Bayesian multi-parameter evidence synthesis for informed indirect treatment comparisons of extrapolated survival outcomes

Daniel J. Sharpe[1], Ashley E. Tate[2], Tuli De[3], Jackie Vanderpuye-Orgle[3]

[1]Parexel International, London, UK; [2]Parexel International, Amsterdam, Netherlands; [3]Parexel International, Billerica, Massachusetts, USA

MSR217

Background

- Differences in follow-up duration between studies leads to bias in indirect treatment comparisons[1] when complex treatment effects, such as durable response and acquired resistance, result in non-proportional hazards[2-7]
- Furthermore, indirect comparisons of cost-effectiveness from immature data require long-term extrapolations, which may present high risk to payers when data are immature[2,3]

Objectives

- We extended Bayesian multi-parameter evidence synthesis (B-MPES) survival models[8-10] to the network meta-analytic setting, for indirect treatment comparisons of extrapolated survival outcomes informed by external data for conditional survival beyond the available study follow-up periods

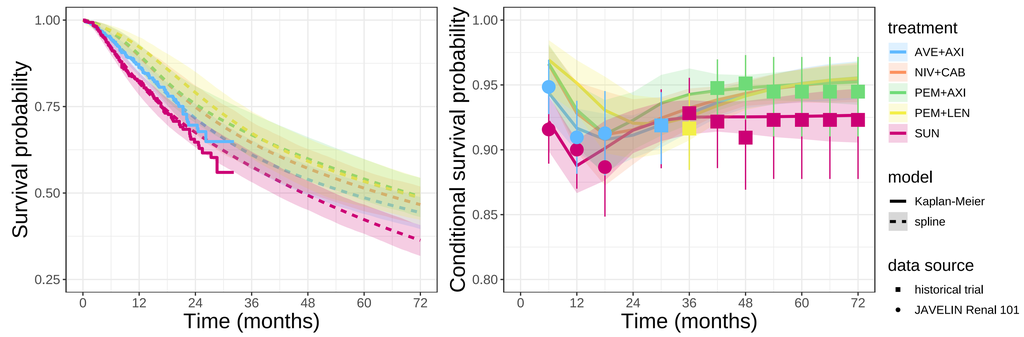
Methods

Network of studies in first-line mRCC

- We analyzed reconstructed interim overall survival data from four randomized phase III studies of first-line immunotherapy plus tyrosine kinase inhibitor (IO+TKI) vs TKI monotherapy (sunitinib) in metastatic renal cell carcinoma[11]
  - Median follow-up ranged from 18.1 to 30.6 months; we hypothesized that this heterogeneity disfavors IO+TKI therapies for which data are more mature in models based on proportional hazards and/or naïve extrapolation
- In the B-MPES model, outcomes were extrapolated using data from a historical phase III trial of dual IO therapy vs sunitinib, with 55 months median follow-up duration[11]
- Treatment effects were quantified by 5-year restricted mean survival time (RMST),[2,12] which provides a useful measure of accrued survival benefit beyond the available follow-up

Parametric spline model and B-MPES formulation

- Survival with the respective treatments was represented by independent 3-knot restricted cubic spline models smoothing the cumulative hazard function,[2,13] with trial factors for the intercept parameter and the first three spline coefficients
- Historical trial data informed extrapolations via additional likelihood contributions[8-10] for 6-month conditional survival beyond the respective median follow-up periods
  - The B-MPES model assumes similarity in longer-term, conditional survival between different IO regimens
  - The historical data were applied in the context of the reference trial (i.e., study of AVE+AXI vs sunitinib), chosen for closest similarity in distribution across baseline MSKCC risk strata (i.e., high, medium, low)[11]
  - Survival outcomes in the sunitinib arms of the reference and historical trials were very similar, so it was believed that no further adjustment of external data was warranted
- B-MPES estimates were compared to those from a naïve 1-knot proportional hazards spline model with trial coefficients on the intercept parameter only and to later trial observations



AVE+AXI = avelumab+axitinib; NIV+CAB = nivolumab+cabozantinib; PEM+AXI = pembrolizumab+axitinib; PEM+LEN = pembrolizumab+lenvatinib; SUN = sunitinib.

