Accuracy of Life Year Gains Predictions for CAR-T Therapy in the Long Term: An Analysis for Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma

Alex Porteous, Dario Gregori, Bryn Hilton

22nd November 2021, ISPOR Europe Oral Presentation, P49

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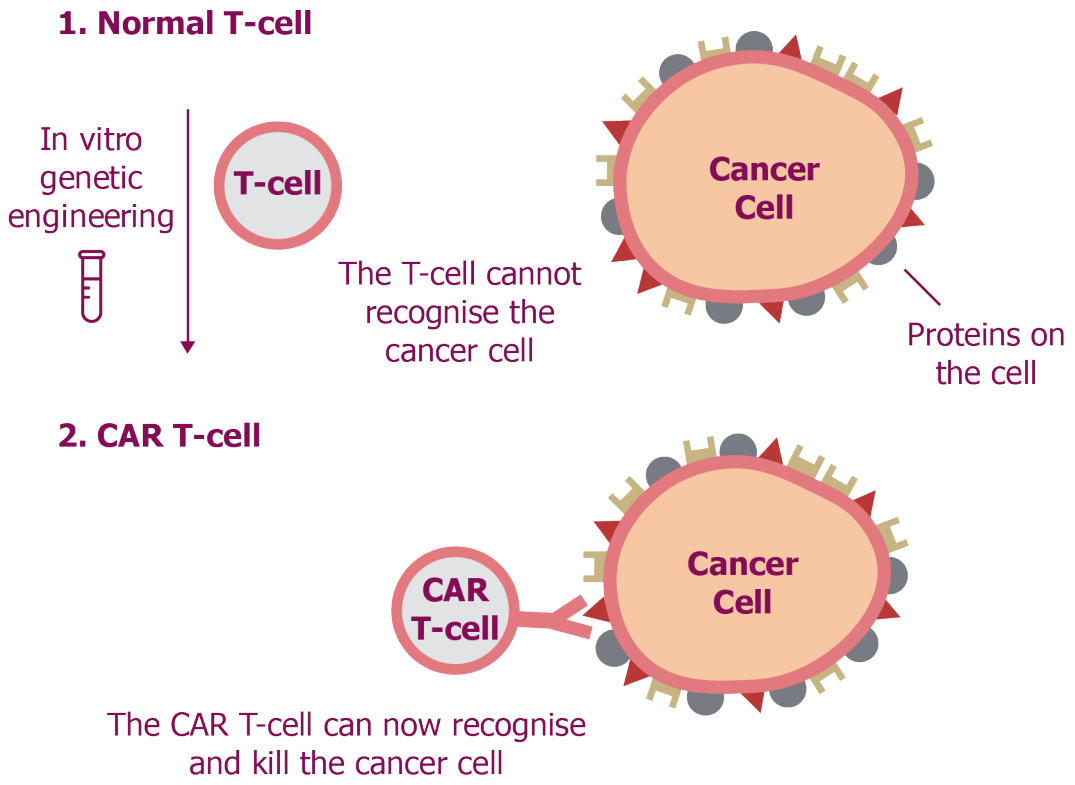
Background

Introduction to CAR-T Therapies

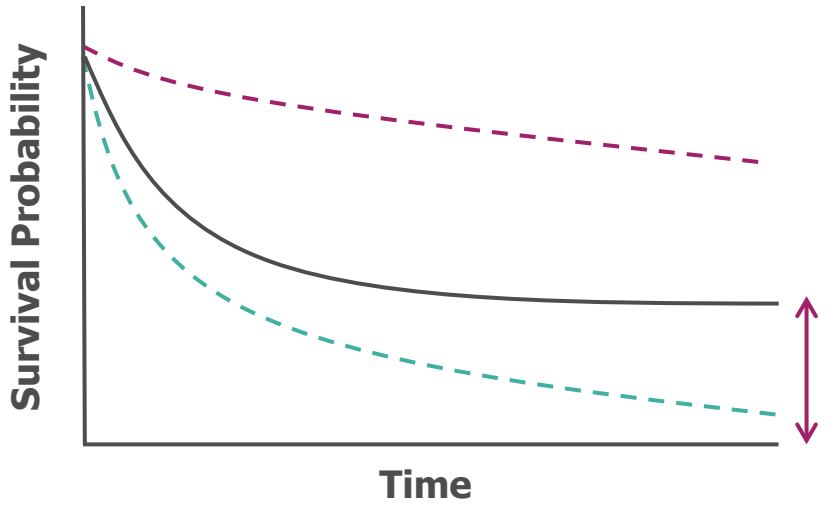
- Chimeric antigen receptor T-cell (CAR-T) therapy is a type of immunotherapy
- CAR-T therapies have an innovative mechanism of action:[1]
  - A sample of the patient's own T-lymphocytes are extracted via apheresis
  - These cells are genetically re-programmed to express a chimeric antigen receptor designed to recognise cancer cell antigens
  - The cells are then re-infused into the patient several weeks later, now able to specifically target cancer cells
- CAR-T therapy differs from traditional oncological treatments in that it aims to provide a functional cure for patients

