical Support Document 21. Flexible Methods for Survival Analysis. 2020.
2. Dias, S., et al. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
3. Bosma NA, et al. Efficacy and Safety of First-line Systemic Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis. Eur Urol Open Sci. 2022 Jan 22;37:14-26. doi: 10.1016/j.euros.2021.12.007.
4. Guyot, P., M.J. et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 12, 9 (2012). https://doi.org/10.1186/1471-2288-12-9.
5. Heeg, B., et al. Novel and existing flexible survival methods for network meta-analyses. J Comp Eff Res. 2022 Sep 12. doi: 10.2217/cer-2022-0044.

Drug abbreviations: ATE, atezolizumab; AVE, avelumab; AXI, axitinib; BEV, bevacizumab; CAB, cabozantinib; IPI, ipilimumab; PEM, pembrolizumab + lenvatinib; NIVO, nivolumab; SUN, sunitinib