MSR24

# A Case Study Using KEYNOTE-010 to Compare and Evaluate Long-Term Survival Estimates from Two Classes of Piecewise Models


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## Objective

To compare the accuracy of long-term survival estimates from a recently developed piecewise exponential model with piecewise models using Kaplan-Meier data adjoined to a parametric tail.

## Background

- Piecewise survival models have been suggested as a flexible alternative to standard parametric models for modeling complex hazard profiles, such as those commonly associated with immune-oncology (IO) therapies.
- One common class of piecewise model uses Kaplan-Meier (KM) data adjoined to a parametric tail (PW-KM) with the cut-point(s) defined through visual inspection of hazard plots for distinct changes or inflection points in the hazard profile.
- However, there are no definitive rules for the selection of the 'best' cut-point(s).[1]
- A method to statistically estimate the cut-point(s) has recently been developed by Cooney et al. (2023) using a piecewise exponential (PWE) model where a constant hazard is assumed within each segment, and separate exponential parametric models are fitted to each segment.[2] The final segment serves as the long-term extrapolation.
- Both model classes are displayed conceptually in **Figure 1**.
- This case study was motivated by the need for continued research into the comparison of method performance so survival models can be appropriately selected and lead to more robust long-term survival estimates.

## Methods

### KEYNOTE-010

- KEYNOTE-010 investigated pembrolizumab, an IO therapy for previously treated, programmed death-ligand 1-positive advanced non-small cell lung cancer.

### Data Generation

- Published overall survival KM curves from two data cut-offs (DCOs) were digitized:
  - First DCO: median follow-up 31.0 months.[3]
  - Second DCO: median follow-up 67.4 months.[4]
- Pseudo individual patient data (IPD) were generated from each DCO using the algorithm described by Guyot et al. (2012).[5]

### Model Fitting

- All models were fitted to pseudo IPD derived from the 31.0-month DCO.
- The PWE model identified a single cut-point at 13 months, and separate exponential models were fitted to each segment.
- For the PW-KM model, five months was selected as a cut-point through visual inspection of hazard plots, as the smoothed hazard plot indicated that at five months, the hazard became monotonically decreasing. A second PW-KM model with a 13-month cut-point was additionally specified to facilitate comparison with the PWE model.
- For the PW-KM models, from the cut-points onward, the six standard parametric tails were fitted to the remaining KM data and adjoined to the KM curves.

### Long-Term Survival Comparison

- To evaluate accuracy of the survival models in estimating long-term survival, restricted mean survival time (RMST) at maximum follow-up from the KEYNOTE-010 67.4-month DCO was compared to the estimated 67.4-month RMST based on extrapolation of the 31.0-month DCO for each model.
- Accuracy was assessed using absolute percentage difference in RMST calculated as:

$$\left| \frac{RMST_{estimated} - RMST_{actual}}{RMST_{actual}} \right|$$

## Results

- RMST from the 67.4-month DCO at maximum follow-up was 22.66 months.
- The 67.4-month DCO KM curve and the survival extrapolations for each model are shown graphically in **Figure 2**.
- Estimated RMST from the PWE model was 21.76 months, and average estimated RMSTs across the parametric tails for the 5- and 13-month PW-KM models were 22.46 (range: 20.52–23.79) and 22.53 (range: 21.71–24.07), respectively.
- Long term survival estimate accuracy results are presented in **Figure 3**.
  - The most accurate model was the 5-month PW-KM model with a GenGamma tail (absolute percentage difference in RMST: 0.64%) followed by the 13-month PW-KM model with a Gompertz tail (absolute percentage difference in RMST: 1.11%) and the 5-month PW-KM with a LogLogistic tail (absolute percentage difference in RMST: 1.14%).
  - The PWE model (absolute percentage difference in RMST: 3.96%) was ranked 7/13 in terms of model accuracy.

