A Case Study Using KEYNOTE-024 to Examine the Impact of Cut-Point Selection on Long-Term Survival Estimates from Piecewise Modeling

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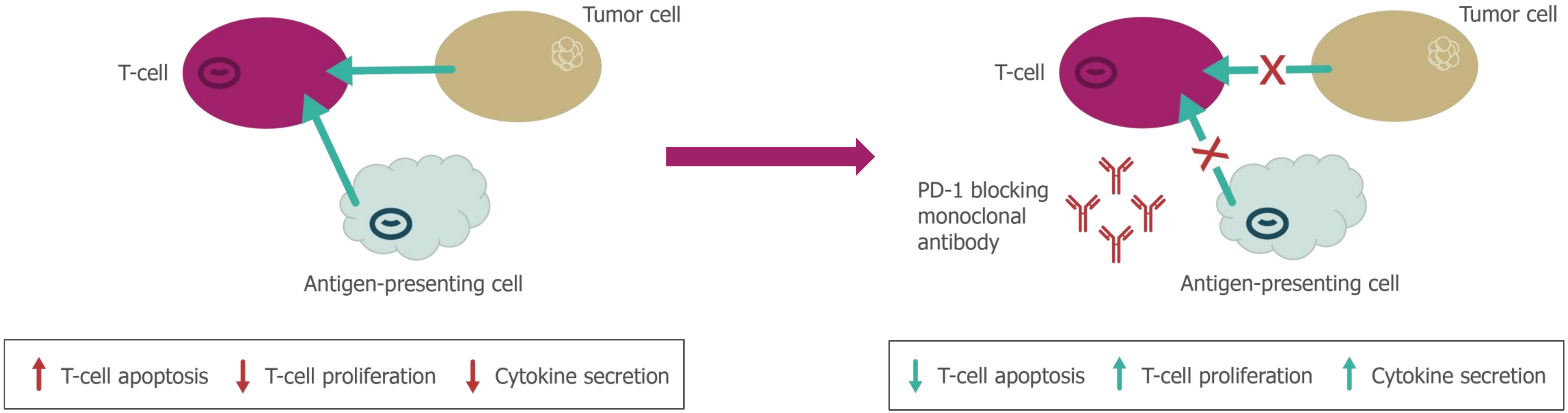
Background

Introduction to Immuno-Oncology Therapies

- Immuno-oncology therapies (IOs) aim to elicit an immune response to destroy malignant cells, whereas conventional anti-cancer therapies act directly on malignant (and healthy) cells
- Immune checkpoint inhibitors, such as programmed cell death protein 1 (PD-1) blocking monoclonal antibodies, are intended to rescue the antitumor immune response from co-inhibitory signalling that may occur in the tumor microenvironment[1]
- IOs differ from conventional anti-cancer therapies in their mechanism of action and length of action

