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ISPOR Europe 2026
8-11 November 2026
Vienna, Austria

MSR194

When the tail wags the dog V:

relative survival disciplines an implausible overall-survival extrapolation in curative-intent bladder cancer (KEYNOTE-905/EV-303)

WHY THIS CASE STUDY

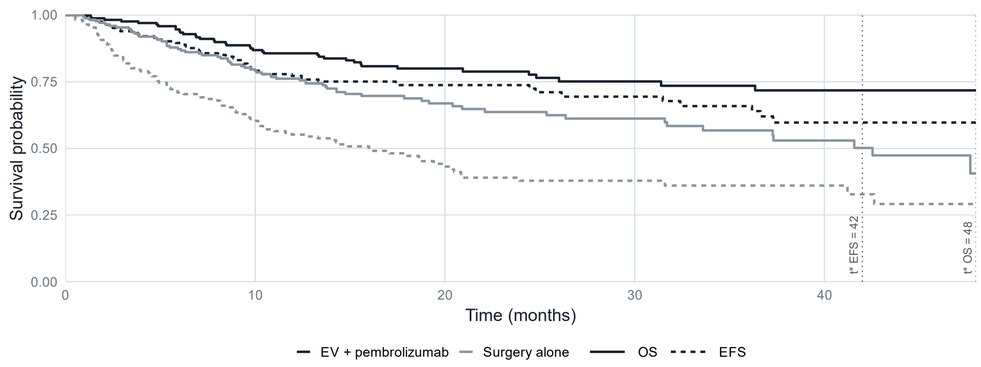
KEYNOTE-905 is the case where the population floor earns its keep. Treatment is given around curative surgery and a substantial fraction of patients are cured, so their mortality is the general population's rather than the disease's. An unconstrained extrapolation reads the plateau in the curves as a near-permanent survival advantage; placing general-population mortality underneath it bounds the same data. Event-free survival, which takes no floor, shows what the unconstrained version claims.

BACKGROUND

Cost-effectiveness models in oncology are driven by extrapolated survival curves, and almost nobody reports how much of the modelled lifetime benefit was seen in the trial and how much was assumed beyond it. We introduced a new framework at ISPOR Philadelphia this year we called *When the tail wags the dog* [1] and in this series we apply the framework to five recent oncology trials each representing a different survival pattern. For each case study we report the share of the incremental gain arising after the data end, where in time that gain sits, and what changes when general-population mortality is placed underneath the extrapolation (relative survival [2]).

KEYNOTE-905 / EV-303

- Cisplatin-ineligible muscle-invasive bladder cancer treated with curative intent; median age 73 years, 78% male.
- **Enfortumab vedotin plus pembrolizumab** around radical cystectomy, against **surgery alone.**
- **Overall survival** — published hazard ratio 0.5 (95% CI 0.33–0.74), two-year survival 79.7% against 63.1%, median not reached against 41.7 months. 38 and 68 deaths among 170 and 174 patients.
- **Event-free survival** — published hazard ratio 0.4 (95% CI 0.28–0.57), two-year 74.7% against 39.4%, median not reached against 15.7 months. 48 and 95 events in the same patients.
- The contrast is the whole case study: the largest floor effect in the series, in the one setting where a cure fraction makes the floor structurally right.
- Vulsteke C, et al. *N Engl J Med* 2026. PMID 41707170.



Kaplan–Meier curves are reconstructed from the published figures [3,4]; all trial results quoted are as reported.

METHODS

Extrapolation

Pseudo-individual patient data were reconstructed from the published Kaplan–Meier curves [3,4]. Eight distributions were fitted jointly — one shared distribution with a treatment covariate on the location parameter and ancillary parameters common to both arms, so the two arms share a hazard shape and differ by a single treatment parameter — over a 40-year horizon [1]. All-cause fits are unconstrained; relative-survival fits model the excess hazard over ONS UK population mortality [2,5]. The median age and sex of the trial population, given in the case study above, index that life table, so the extrapolation sits above the mortality a general-population cohort of the same age and sex would experience.

t* separates the observed period from the extrapolated one and is not simply the maximum trial follow-up. Instead it is a judgement call, made from a reading of the reverse Kaplan–Meier curve for censoring [1]: it marks the end of reliable follow-up, before the risk sets are spent and before the two arms' censoring patterns diverge. t* is marked on the reconstructed Kaplan–Meier curves above.

Fits are compared on the Akaike and Bayesian information criteria (AIC and BIC), the standard fit statistics for choosing between parametric survival models. Both are reported for all eight distributions on each basis.