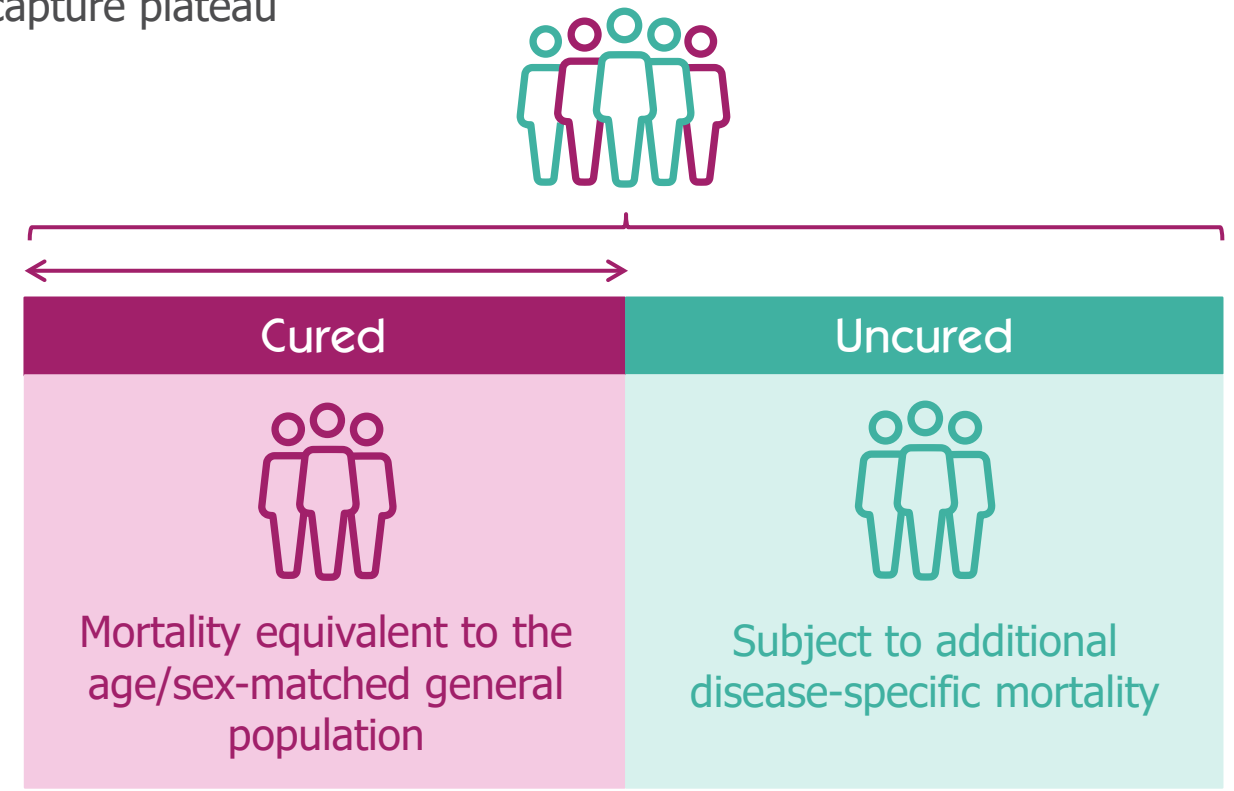


1. Cancer Research UK (2021), CAR T-cell therapy. Available at: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/immunotherapy/types/CAR-T-cell-therapy
Abbreviations: CAR-T: chimeric antigen receptor T-cell

Uncertainty in CAR-T Survival Extrapolations

- Survival profiles for CAR-T therapies commonly exhibit a plateau, which may not be accurately captured by standard parametric distributions
- Mixture cure models (MCMs) represent an alternative approach where it is assumed the population comprises a mix of 'cured' and 'uncured' patients, which may better capture plateau