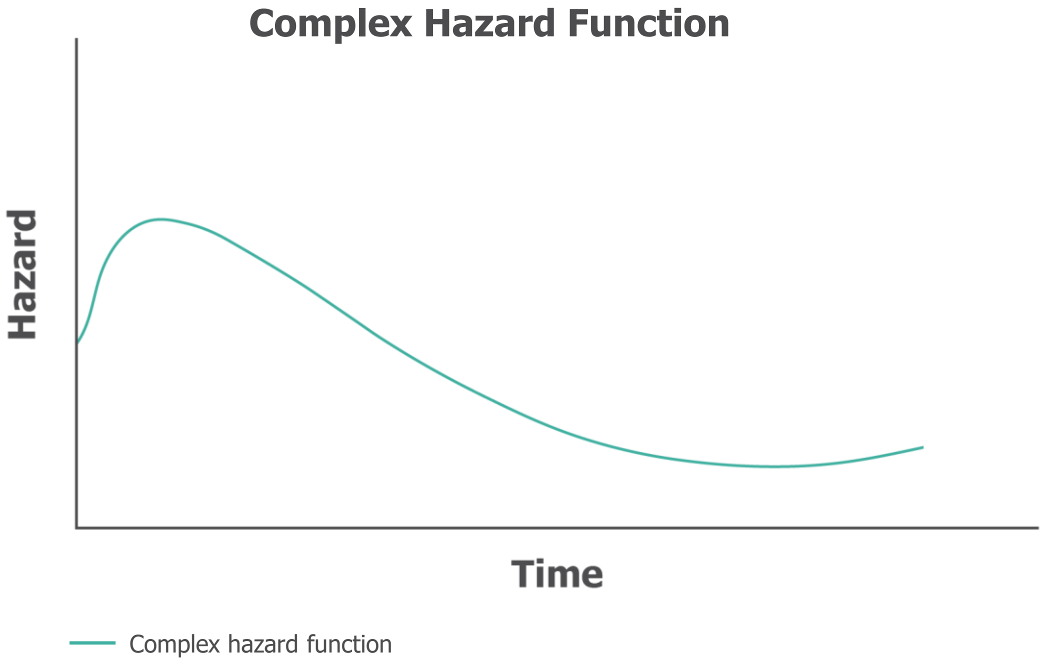


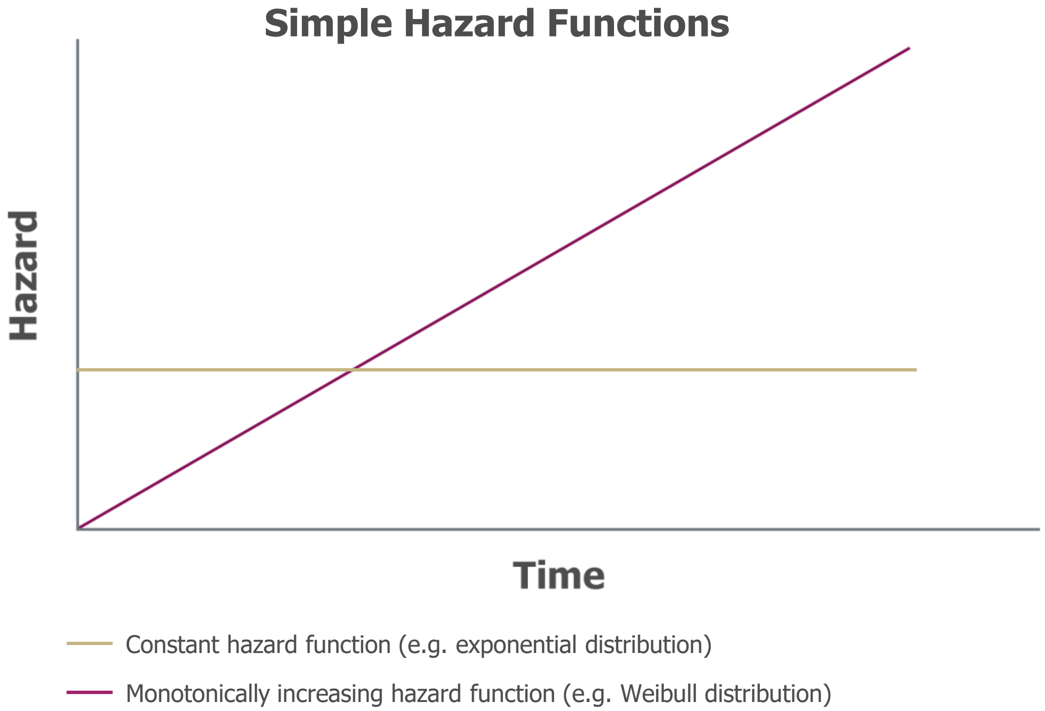
1. Zhang Y. *et al.* The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol. 2020 Aug;17(8):807–821.

Abbreviations: IO: immuno-oncology therapy; PD-1: programmed cell death protein 1.

Uncertainty in IO Survival Extrapolations

- The distinctive mechanism of action for IOs may be associated with long-term survival and/or delayed onset of treatment effects
- These characteristics of IOs may result in more complex hazard functions compared with conventional anti-cancer therapy that standard parametric functions may not accurately reflect



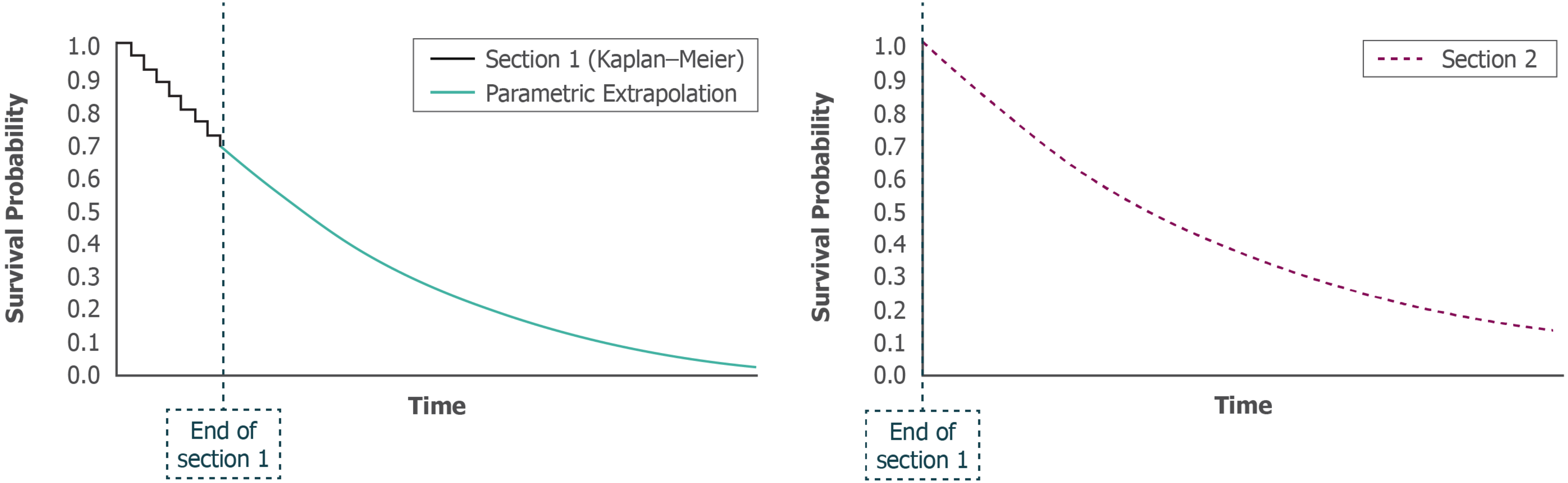


Hazard function = Event probability at time (t) conditional upon survival until time (t)

Abbreviations: IO: immuno-oncology therapy.