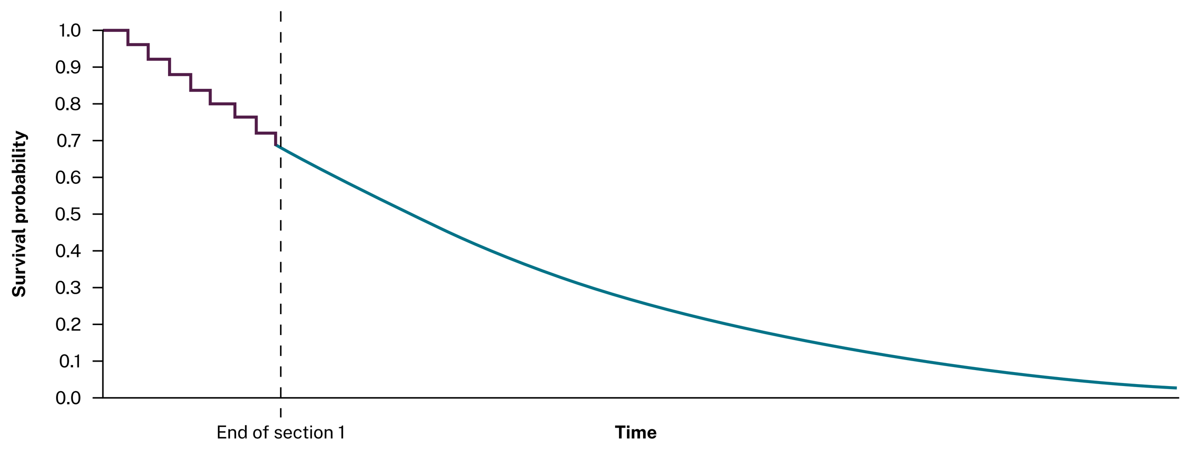
## Conclusion

- In this case study, the PWE model did not perform better than the PW-KM models in estimating long-term survival, on average.
  - In terms of absolute percentage difference, the PWE, 5-month PW-KM, and 13-month PW-KM models all performed similarly, with the 13-month PW-KM performing best by a slight margin.
- Although the cut-point was identified objectively for the PWE model, specifying the model to use constant hazards may limit its accuracy particularly for the final segment where the exponential model cannot reflect a decreasing hazard in the KM tail.
  - Biological plausibility and hazard plots should be assessed to validate the required hazard assumptions.
  - Nonetheless, the fact that the PW-KM using the cut-point identified by the PWE model performed best suggests that further research into objectively identifying cut-points should be explored.
- Limitations of this research are that it was a single case study and may not be generalizable, and that 'accuracy' was measured against realized RMST from long-term observed KM data that are themselves uncertain.