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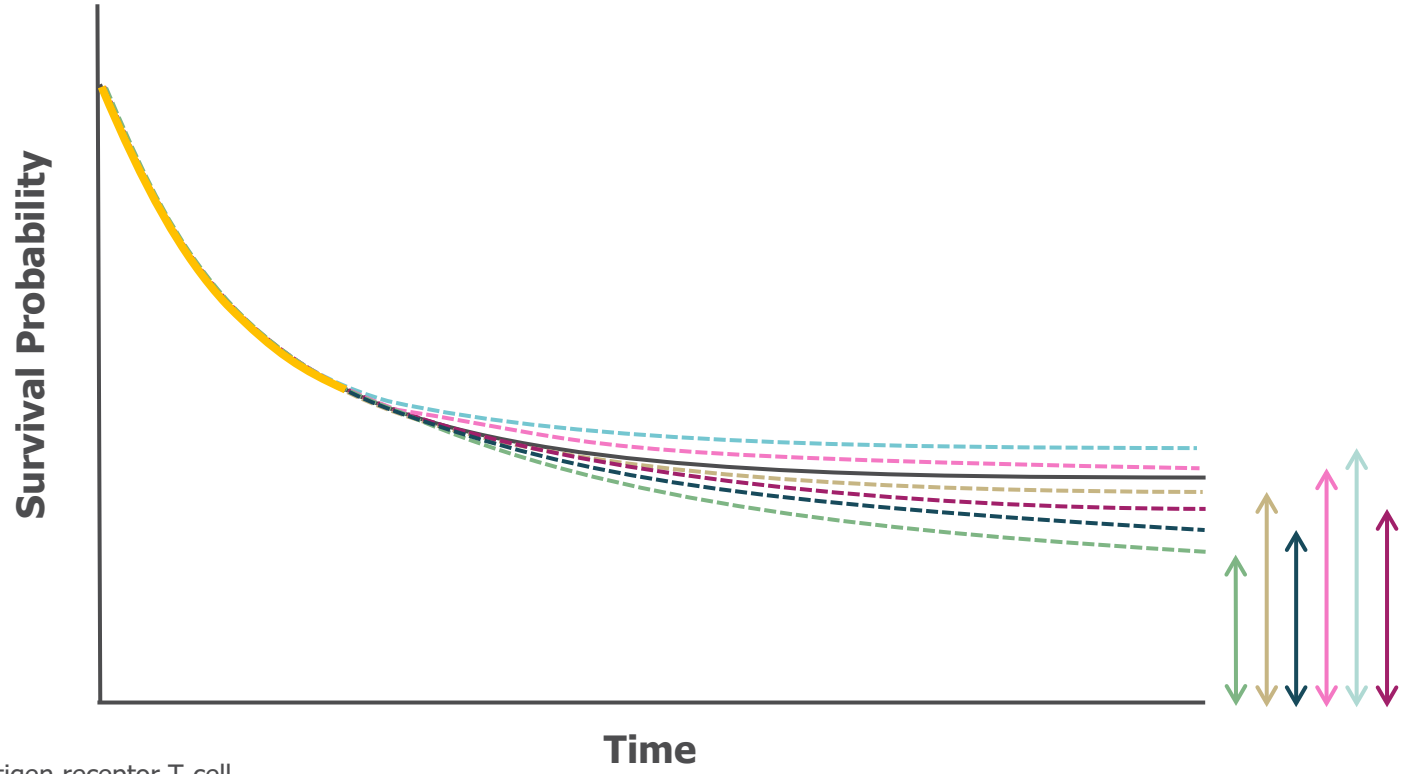
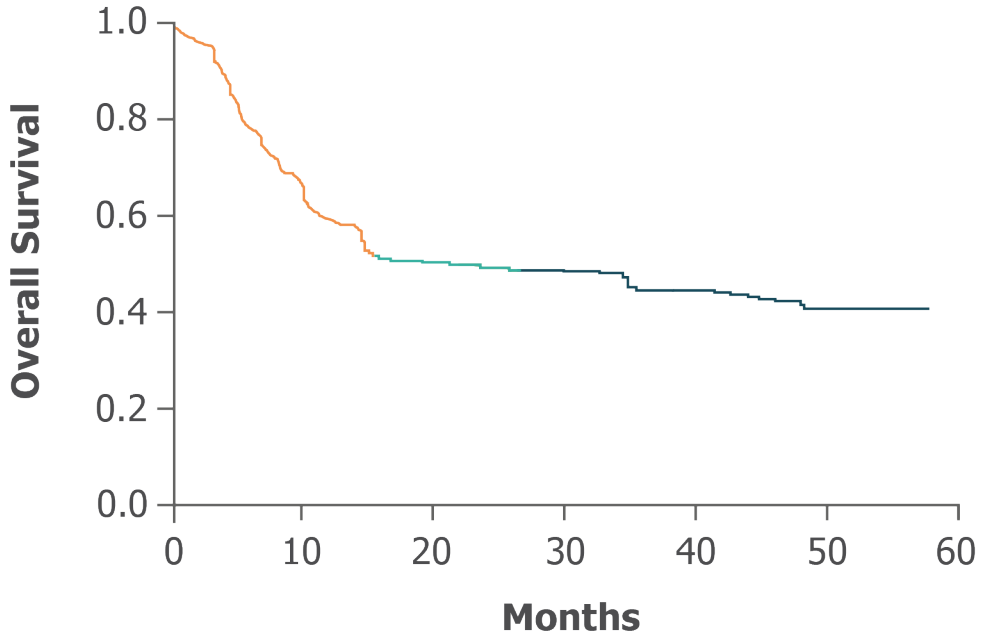
- Immature data leads to uncertainty in long-term survival extrapolations, reflected by variation in cure fractions