Piecewise Survival Models (1/2)

- Piecewise survival models have been suggested as a flexible alternative to standard parametric models for modeling complex hazard profiles[1]
- One piecewise approach uses the Kaplan–Meier (KM) curve for the initial section of the extrapolation, and different survival distributions are then fitted from and adjoined to a pre-determined point on the KM curve[2]



Survival probability at time (t) = Survival at end of section 1 x Survival at time (t) in section 2

1. Latimer N. NICE DSU Technical Support Document 14: Survival Analysis for Economic Evaluations Alongside Clinical Trials – Extrapolation With Patient-Level Data, Version 2: National Institute for Health and Care Excellence, Decision Support Unit, 2013; 2. Rutherford MJ. *et al.* NICE DSU Technical Support Document 21. Flexible Methods for Survival Analysis. 2020.
Abbreviations: KM: Kaplan–Meier.

Piecewise Survival Models (2/2)

Strengths

- Piecewise models are more flexible than standard parametric models
- They may be more biologically plausible for IOs with distinct mechanisms of action
- Other flexible models can also be implemented in a piecewise approach

Limitations

- There are no definitive rules for the selection of the ‘best’ cut-point as found in a review of survival extrapolation methods in the 20 most recent oncology submissions to the National Institute for Health and Care Excellence (NICE), as of 10 December, 2021[1]
- Numbers at risk on which to fit parametric models are reduced in later segments of the KM curve
- If the cut-point or models used for each section are not appropriate, results will not be reliable

The selection of cut-points is often a point of contention when using piecewise models

1. Liu, B. L., and Matthew Griffiths. "EE111 Adoption of Piecewise Modelling: A Review of Nice Health Technology Appraisals in Oncology." Value in Health 25.7 (2022): S356.

Abbreviations: IO: immuno-oncology therapy; KM: Kaplan–Meier; NICE: National Institute for Health and Care Excellence.

Objective

The objective of this study was to answer the following questions:

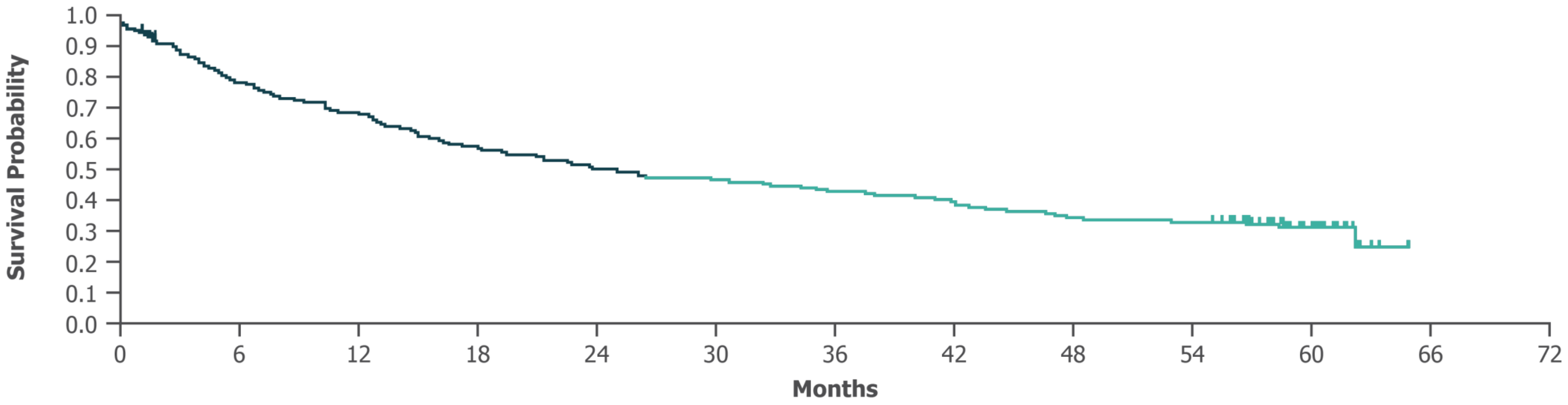
1. How accurate are piecewise model long-term survival estimates compared with standard parametric model estimates for an IO
2. How influential is the selection of cut-point on long-term survival estimates and accuracy

Abbreviations: IO: immuno-oncology therapy.

Methods

KEYNOTE-024

- KEYNOTE-024 investigated pembrolizumab, a PD-1 monoclonal antibody for the treatment of patients with previously untreated advanced non-small cell lung cancer, and was selected as a case study given multiple data-cuts were available[1,2]
- Published overall survival (OS) data are available from two data-cuts
  – 1st data-cut: median follow-up 25.2 months (longest duration of published OS data was 33.0 months)
  – 2nd data-cut: median follow-up 59.9 months (longest duration of published OS data was 65.8 months)



1. Reck M. *et al.* Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol. 2019 Mar 1;37(7):537–546; 2. Reck M. *et al.* Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥50. J Clin Oncol. 2021 Jul 20;39(21):2339–2349.

