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Modelling Overall Survival in Immunotherapy Using Parametric Techniques: Avelumab in Previously Treated Metastatic Merkel Cell Carcinoma

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Background and Objectives

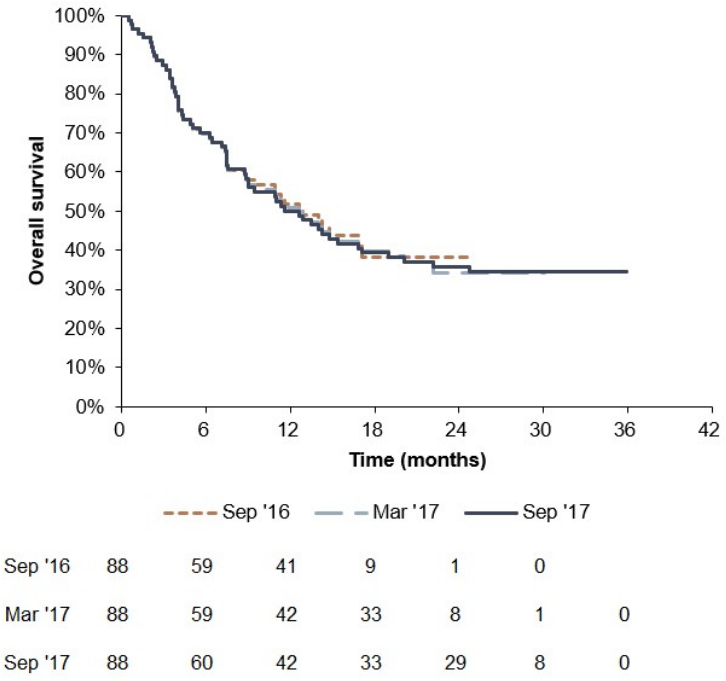
- Avelumab (an anti–PD-L1 immune-checkpoint inhibitor) was recently approved in the United States, Europe, and Japan, among others, for the treatment of patients with metastatic Merkel cell carcinoma (mMCC)
- Safety and efficacy data are available from the JAVELIN Merkel 200: Part A trial of 88 patients with previously treated mMCC (NCT02155647)
- The availability of increasingly maturing data from JAVELIN Merkel 200: Part A allows for the production (and subsequent validation) of overall survival (OS) extrapolations
- This analysis compares observed and extrapolated OS estimates from multiple data cuts using standard parametric and spline-based approaches

EMA approval: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004338/WC500231832.pdf
FDA approval: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm547965.htm
JAVELIN Merkel 200: Part A study publication: Kaufman *et al.*, (2016) https://www.ncbi.nlm.nih.gov/pubmed/27592805

Data

- This analysis compares observed and extrapolated OS estimates from 3 data cuts from Part A of the JAVELIN Merkel 200 trial
- Each data cut constitutes a different period of minimum follow-up (MFU) for all patients:
  - Data cut Sep-2016
    - 12 months' MFU
  - Data cut Mar-2017
    - 18 months' MFU
  - Data cut lock Sep-2017
    - 24 months' MFU

Kaplan-Meier plot of OS for each data cut



12 months' MFU: Kaufman *et al.*, (2018) https://www.ncbi.nlm.nih.gov/pubmed/29347993
18 months' MFU: D'Angelo *et al.*, (2018) http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.5_suppl.192
24 months' MFU: Nghiem *et al.*, (2018) https://meetinglibrary.asco.org/record/161628/abstract