Estimates are in the context of the reference trial (JAVELIN Renal 101).

Shaded areas indicate 95% credible intervals of the parametric models. Points and whiskers show prior expectation and associated uncertainty derived from trial data. Note that estimates for all IO+TKI therapies were informed by the same historical trial data (for dual IO therapy), applied after the median follow-up period in the respective trials.

Figure 1: (Left) Survival and (right) 6-month conditional survival probabilities estimated from the B-MPES model.

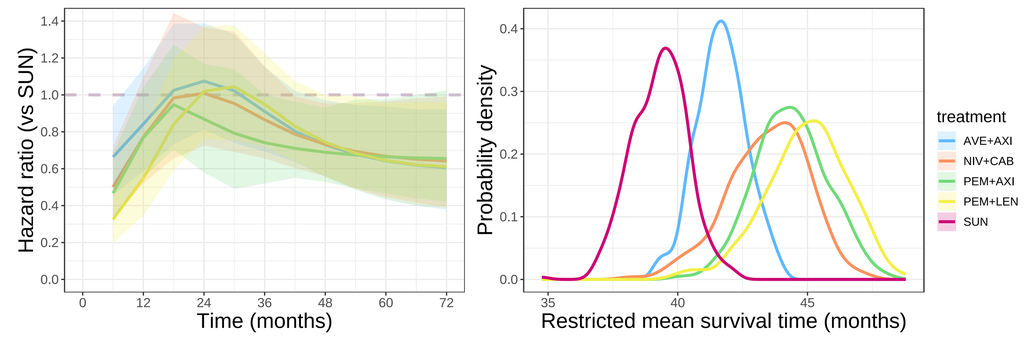


Figure 2: (Left) Estimated hazard ratio (vs SUN) for IO+TKI therapies. (Right) Posterior densities for 5-year RMST.

Results and Discussion

- In the B-MPES model, the historical data enforced a trend wherein conditional survival with IO+TKI therapies was consistently greater vs sunitinib from 36 months onwards (Fig. 1), and ensured that uncertainty in extrapolated survival was more reasonable than in the naïve model (Table 1)
- The B-MPES model captured strong deviations from proportional hazards in the IO+TKI vs sunitinib treatment effects (Fig. 2a), reflecting the trend in the historical study
- The B-MPES model overestimated absolute 5-year survival in both arms of the reference trial, suggesting confounding in prognostic factors, but not necessarily in treatment effect modifiers, between the reference and historical studies
- The B-MPES model predicted that the PEM+LEN, PEM+AXI, and NIV+CAB regimens were closely competitive (respective SUCRA[14]: 0.84, 0.75, 0.60) (Fig. 2b, Table 1)
  - Differences in 5-year survival vs sunitinib were slightly overestimated (e.g., for NIV+CAB: 9% est. vs 5% obs.)
  - The naïve model (resp. SUCRA: 0.68, 0.65, 0.78) and meta-analysis of hazard ratios[11] instead slightly favored NIV+CAB, for which data were least mature
- The B-MPES model assumed similarity in long-term hazards between the sunitinib arms of the current and historical studies. This assumption led to overestimating the later trial-observed treatment effects of IO+TKI vs sunitinib, as subsequent IO therapy was less prevalent in the historical trial, but still presented a useful and well-defined scenario

Table 1: Survival estimates [95% CrIs] from network meta-analyses based on B-MPES and naïve spline models.