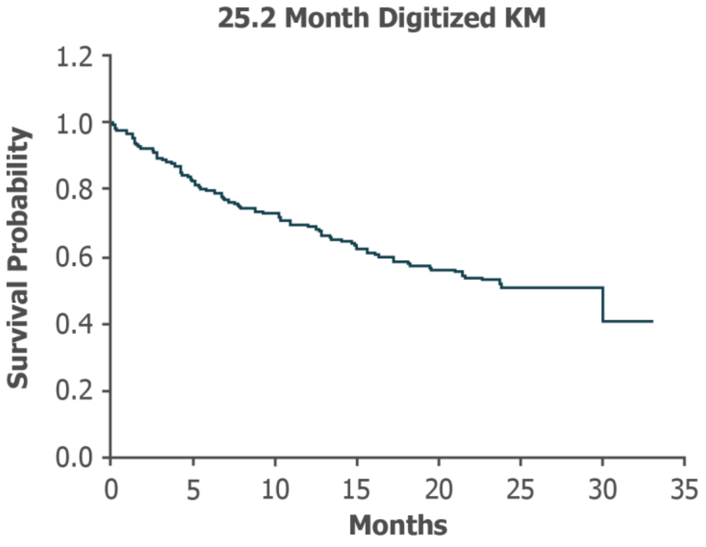
Abbreviations: IO: immuno-oncology therapy; OS: overall survival; PD-1: programmed cell death protein 1.

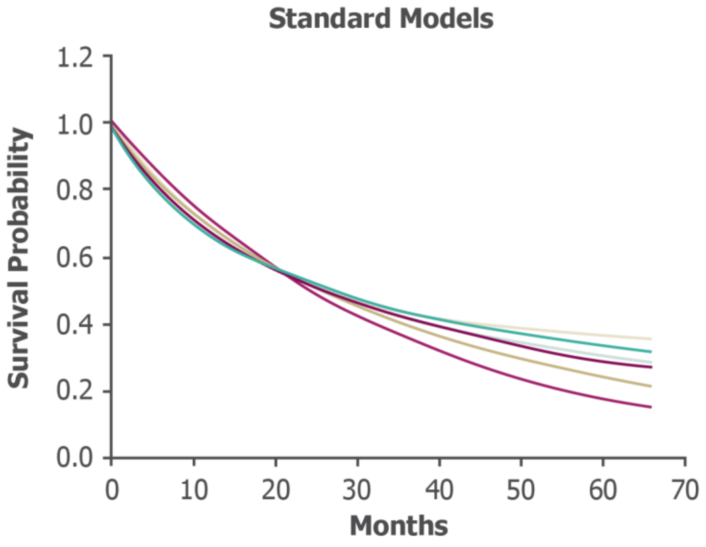
Methodology – Standard Parametric Models

- Published overall survival (OS) KM curves of pembrolizumab for each KEYNOTE-24 data-cut were digitized[1,2]
- Pseudo individual patient data (IPD) were generated using the algorithm described by Guyot *et al.* (2012)[3]
- The six standard parametric models were fitted to the pseudo IPD derived from the 25.2-month data-cut
- Statistical fit was assessed for every curve for each data-cut using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC)

Standard Parametric Models

- Exponential
- Weibull
- LogNormal
- LogLogistic
- Gompertz
- GenGamma





1. Reck M. *et al.* Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol. 2019 Mar 1;37(7):537–546; 2. Reck M. *et al*. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥50. J Clin Oncol. 2021 Jul 20;39(21):2339–2349; 3. Guyot P. *et al*. Enhanced Secondary Analysis of Survival Data: Reconstructing the Data from Published Kaplan–Meier Survival Curves. BMC medical research methodology 2012;12:1–13.

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; IPD: individual patient data; KM: Kaplan–Meier; OS: overall survival.

Methodology – Piecewise Models

- For the piecewise models, 3-, 8- and 14-months were chosen as cut-points by visually inspecting where distinct changes in the hazard profile occurred on smoothed, cumulative, and log cumulative hazard plots of the pseudo IPD from the 25.2-month data-cut
- From the cut-points onwards, the six standard parametric tails were fitted to the remaining KM data and adjoined to the KM curves at the respective cut-point

