The Institute for Clinical and Economic Review (ICER) Assessment Approaches to Survival Extrapolation: A Review and Case Study

ISPOR MSR11

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Introduction

- Survival extrapolation is crucial to derive cancer treatments' cost-effectiveness results like life years. Therefore, it is a major driver of cost-effectiveness model outcomes in oncology evaluations.
- The Institute for Clinical and Economic Review (ICER)'s survival curve extrapolation and selection and model transparency vary across assessments, creating uncertainty for those relying on the estimates.
- We reviewed ICER's survival extrapolation practices and assessed how broader candidate model consideration may improve fitness and robustness.

Objective

- **This research aims at critically reviewing and case studying ICER's survival extrapolation approaches.**

Methods

Data source

- All ICER assessment final evidence reports published between 2016 and 2025 (n=88) were reviewed.
- The most recent case, the 2021 multiple myeloma assessment on idecabtagene vicleucel (ide-cel),[1] was examined in depth.

Case study population

- Patients with relapsed and refractory myeloma after at least three previous regimens including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody.

Outcomes

- Ide-cel's overall survival (OS) extrapolation curves throughout a patient's lifetime horizon
- Curve fitness statistics including Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)

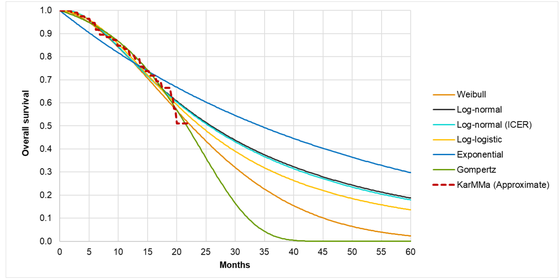
Statistical analyses

- PlotDigitizer© was used to digitize ide-cel's OS Kaplan-Meier (KM) curve published in the final evidence report.[1]
- Guyot et al. (2012)'s algorithm was applied to impute the OS individual patient data.[2]
- An expanded set of candidate models (gamma, generalized gamma, and Royston-Parmar splines models) was compared and assessed in terms of curve fitness (AIC and BIC) and robustness.[3]
- All estimation was conducted in R.

Results

- 8% ICER evidence reports (7 out of 88) conducted survival extrapolation and consistently implemented the same five curve candidates: exponential, log-normal, log-logistic, Gompertz, Weibull.
- In the 2021 assessment,[1] ICER selected log-normal (shape=3.24, scale=0.93) out of its five candidates based on the minimum AIC criteria (**Figure 1**).

Figure 1. Replicating ICER's overall survival extrapolations for ide-cel



ICER, Institute for Clinical and Economic Review.

Table 1. AIC and BIC for one-piece curves

Model	Exponential	Gamma	Gen. Gamma	Gompertz	Log-Logistic	Log-Normal	Weibull (AFT)
AIC	276.49	266.43	268.41	268.70	266.74	266.70	266.55
BIC	279.34	272.14	276.97	274.41	272.44	272.40	272.25
Rank AIC	7	1	5	6	4	3	2
Rank BIC	7	1	6	5	4	3	2
Mean AIC-BIC	277.91	269.29	272.69	271.55	269.59	269.55	269.40
Mean rank	7	1	6	5	4	3	2

AFT, accelerated failure time; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Gen. Gamma, generalized gamma.

Figure 2. Adding gamma and generalized gamma curves to the extrapolation

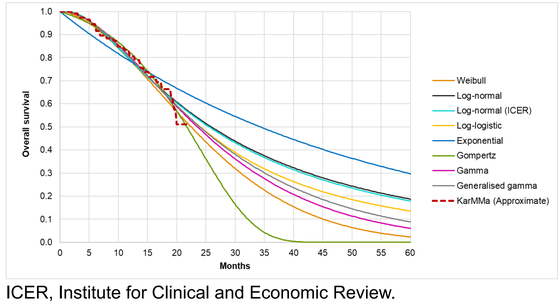


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Table 2. AIC and BIC for spline models