Abbreviations: CAR-T: chimeric antigen receptor T-cell

Axicabtagene Ciloleucel

- Axicabtagene Ciloleucel (Axi-Cel) provides a case study of the challenges associated with CAR-T therapy survival extrapolations
- Axi-Cel is indicated in the treatment of refractory large B-cell lymphoma
- The pivotal trial for Axi-Cel in this indication is ZUMA-1 (NCT02348216); published overall survival (OS) data are available from three data-cuts
  - 1st data-cut: median follow-up 15.4 months[1]
  - 2nd data-cut: median follow-up 27.1 months[2]
  - 3rd data-cut: median follow-up 39.1 months[3]



KM Data

— First interim data cut (median follow-up 15.4 months)
— Second interim data cut (median follow-up 27.1 months)
— Long-term observed KM data (median follow-up 39.1 months)

1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. New England Journal of Medicine 2017;377:2531-2544. 2. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. The Lancet oncology 2019;20:31-42. 3. Highlights in CAR T-cell therapy from the 62nd American Society of Hematology annual meeting and exposition. Available at: ho0321sup10v2.pdf (hematologyandoncology.net)
Abbreviations: Axi-Cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; Kaplan–Meier; OS: overall survival

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  - 3rd data-cut: median follow-up 39.1 months

- OS data for ZUMA-1 were not sufficiently mature to be able to estimate a robust cure fraction for OS[1]
- Preferred an approach based on standard parametric extrapolation followed by general population mortality (GPM) from a specific timepoint[1]

TA559 Evidence Review Group (ERG)

Concluded that the OS gain was likely between the company's and the ERG's estimates[2]

TA559 NICE Committee

1. TA559: Evidence Review Group's Report. Available at: https://www.nice.org.uk/guidance/ta559/documents/committee-papers-3 2. TA559: Final Appraisal Document. Available at: https://www.nice.org.uk/guidance/ta559/documents/final-appraisal-determination-document

Abbreviations: Axi-Cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; ERG: evidence review group; GPM: general population mortality; NICE: National Institute for Health and Care Excellence; OS: overall survival

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Objective

To retrospectively analyse the accuracy of OS extrapolations from the interim data cuts of ZUMA-1 in predicting realised long-term life years

Abbreviations: Axi-Cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; OS: overall survival

Methods

Methodology (1/2)

- Published Kaplan–Meier data for each ZUMA-1 data-cut were digitised
- Pseudo individual patient data were generated using the algorithm described by Guyot *et al.* (2012)[1]
- Survival extrapolations were fitted to each of the data-cuts

Standard Parametric Models

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

Flexible Spline Models

- Hazard 1 knot
- Hazard 2 knots
- Odds 1 knot
- Odds 2 knots
- Normal 1 knot
- Normal 2 knots

Mixture Cure Models

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

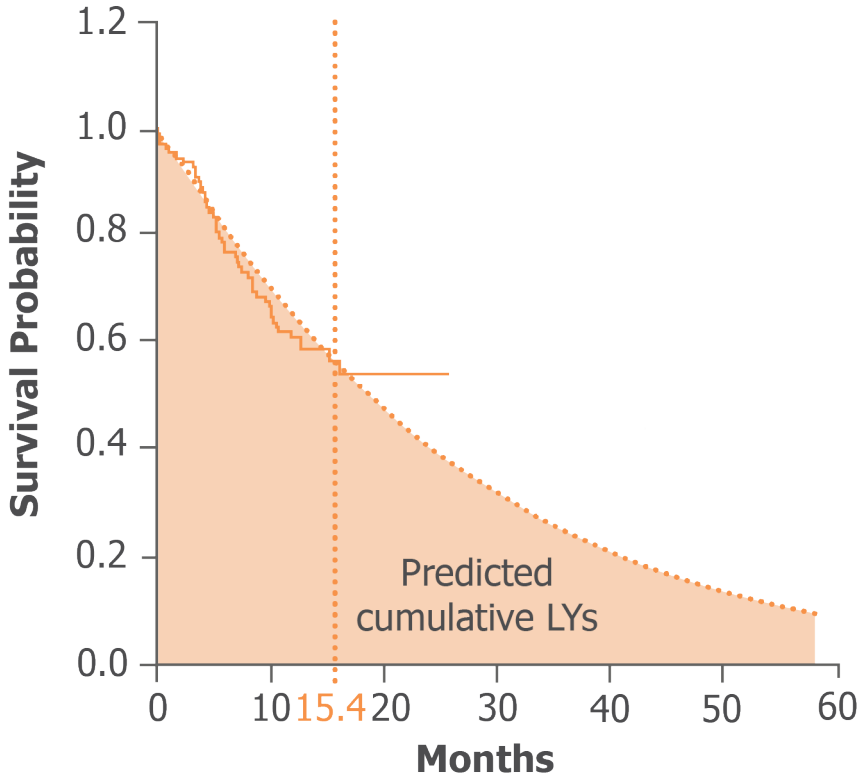
- Statistical fit was assessed for every curve for each data-cut using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC)