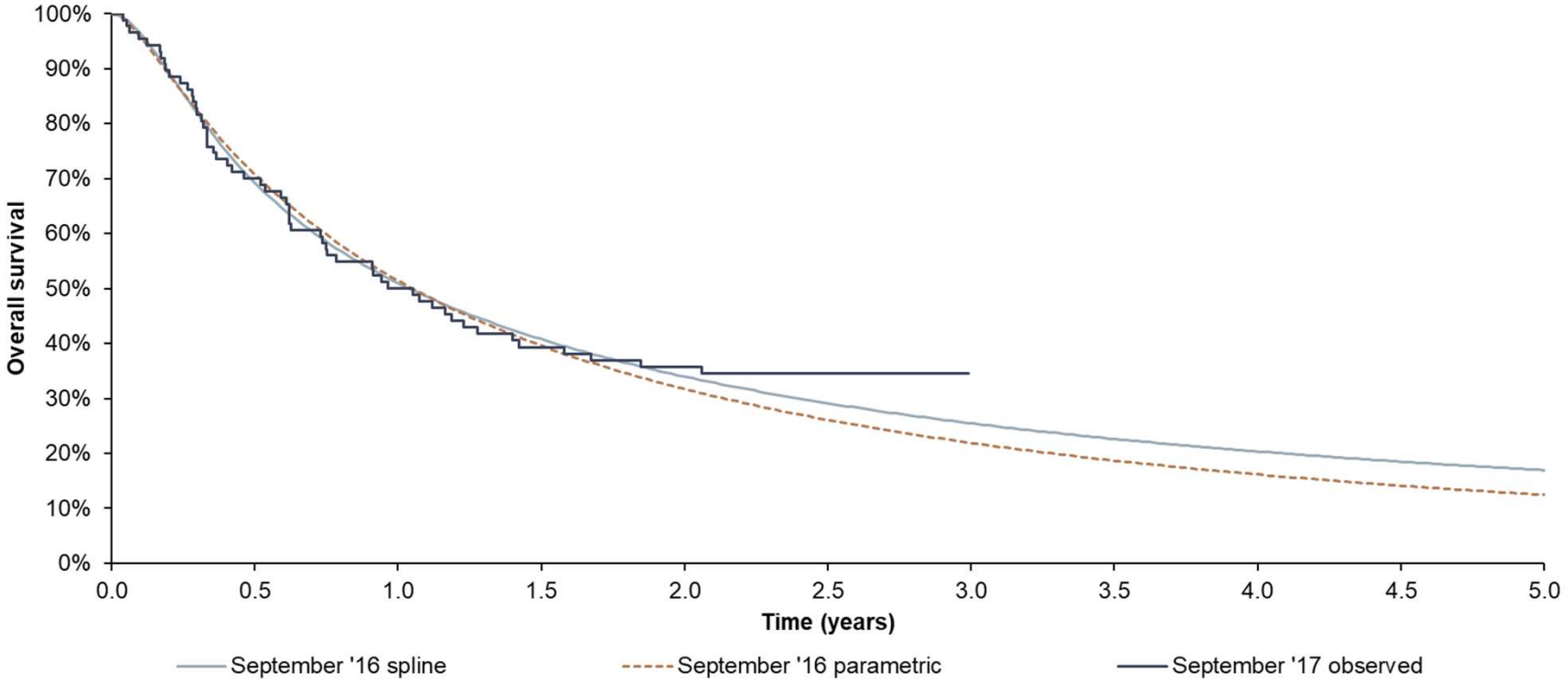
Methods

- Standard parametric and spline-based models were fitted to OS data from Part A of JAVELIN Merkel 200 for each data cut
- All survival models were fitted in the statistical software R using the flexsurv package
  - The standard parametric survival models considered were the exponential, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull (routinely considered to inform the estimation of OS in health technology assessment
  - The spline-based models considered were natural restricted cubic spline models. The spline-based models were fitted with 1-3 internal knots using each of the 3 functional forms permitted by flexsurv. Knot locations were selected according to the percentiles of the log-uncensored survival times
- The selection of the best-fitting parametric survival model was determined through a combination of visual fit to the observed OS data, statistical goodness-of-fit (measured by Akaike's information criterion [AIC]), and the plausibility of long-term extrapolation (based on clinical expert input)

R package flexsurv documentation: https://cran.r-project.org/web/packages/flexsurv/flexsurv.pdf