	B-MPES spline model			Naïve, proportional hazards spline model		
Treatment	**5-year RMST (mo.)**	**5-year survival (%)**	**SUCRA**	**5-year RMST (mo.)**	**5-year survival (%)**	**SUCRA**
AVE+AXI	41.7 [39.7-43.6]	48.6 [43.9-53.0]	0.308	40.3 [37.2-43.4]	40.8 [31.1-51.1]	0.352
NIV+CAB	43.5 [40.1-46.1]	51.4 [44.7-56.5]	0.596	43.4 [38.0-47.7]	50.2 [34.5-64.2]	0.779
PEM+AXI	44.4 [41.6-47.0]	54.1 [47.8-59.8]	0.745	42.3 [38.6-45.6]	46.2 [35.7-56.3]	0.647
PEM+LEN	44.9 [41.6-47.6]	53.3 [46.1-59.8]	0.839	42.7 [38.7-46.8]	47.0 [34.6-59.4]	0.684
SUN	39.3 [37.2-41.3]	42.3 [38.2-46.7]	0.012	38.0 [35.5-40.6]	38.9 [31.8-46.1]	0.038

SUCRA = surface under cumulative ranking curve.[14] Greater values indicate higher treatment ranking. Survival estimates are in the context of the reference trial (of AVE+AXI vs SUN).

Conclusions

- Employing B-MPES models in a network meta-analysis framework provides an approach to generate reliable estimates of relative treatment effects over an extrapolated time horizon, by leveraging historical data with extended follow-up
  - B-MPES models attenuated bias that disfavored experimental treatments for which study data were more mature, addressing a key problem in more simplistic meta-analyses
  - Confounding between current and historical data may be partially addressed by selecting a suitable reference trial

REFERENCES

[1] Riley RD, et al. Using individual participant data to improve network meta-analysis projects. BMJ Evid Based Med. 2022; 28(3):197-203.
[2] Freeman SC, et al. Challenges of modelling approaches for network meta-analysis of time-to-event outcomes in the presence of non-proportional hazards to aid decision making. Stat Methods Med Res; 31(5): 839-61.
[3] Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011; 11:61.
[4] Ouwens MJNM, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Res. Synth. Methods 2010; 1(3-4):258-71.
[5] Cope S, et al. A comparison of alternative network meta-analysis methods in the presence of non-proportional hazards: a case study in first-line advanced or metastatic renal cell carcinoma. Value Health 2023; 26(4):465-76.
[6] Petersohn S, et al. Challenges in conducting fractional polynomial and standard parametric network meta-analyses of immune checkpoint inhibitors for first-line advanced renal cell carcinoma. J Comp Eff Res 2023;12(8): e230004.
[7] Heeg B, et al. Novel and existing flexible survival methods for network meta-analyses. J Comp Eff Res 2022; 11(15):1121-33.
[8] Guyot P, Ades AE, Beasley M, Lueza B, et al. Extrapolation of survival curves from cancer trials using external information. Med Decis Making 2016; 37(4): 353-66.
[9] Jackson CH. survextrap: a package for flexible and transparent survival extrapolation. BMC Med Res Methodol. 2023; 23(1): 282.
[10] Sharpe DJ, et al. A Bayesian model leveraging multiple external data sources to improve the reliability of lifetime survival extrapolations in metastatic non-small cell lung cancer. Med Decis Making 2025; 46(2):174-88.
[11] 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; 37:14-26.
[12] Wei Y, Royston P, Tierney JF, Parmar MKB. Meta-analysis of time-to-event outcomes from randomized trials using restricted mean survival time: application to individual participant data. Stat Med 2015; 34:2881-98.
[13] Freeman SC, Carpenter JR. Bayesian one-step IPD network meta-analysis of time-to-event data using Royston-Parmar models. Res Synth Methods 2017; 8:451-64.
[14] Salanti G, et al. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011; 64(2):163-71.

Contact: Daniel.Sharpe@parexel.com

www.parexel.com

Presented at ISPOR 2026; 17-20 May 2026; Philadelphia, PA, USA