1. Guyot P, Ades A, Ouwens MJ, 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.

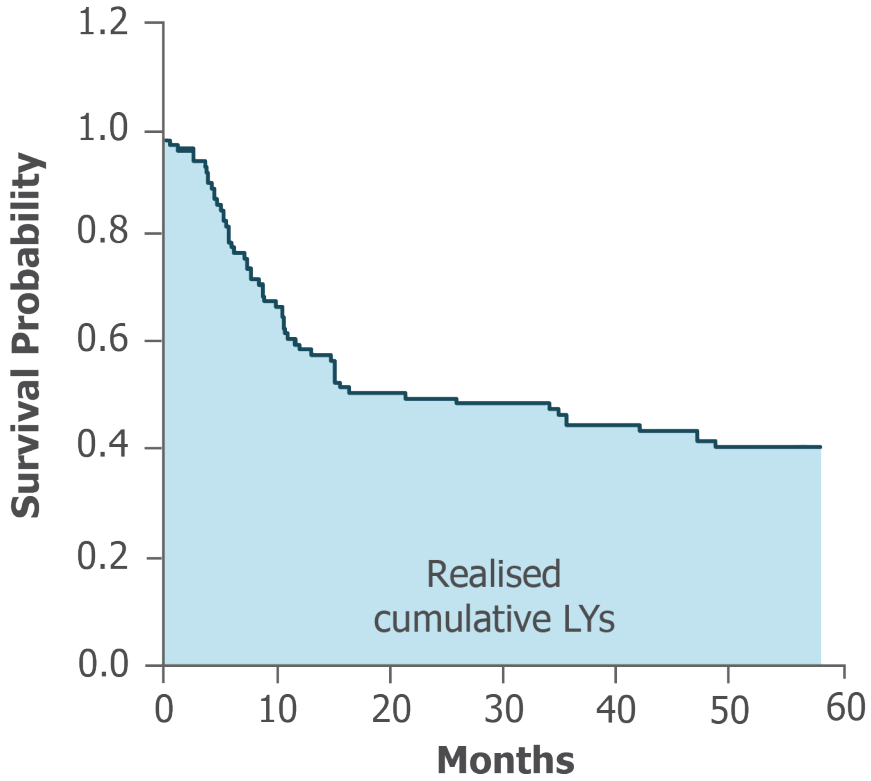
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion

Methodology (2/2)

1. The predicted cumulative life years were calculated for each model over a 58-month time horizon (longest duration of published OS data)



2. Predicted life years were then compared to realised cumulative life years over this period (calculated as an absolute percentage difference)



KM Data **Extrapolation**

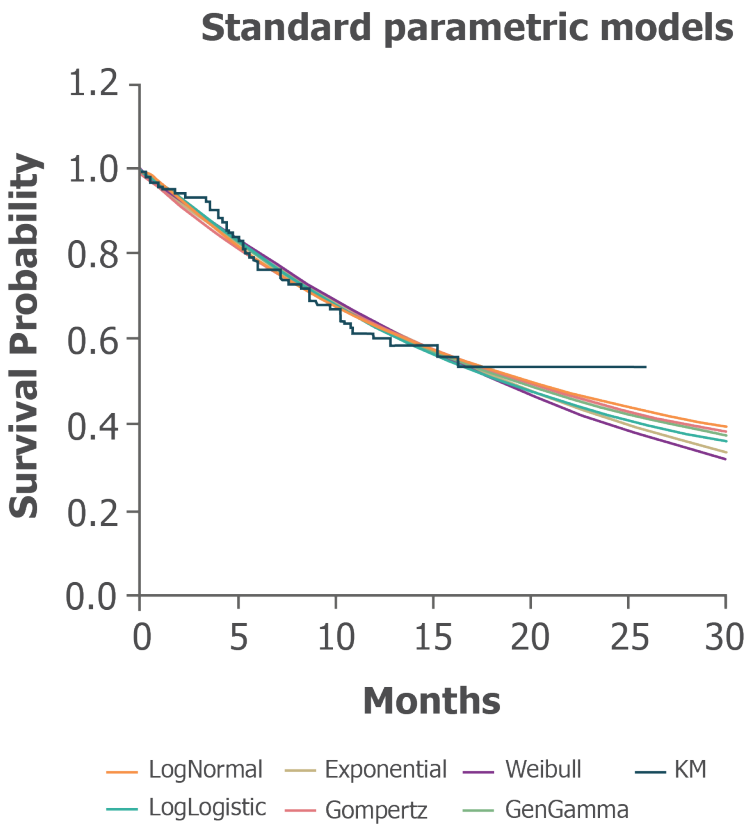
First interim data cut (median follow-up 15.4 months)