Model	Hazards, 1 knot	Hazards, 2 knots	Hazards, 3 knots	Odds, 1 knot	Odds, 2 knots	Odds, 3 knots	Normal, 1 knot	Normal, 2 knots	Normal, 3 knots
AIC	268.33	268.56	270.68	268.71	268.62	270.78	268.47	268.64	270.78
BIC	276.89	279.97	284.94	277.27	280.03	285.04	277.03	280.05	285.04
Rank AIC	1	3	7	6	4	9	2	5	8
Rank BIC	1	4	7	3	5	9	2	6	8
Mean AIC-BIC	272.61	274.26	277.81	272.99	274.32	277.91	272.75	274.35	277.91
Mean rank	1	4	7	3	5	9	2	6	8

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

- However, among the ICER unused one-piece survival curve candidates, gamma (shape=2.2337, rate = 0.0812) displayed lower AIC and BIC than log-normal (**Table 1, Figure 2**).
- Gamma's robustness was supported by very similar OS estimates (±0.1% before Month 24) from hazards-1 knot spline model (coefficients=-6.631, 2.156, 0.136; knot locations=0.6909, 2.2869, 2.9935) (**Table 2, Figure 3**).
- Furthermore, log-normal overestimated the OS after Month 20 (**Figure 4**), especially towards the KM curve tail, leading to higher undiscounted lifetime-horizon (baseline age = 61 years) life years (3.3) than gamma (2.3) or hazards-1 knot (2.2) (**Figure 5**).

Figure 3. Testing spline models

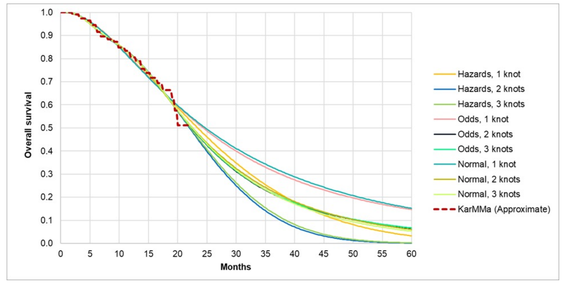

Figure 4. Overall survival extrapolations for ide-cel throughout 5 years

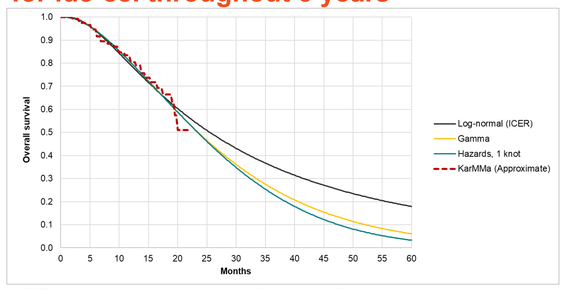

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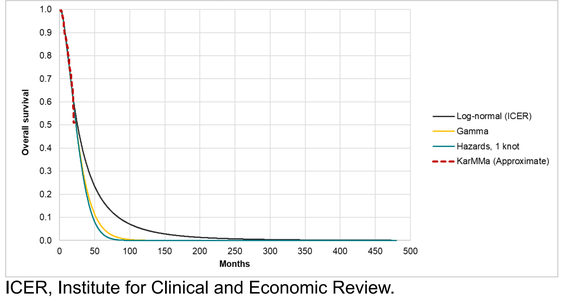
Figure 5. Overall survival extrapolations for ide-cel throughout 40 years



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Limitations

- Only the 2021 multiple myeloma assessment was case studied. However, the other six oncology assessment used the same extrapolation approaches.
- Further investigation can test other candidate models.

Conclusions

- **Our findings suggest that ICER's restricted set of survival candidate models may overlook better-fitting alternatives.**
- **Incorporating additional model candidates like spline models, routinely reporting both AIC and BIC, and more transparently documenting visual inspection and clinical plausibility validation would enhance reproducibility and reduce uncertainty in life year estimates - ultimately improving the accuracy of cost-effectiveness results.**

Disclosures

This study was conducted by Genesis Research Group. Tingting Qu was a previous employee of Genesis Research Group. Marko Zivkovic, Zhengfan Wang, Agota Szende are employees of Genesis Research Group.

References

1. Institute for Clinical and Economic Review. Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma Final Report. 2021.
2. Guyot P, et al. *BMC Medical Research Methodology*. 2012;12(1):9. doi:10.1186/1471-2288-12-9.
3. Royston P, Parmar MKB. *Statistics in Medicine*. 2002;21(15):2175–2197. doi:https://doi.org/10.1002/sim.1203

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Presented at the ISPOR 2026, May 17 - May 20, Philadelphia, PA