Piecewise Models

KM Curves

- 3-month cut-point
- 8-month cut-point
- 14-month cut-point

+

Parametric Tails

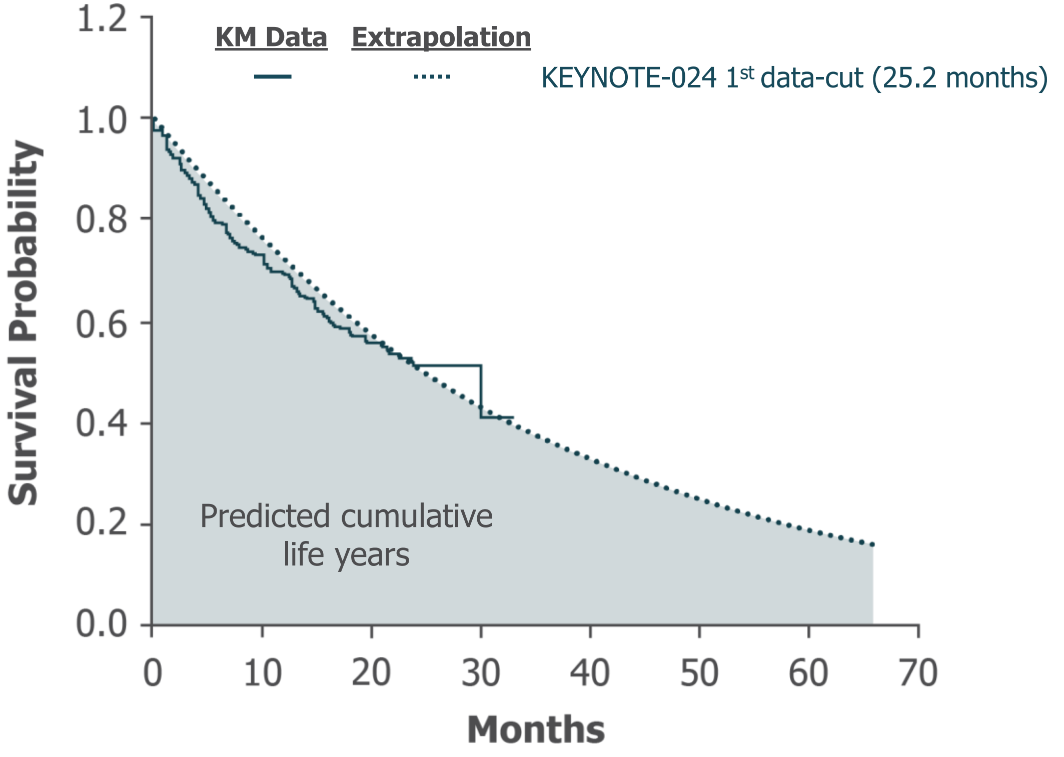
- Exponential
- Weibull
- LogNormal
- LogLogistic
- Gompertz
- GenGamma

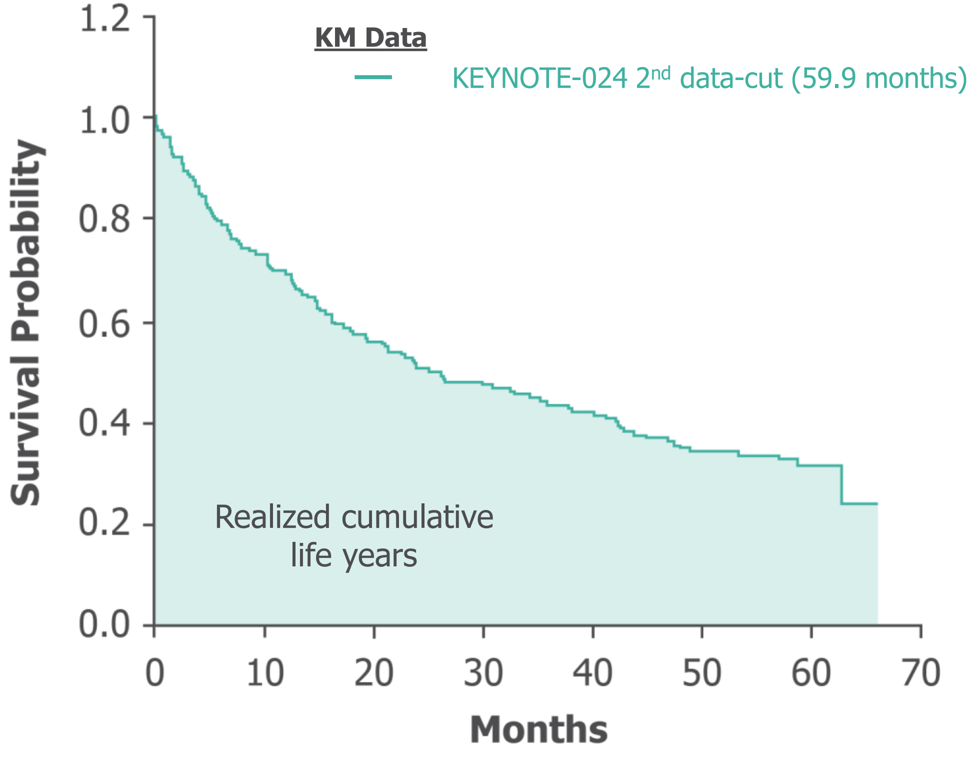
Abbreviations: IPD: individual patient data; KM: Kaplan–Meier.