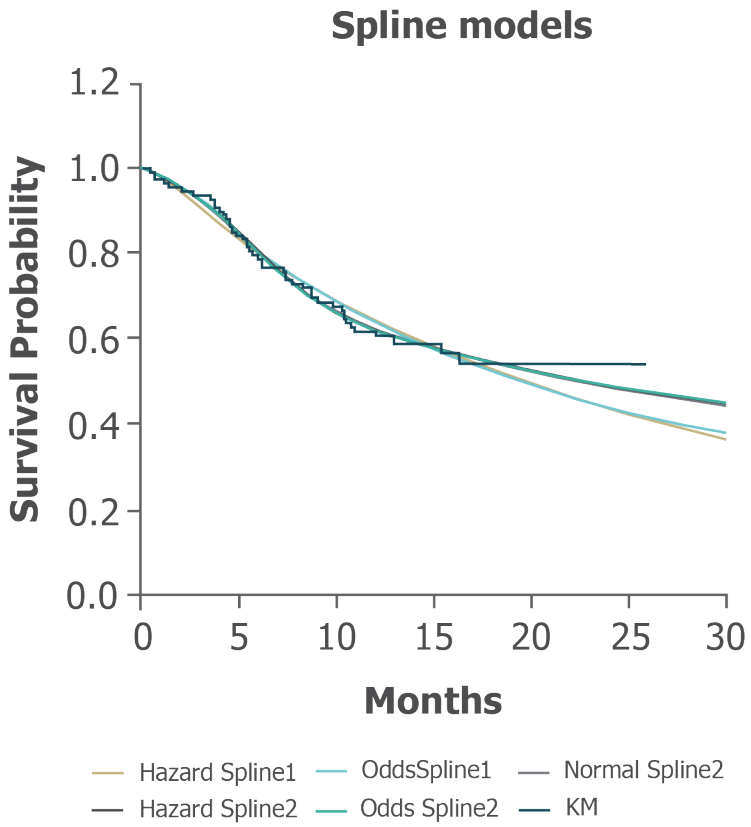
Long-term observed KM data cut (median follow-up 39.1 months)

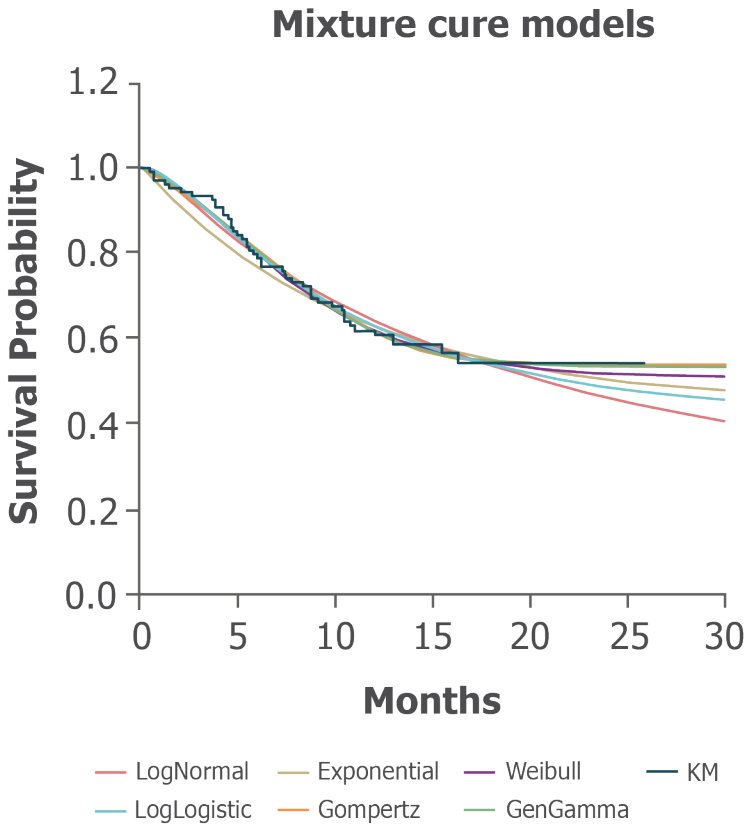
Abbreviations: LY: life year; KM: Kaplan–Meier; OS: overall survival

Results

Results – Survival Extrapolations (Visual Fit)







Extrapolations based on first data cut (median follow-up 15.4 months)