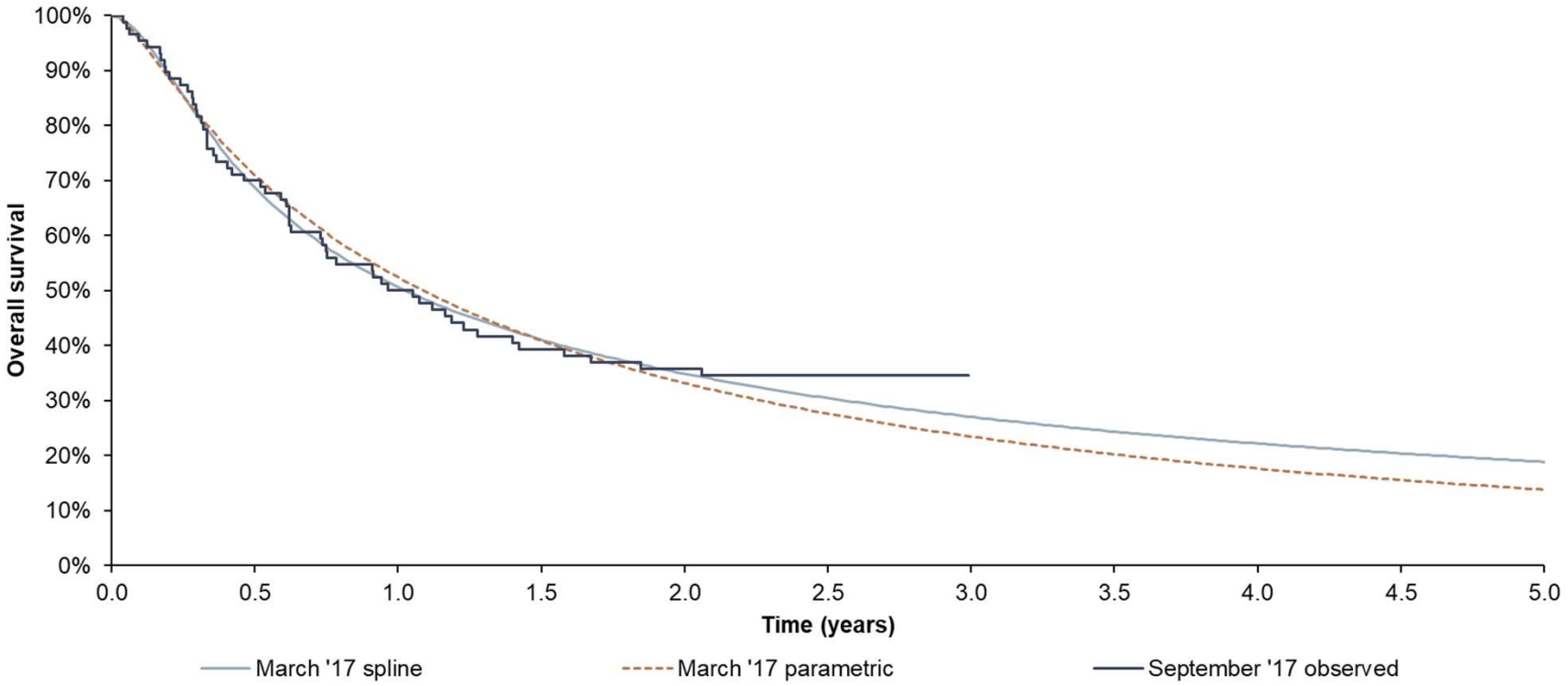
Results

Extrapolation from September '16 (12 months' MFU) data cut



Best-fitting standard parametric model: log-normal, best-fitting spline model: 1-knot odds