Methodology – Life Year Calculations

1. The predicted cumulative life years (LYs) were calculated for each model over a 65.8-month time horizon (longest duration of published OS from the 59.9-month data-cut)[1]

2. Predicted LYs were then compared to realized cumulative LYs over this period (calculated as an absolute percentage difference) to determine long-term survival estimate accuracy



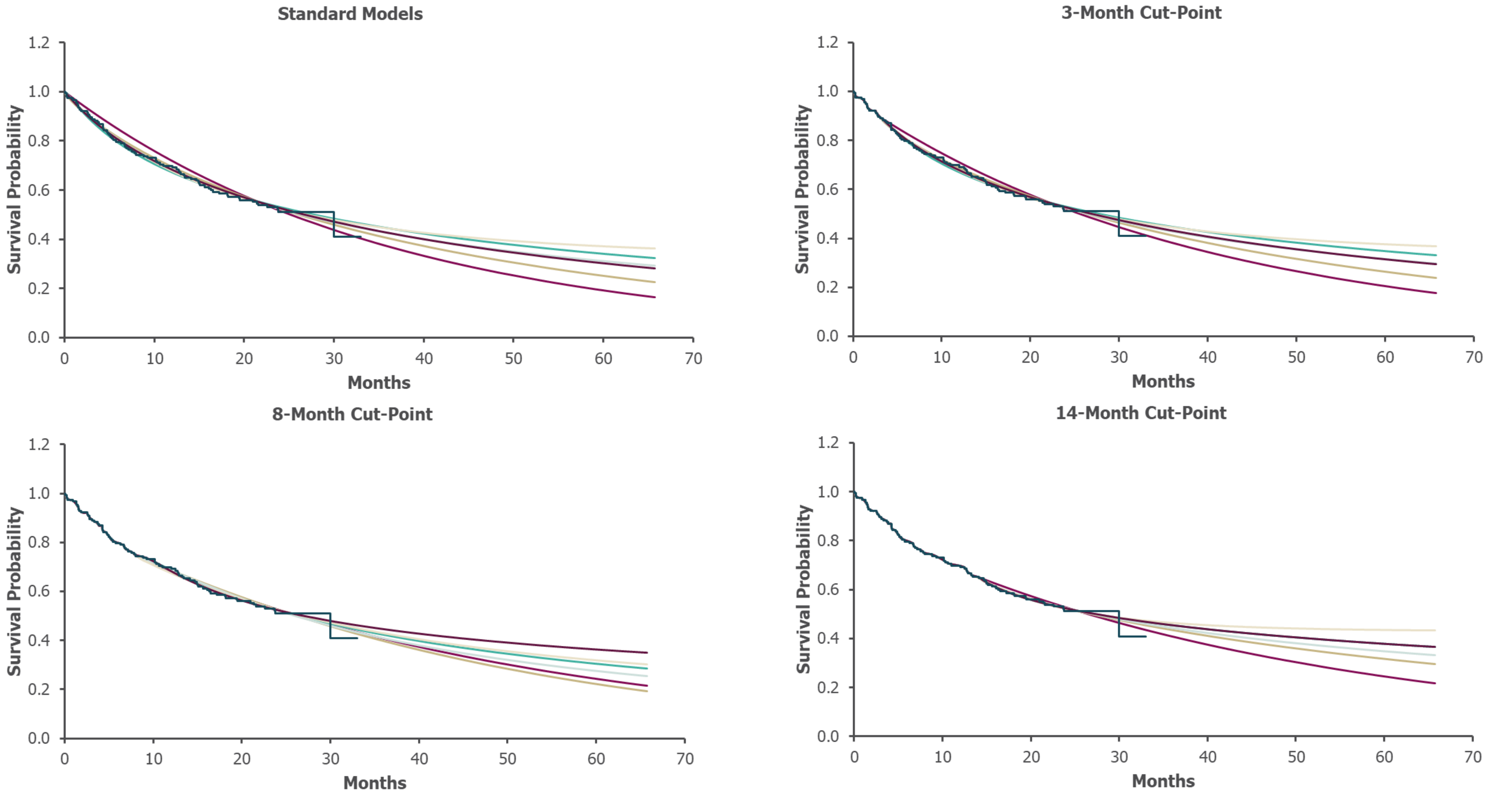


1. Reck M. *et al.* Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥50. J Clin Oncol. 2021 Jul 20;39(21):2339–2349.

Abbreviations: KM: Kaplan–Meier; LY: life year; OS: overall survival.

Results

Results – Survival Extrapolations (Visual Fit)



Month	Number at risk
0	154
3	136
8	113
14	99

Extrapolations derived from 25.2 month data-cut

KM data from 25.2 month data-cut

Abbreviations: KM: Kaplan–Meier.

Results – Survival Extrapolations (Statistical Fit, 1/2)

Goodness-of-Fit Statistics (1/2)

Type of model	Parametric model	AIC	BIC	AIC rank	BIC rank
Standard parametric	Exponential	681.55	684.59	6	1
	Weibull	680.11	686.18	4	5
	LogNormal	679.97	686.04	3	4
	LogLogistic	678.80	684.88	2	3
	Gompertz	678.58	684.65	1	2
	GenGamma	680.92	690.04	5	6
Piecewise model with 3-month cut-point	Piecewise Exponential	542.41	545.45	5	1
	Piecewise Weibull	541.87	547.95	4	5
	Piecewise LogNormal	541.61	547.68	3	4
	Piecewise LogLogisitic	541.05	547.12	2	3
	Piecewise Gompertz	540.91	546.98	1	2
	Piecewise GenGamma	542.95	552.06	6	6

Lower AIC/BIC indicate better fit. However standard models and models with different cut-points cannot be directly compared due to differing numbers at risk on which the models were fit