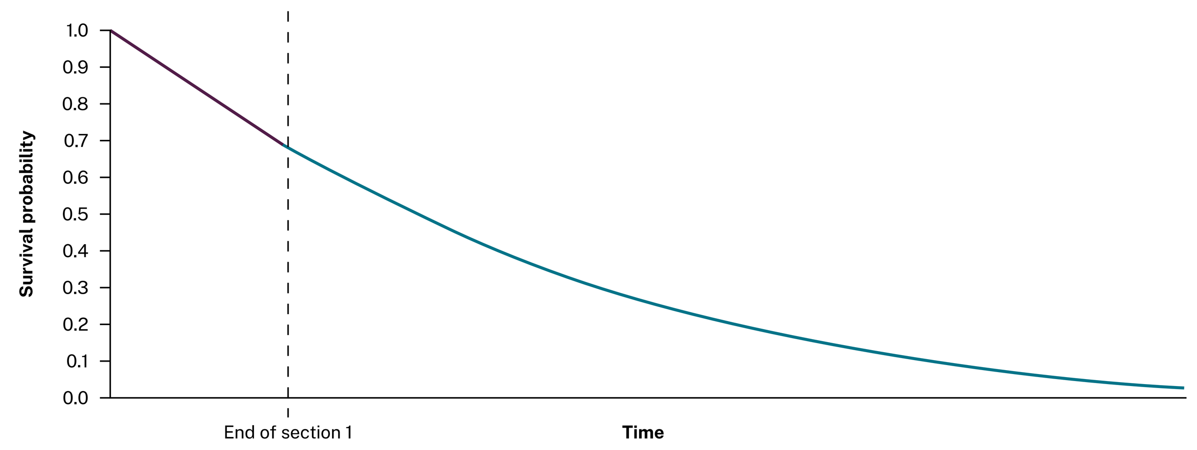
### FIGURE 1

Conceptual presentation of piecewise models

**A.** PW-KM model




**B.** PWE model

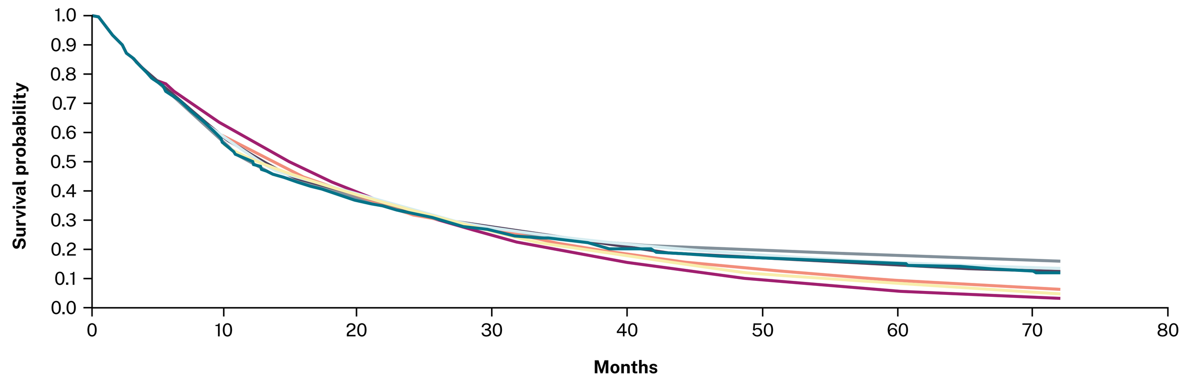



### FIGURE 2

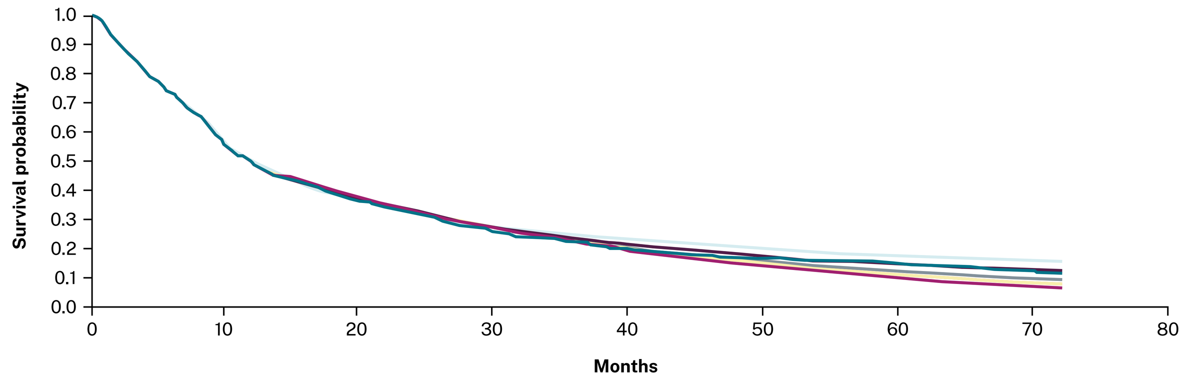
Survival extrapolations (visual fit)

PWE — 67.4-Month DCO KM — GenGamma — Gompertz — LogLogistic — LogNormal — Weibull — Exponential

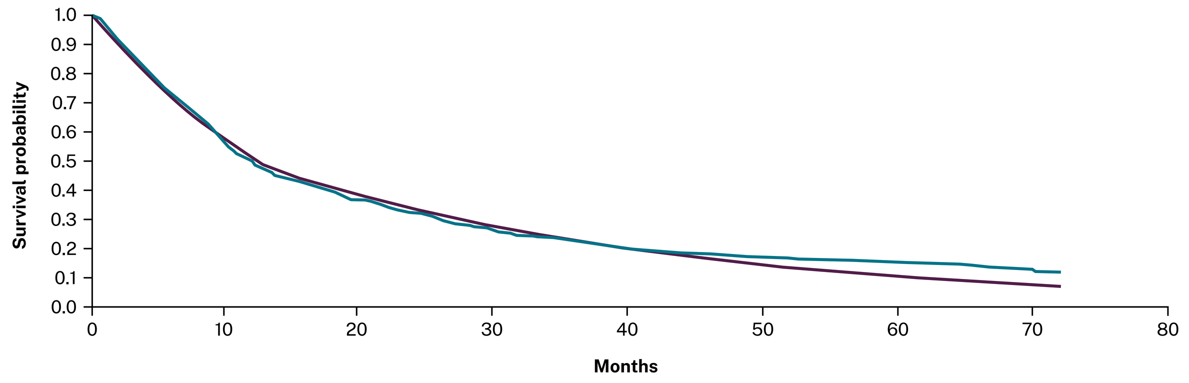
**A.** 5-month cut-point PW-KM




**B.** 13-month cut-point PW-KM




**C.** PWE model




### FIGURE 3

Long-term survival prediction accuracy

Absolute percentage difference in RMST — Mean absolute percentage difference in RMST


**Abbreviations:** DCO: data cut-off; IO: immune-oncology; IPD: individual patient data; KM: Kaplan-Meier; PWE: piecewise exponential; PW-KM: piecewise model using Kaplan-Meier data adjoined to a parametric tail; RMST: restricted mean survival time.


**References:** [1]Liu B. et al. Presented at ISPOR, 15–18 May 2022. Washington DC, USA. EE111; [2]Cooney P. et al. Value Health 2023;26(10):1510–1517; [3]Herbst RS. et al. Ann Oncol 2019;30(2):281–289; [4]Herbst RS. et al. J Thorac Oncol 2021;16(10):1718–1732; [5]Guyot P. et al. BMC Med Res Methodol 2012;12:9.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