Kaplan–Meier data from first data cut (median follow-up 15.4 months)

Abbreviations: KM: Kaplan–Meier

Results – Survival Extrapolations (Statistical Fit)

Goodness-of-Fit Statistics

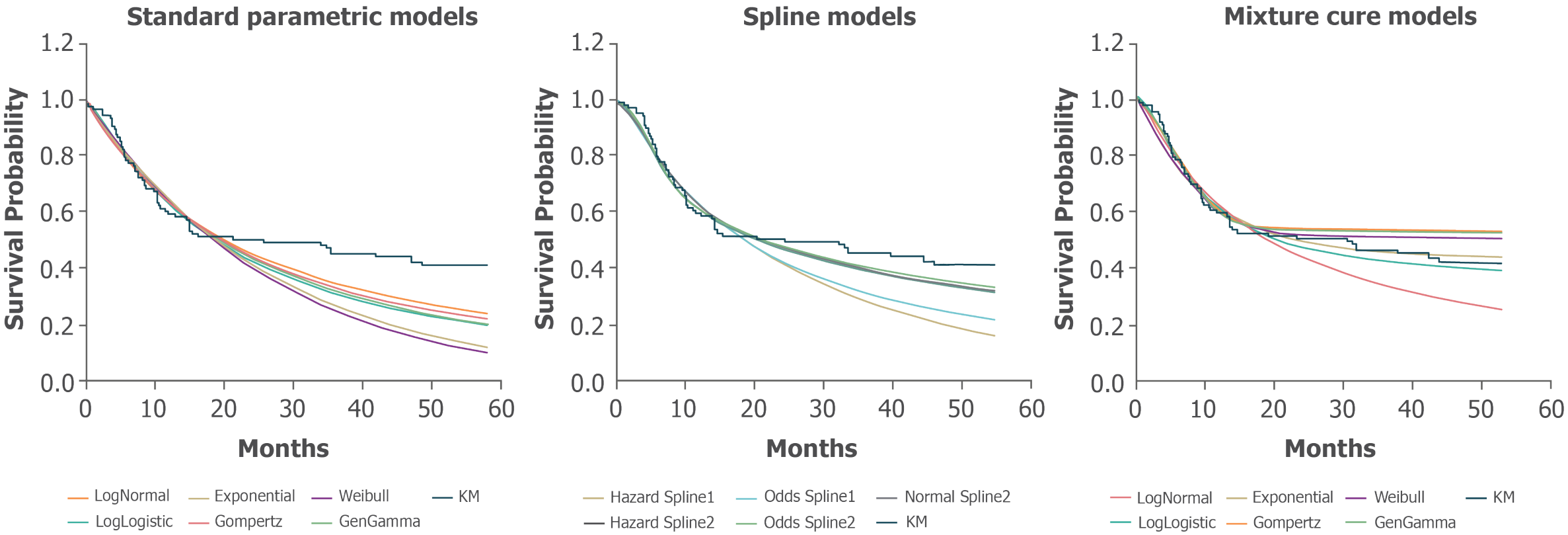
	Model	AIC	BIC	AIC rank	BIC rank
Standard parametric	Exponential	398.94	401.62	3	1
	Weibull	400.78	406.15	13	8
	LogNormal	399.49	404.86	8	3
	LogLogistic	399.01	404.37	4	2
	Gompertz	400.61	405.97	12	6
	GenGamma	401.24	409.29	15	11
Splines	Hazard Spline1	401.64	409.69	17	13
	Hazard Spline2	399.46	410.19	7	15
	Odds Spline1	400.87	408.92	14	10
	Odds Spline2	399.52	410.25	9	16
	Normal Spline1	DNC	DNC	DNC	DNC
	Normal Spline2	399.72	410.45	10	17
Mixture cure	Exponential	400.34	405.70	11	4
	Weibull	398.09	406.14	2	7
	LogNormal	401.49	409.54	16	12
	LogLogistic	399.35	407.40	5	9
	Gompertz	397.70	405.75	1	5
	GenGamma	399.36	410.09	6	14

MCM Cure Fractions

Model	Estimated cure fraction
Exponential	29%
Weibull	52%
LogNormal	3%
LogLogistic	37%
Gompertz	54%
GenGamma	54%

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DNC: Did not converge; MCM: mixture cure model

Results – Survival Extrapolations (Prediction Accuracy)