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

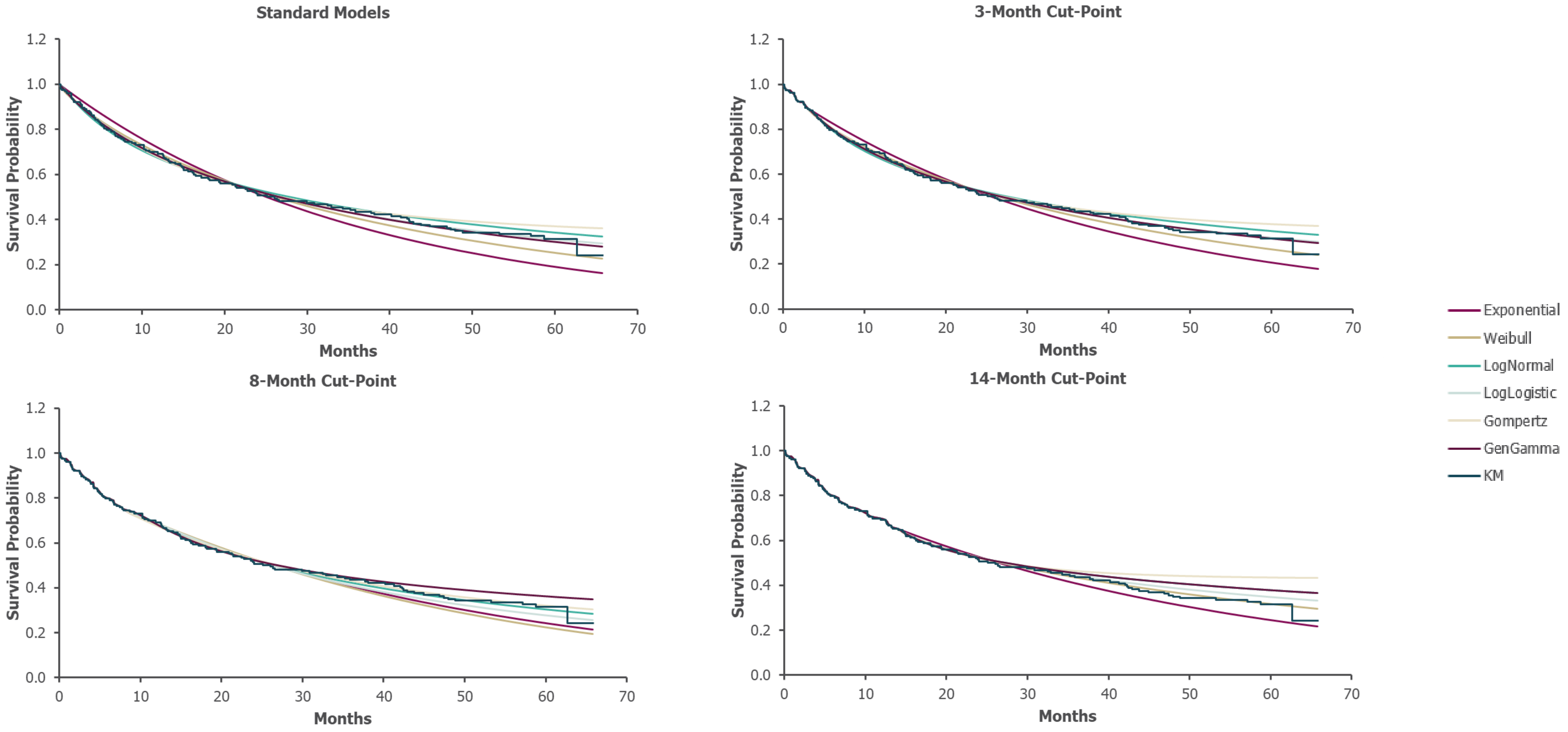
Results – Survival Extrapolations (Statistical Fit, 2/2)

Goodness-of-Fit Statistics (2/2)

Type of model	Parametric model	AIC	BIC	AIC rank	BIC rank
Piecewise model with 8-month cut-point	Piecewise Exponential	340.90	343.94	3	1
	Piecewise Weibull	342.75	348.83	6	5
	Piecewise LogNormal	339.59	345.67	1	2
	Piecewise LogLogisitic	341.58	347.66	4	3
	Piecewise Gompertz	342.59	348.66	5	4
	Piecewise GenGamma	340.53	349.64	2	6
Piecewise model with 14-month cut-point	Piecewise Exponential	1019.87	1022.90	6	6
	Piecewise Weibull	1010.66	1016.73	2	2
	Piecewise LogNormal	1012.06	1018.13	5	4
	Piecewise LogLogisitic	1009.58	1015.65	1	1
	Piecewise Gompertz	1011.17	1017.25	3	3
	Piecewise GenGamma	1011.19	1020.30	4	5

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Results – Survival Extrapolations (Prediction Accuracy)