Transparency statistics

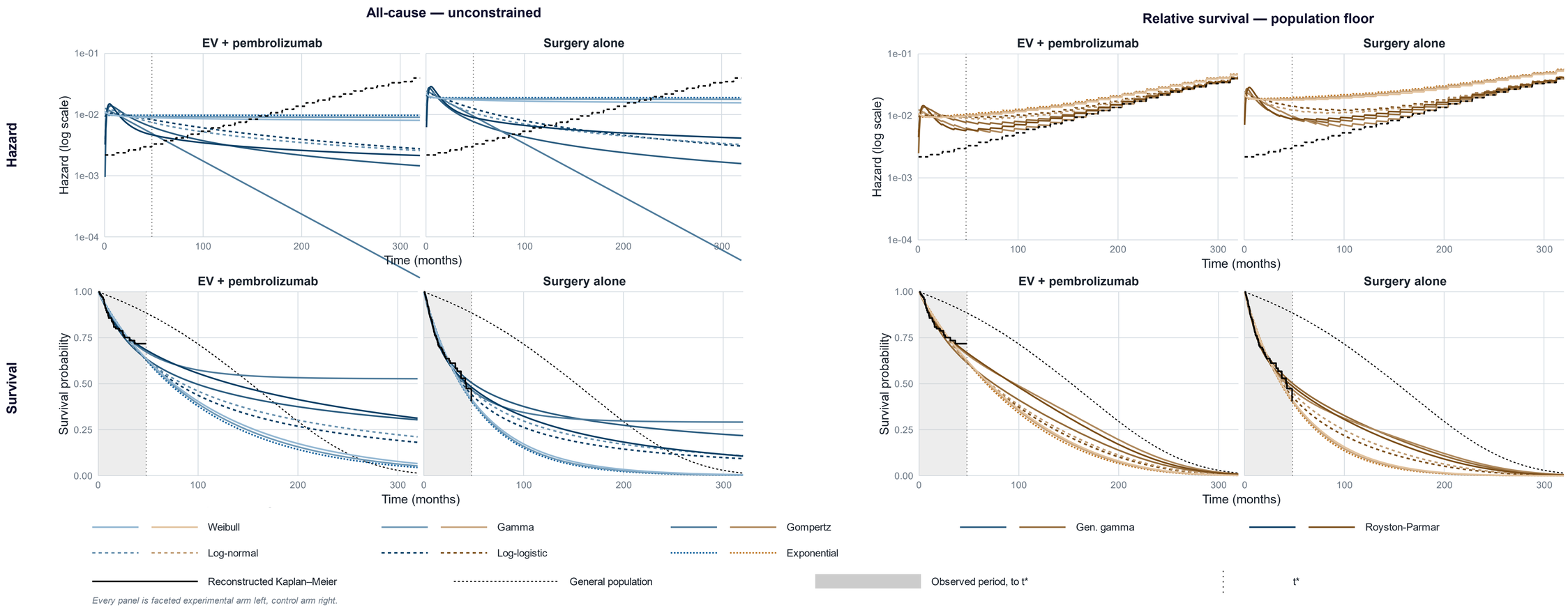
The area under each survival curve up to t* is the Restricted Mean Survival Time (RMST) and the period beyond t* is the Extrapolated Mean Survival Time (EMST). Added together they give the Unrestricted Mean Survival Time (UMST), which is the quantity that is compared between arms in an HTA / cost-effectiveness analysis:

- **ΔUMST** = ΔRMST + ΔEMST

From these quantities we form two transparency statistics [1]:

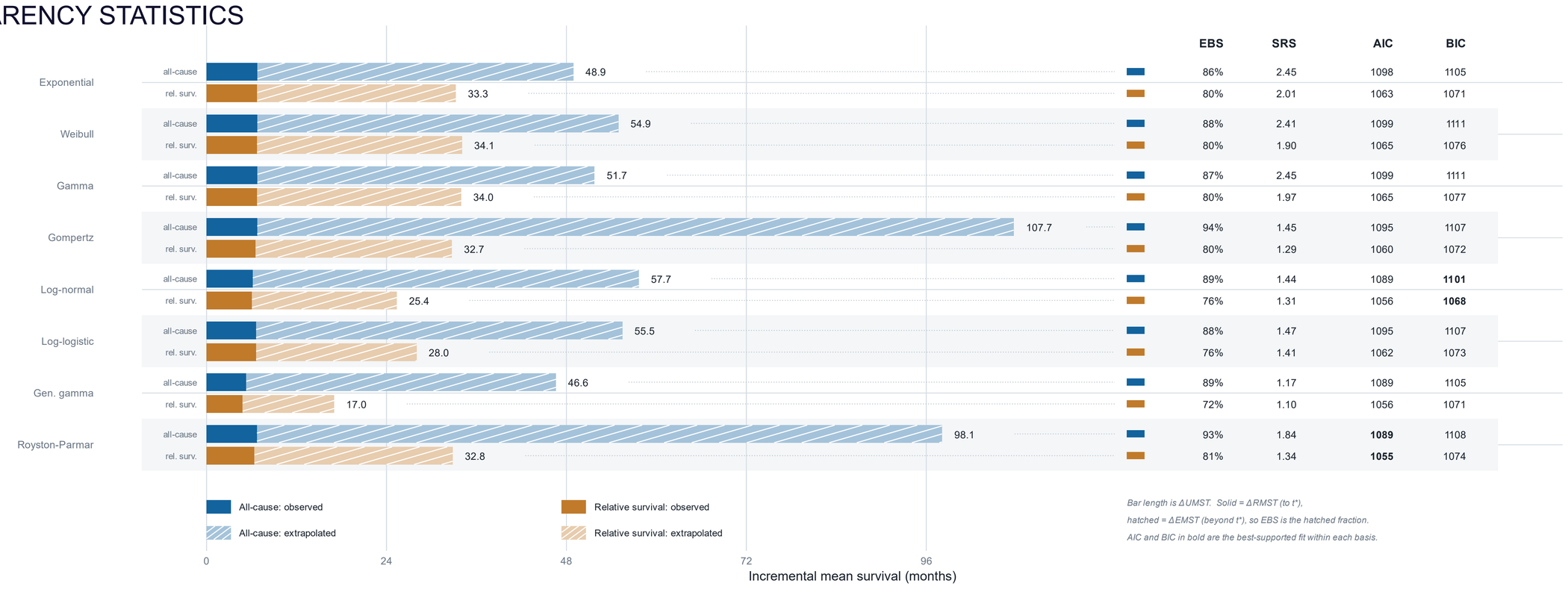
- **EBS** = ΔEMST / ΔUMST — the share of the incremental gain arising beyond the observed data.
- **SRS** = $(EMST_T/EMST_C) / (RMST_T/RMST_C)$ — above 1, the gain is concentrated in the extrapolated tail.

THE EXTRAPOLATION



Every panel is faceted experimental arm left, control arm right.

TRANSPARENCY STATISTICS



		EBS	SRS	AIC	BIC
Exponential	all-cause	86%	2.45	1098	1105
	rel. surv.	80%	2.01	1063	1071
Weibull	all-cause	88%	2.41	1099	1111
	rel. surv.	80%	1.90	1065	1076
Gamma	all-cause	87%	2.45	1099	1111
	rel. surv.	80%	1.97	1065	1077
Gompertz	all-cause	94%	1.45	1095	1107
	rel. surv.	80%	1.29	1060	1072
Log-normal	all-cause	89%	1.44	1089	**1101**
	rel. surv.	76%	1.31	1056	**1068**
Log-logistic	all-cause	88%	1.47	1095	1107
	rel. surv.	76%	1.41	1062	1073
Gen. gamma	all-cause	89%	1.17	1089	1105
	rel. surv.	72%	1.10	1056	1071
Royston-Parmar	all-cause	93%	1.84	**1089**	1108
	rel. surv.	81%	1.34	**1055**	1074

Bar length is ΔUMST. Solid = ΔRMST (to t), hatched = ΔEMST (beyond t*), so EBS is the hatched fraction.*
AIC and BIC in bold are the best-supported fit within each basis.

CONCLUSION

With a cure fraction in play, the population floor turns a divergent extrapolation into a bounded one.

Unconstrained, the modelled overall-survival gain ranges from 47–108 months and the fits that read the plateau as permanent sit at the top of it. With general-population mortality underneath, the same eight distributions give 17–34 months: the excess hazards converge onto the population line, which is what a long-term-survivor fraction looks like when it is modelled rather than assumed. EBS remains high at 72–81% — the endpoint is immature and the floor does not change that — but the magnitude is bounded, and event-free survival at 39–148 months shows what the unconstrained version would have claimed. Costless where excess mortality dominates and decisive where it does not, the floor belongs in the standard toolkit.

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DISCLOSURES

The analysis was conducted by Occam Research Ltd as relationship investment; no trial-sponsor funding. Public data only. AI-assisted content disclosable per ISPOR policy: scaffolding and drafting assistance were used, and all analysis and outputs were validated by the authors.