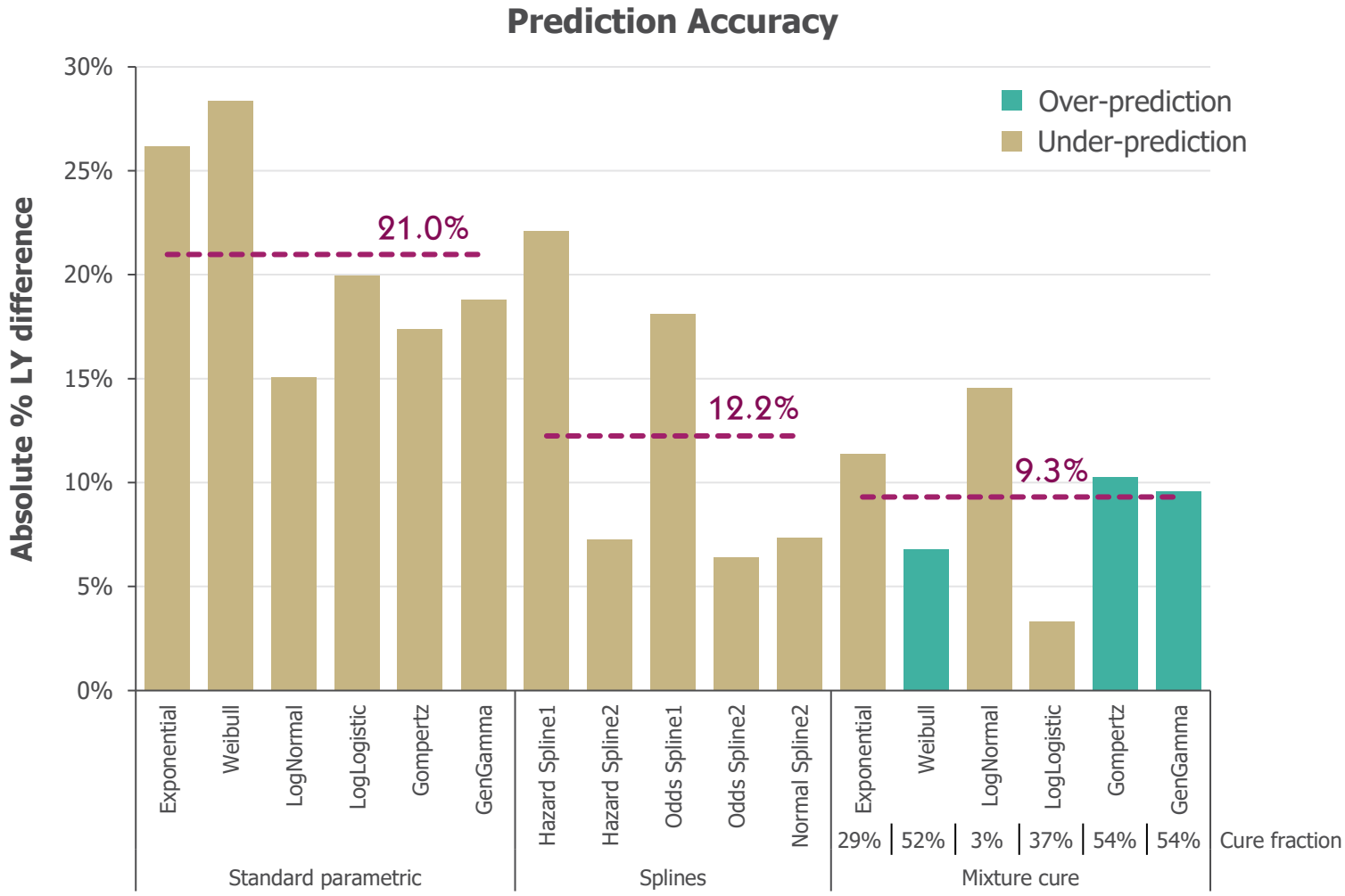
Extrapolations based on first data cut (median follow-up 15.4 months)

Kaplan–Meier data from final data cut (median follow-up 39.1 months)

Abbreviations: KM: Kaplan–Meier

Results – Life Year Comparisons

- Of the models fitted to the earliest data cut, MCMs provided the best predictions of realised LYs
- Standard parametric curves offered the poorest accuracy in survival predictions
- Similar findings were observed for extrapolations based on the second data cut (representing 11.7 months additional follow-up; data not presented)



Results have been updated from the abstract following identification of a minor error in analysis. Normal Spline1 did not converge.
Abbreviations: LY: life year; MCM: mixture cure model

Summary and Conclusions

Conclusions

Standard parametric models may be inappropriate when extrapolating immature data in therapies providing a functional cure

MCMs may provide a reasonable alternative and align with clinical plausibility of functional cure

In this case study, despite variation in cure fractions, MCMs provided the best predictions of long-term survival on average; in contrast to the view of the ERG in TA559, variation in cure fraction should not justify rejection of MCMs in favour of standard parametric approaches

Abbreviations: ERG: evidence review group; MCM: mixture cure model

Acknowledgements

Alex Porteous

Dario Gregori

Bryn Hilton

Contact details: alex.porteous@costellomedical.com

Thank you