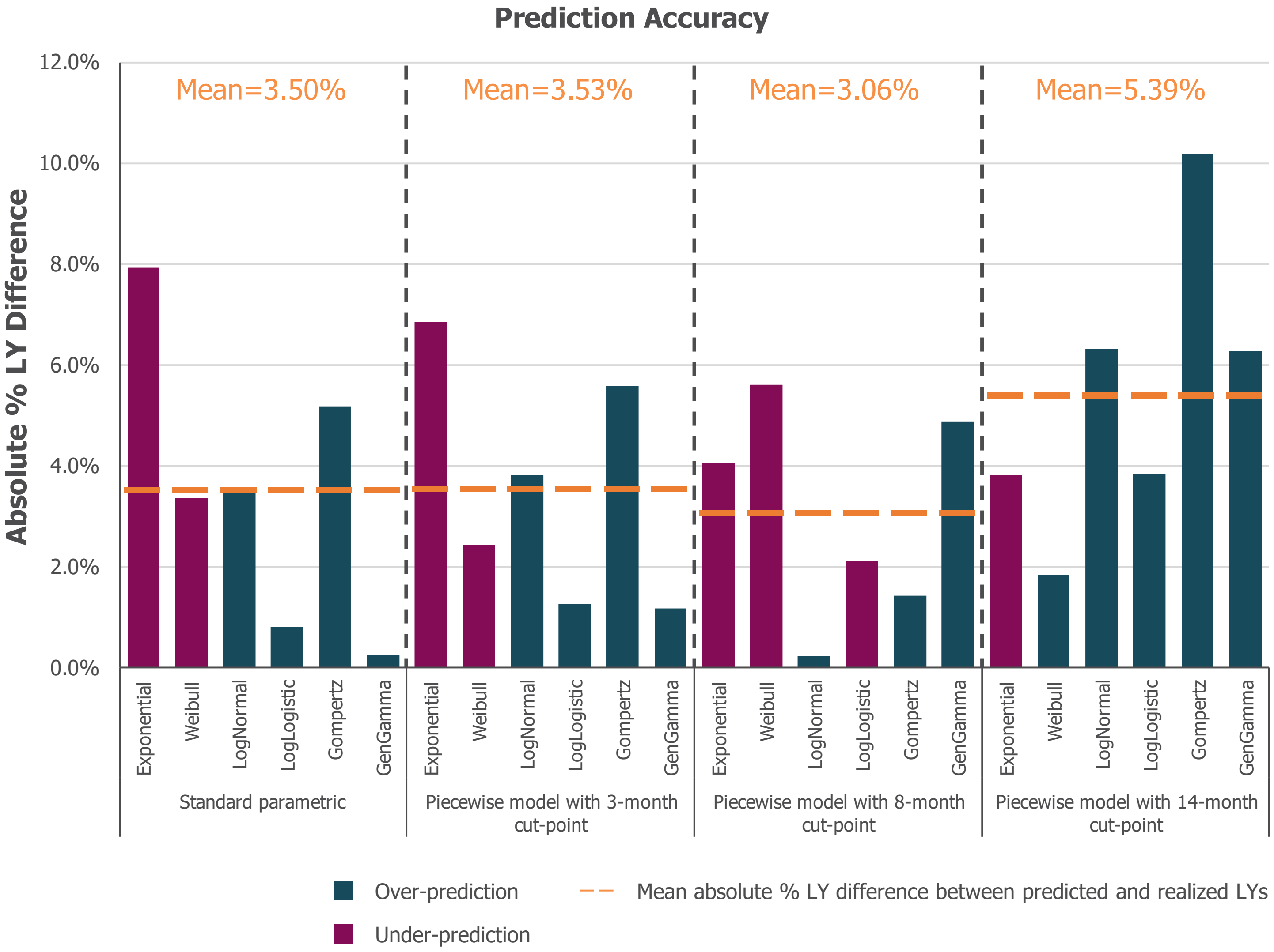
Extrapolations derived from 25.2 month data-cut

KM data from 59.9 month data-cut

Abbreviations: KM: Kaplan–Meier.

Results – Life Year Comparisons

- The realized LYs from the KEYNOTE-024 59.9-month data-cut were 2.71
- Average predicted LYs across the standard parametric models were 2.70. Average mean LYs varied across piecewise models with different cut-points:
  - 3-month: 2.72
  - 8-month: 2.68
  - 14-month: 2.82
- The most accurate model was the 8-month piecewise model with a LogNormal tail (absolute % LY difference=0.24%)
- On average, models based on the 14-month cut-point performed the worst



Abbreviations: LY: life year.

Summary and Conclusions

Conclusions

Despite being more flexible, the piecewise models in this case study did not perform better than standard parametric models in estimating long-term survival based on average predicted LYs, although the 3- and 8-month cut-point models performed similarly to standard parametric models

In terms of mean absolute % LY difference between predicted and realized LYs, the 3-month cut-point models performed similarly to the standard parametric models, and the 8-month cut-point models performed better. The spread in under/over prediction also appeared to decrease with the 3- and 8-month cut-point models

The piecewise model with 8-month cut-point and LogNormal tail performed the best, followed by standard Generalized Gamma and LogLogistic parametric models, but the differences among them were marginal (0.24% vs 0.26% vs 0.80%)

The 14-month cut-point models on average performed the worst. The reduced accuracy at later timepoints likely reflected the reduced number at risk on which to fit the parametric tails

Abbreviations: LY: life year.

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Thank You