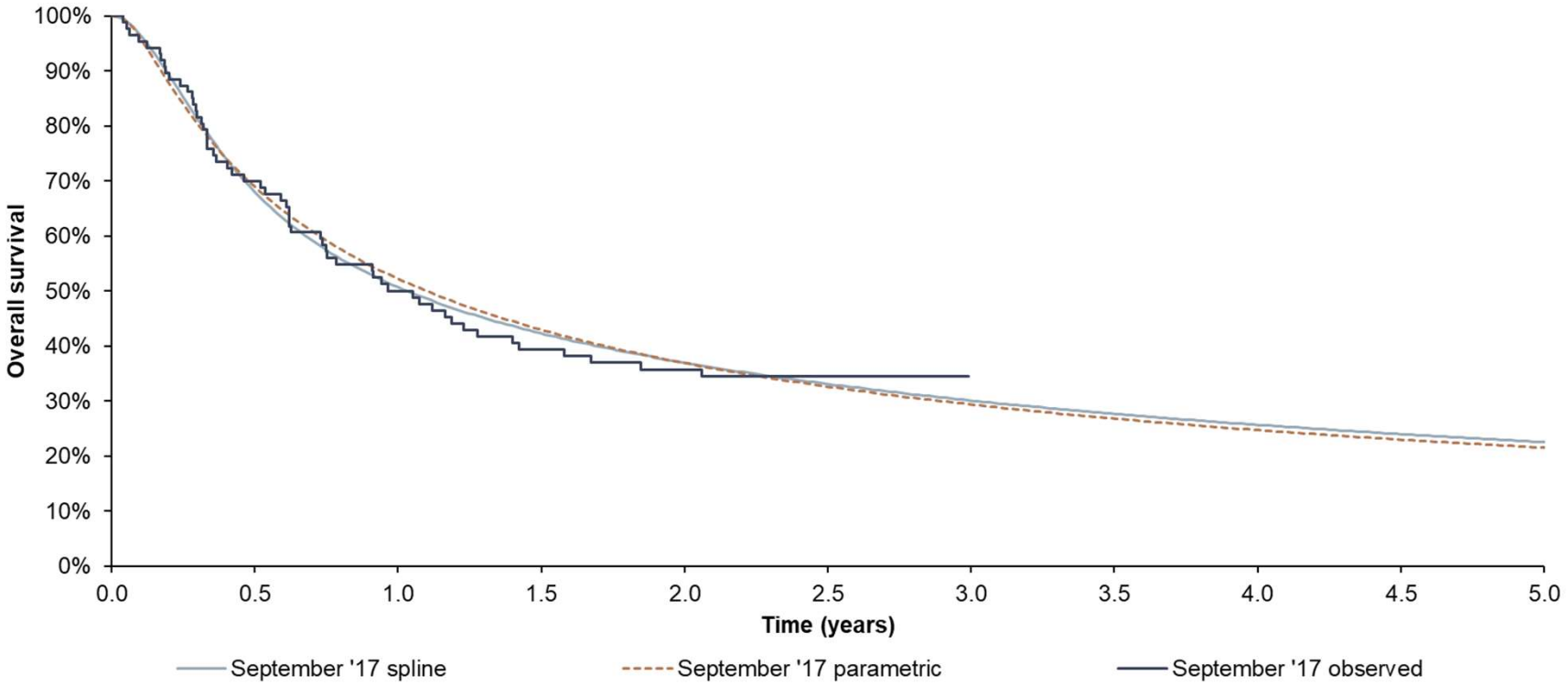
Results
Extrapolation from March '17 (18 months' MFU) data cut



Best-fitting standard parametric model: log-normal, best-fitting spline model: 1-knot odds

Results

Extrapolation from September '17 (24 months' MFU) data cut



Best-fitting standard parametric model: generalised gamma, best-fitting spline model: 1-knot odds

Results
Summary

Assessment time			12 months	18 months	24 months	
Observed survival						
September 2016 (12 months' MFU) data cut			51.8%	38.3%	38.3%	
March 2017 (18 months' MFU) data cut			50.8%	39.9%	34.3%	
September 2017 (24 months' MFU) data cut			50.1%	39.3%	35.8%	
Assessment time	**Model**	**AIC**	**12 months**	**18 months**	**24 months**	**60 months**
Standard parametric survival						
September 2016 (12 months' MFU) data cut	Log-normal	377.70	51.5%	39.3%	31.8%	12.4%
March 2017 (18 months' MFU) data cut	Log-normal	431.54	52.5%	40.7%	33.3%	13.8%
September 2017 (24 months' MFU) data cut	Log-normal	455.31	54.1%	42.9%	35.8%	16.2%
	Generalised gamma	454.68	52.3%	42.8%	37.0%	21.5%
Spline-based survival						
September 2016 (12 months' MFU) data cut	1-knot odds	379.26	51.5%	40.5%	34.1%	16.9%
March 2017 (18 months' MFU) data cut	1-knot odds	432.29	50.7%	40.9%	35.0%	18.9%
September 2017 (24 months' MFU) data cut	1-knot odds	453.81	50.8%	42.1%	37.1%	22.5%

Best-fitting models presented for each data cut.

Conclusions

- Spline-based models provided a more accurate estimation of the observed 24-month OS based on extrapolation from earlier data than standard parametric approaches
- Longer-term survival estimates from the spline-based models were more aligned with clinical expectations of immunotherapy, ie, an emergent plateau in OS associated with the immune-response effect of treatment
- Limitations and further research:
  - Landmark or cure-based models may also reflect the expected immune-response effect in OS but require explicit assumptions about the estimation of long-term OS (such as the OS for cured patients, the prognostic importance of response, and the difference in the hazard of death by response)
  - Longer-term data are required to validate OS extrapolations

Thank you

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