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When the tail wags the dog III:

a persist-versus-fade extrapolation choice and the Survival Ratio Shift (RASolute302)

WHY THIS CASE STUDY

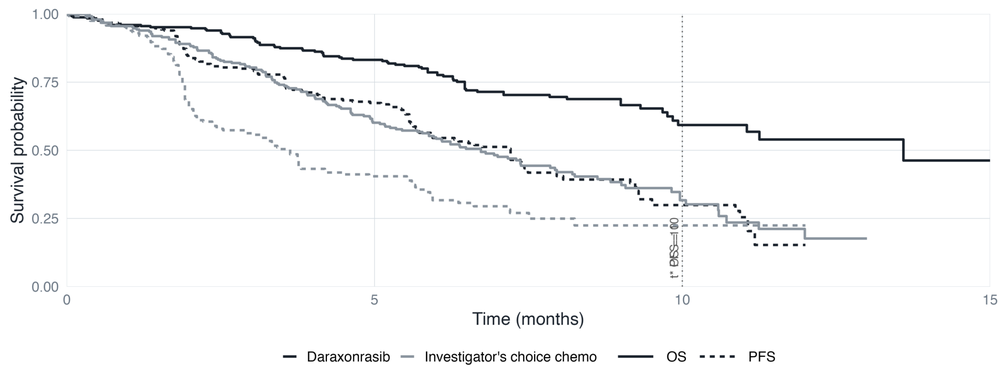
RASolute302 is the case where the extrapolation splits in two. Overall survival more than doubled on the shortest follow-up in the series: by 10 months 30.6% and 53.6% of patients had died and the curves stood at 0.59 and 0.32, with the data ending at 15 months. Beyond that the eight distributions separate into two camps: the increasing-hazard family keeps the excess hazard rising, and the long-tailed family turns it over. Both describe the observed data. It leans one way, and not far enough to settle the size. That is a clinical question — does the excess mortality of treated pancreatic cancer persist, or fade — wearing the clothes of a statistical one.

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]).

RASolute302

- Previously treated metastatic pancreatic ductal adenocarcinoma; median age 65 years, 55% male.
- **Daraxonrasib,** a RAS(ON) multiselective inhibitor, against **investigator's choice chemotherapy.**
- **Overall survival** — published hazard ratio 0.4 (95% CI 0.30–0.53), medians 13.2 against 6.7 months. 79 and 141 deaths among 248 and 252 patients.
- **Progression-free survival** — published hazard ratio 0.49 (95% CI 0.38–0.64), medians 7.2 against 3.6 months. 127 and 130 progression events in the same patients.
- The contrast is the whole case study: the modelled overall-survival gain exceeds the progression-free gain, on a median follow-up under nine months.
- O'Reilly EM, et al. *N Engl J Med* 2026. PMID 42223072.



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

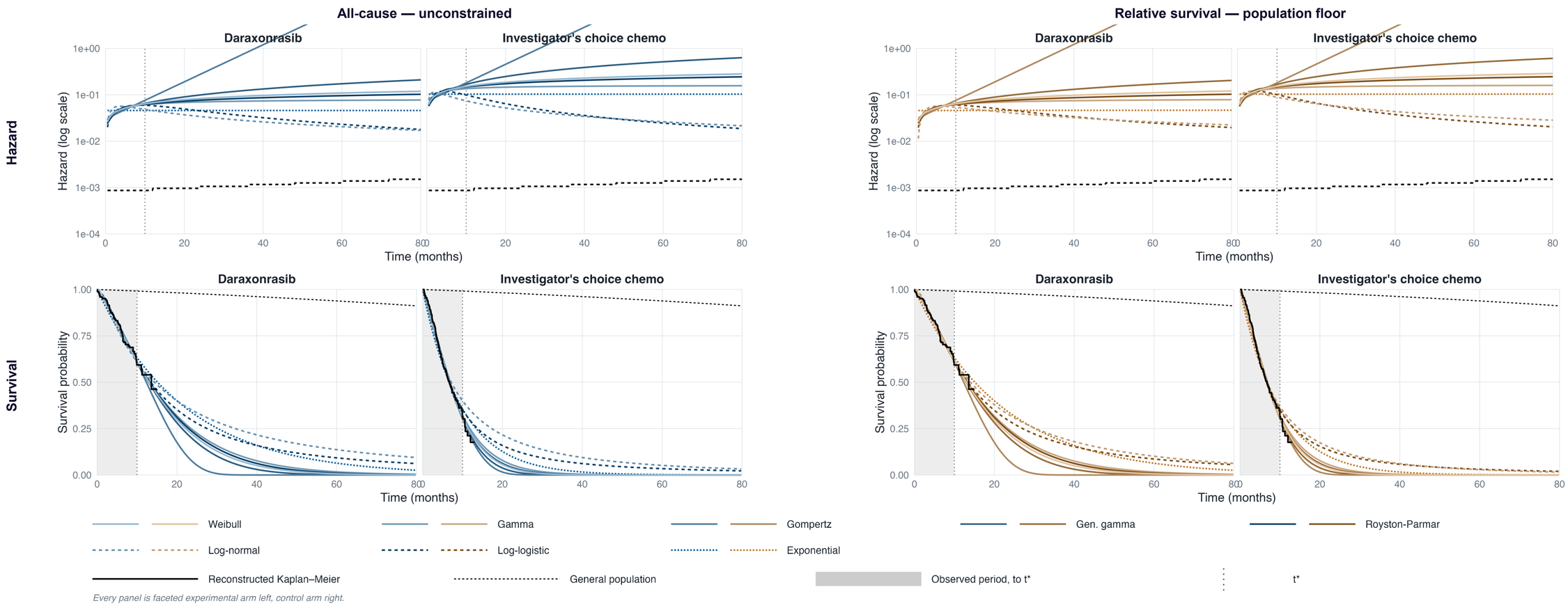
The area under each survival curve up to t* is the Restricted Mean Survival Time (RMST) and the period beyond t* is the Extrapolated Mean Survival Time (EMST). Added together they give the Unrestricted Mean Survival Time (UMST), which is the quantity that is compared between arms in an HTA / cost-effectiveness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

- **ΔUMST** = ΔRMST + ΔEMST

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

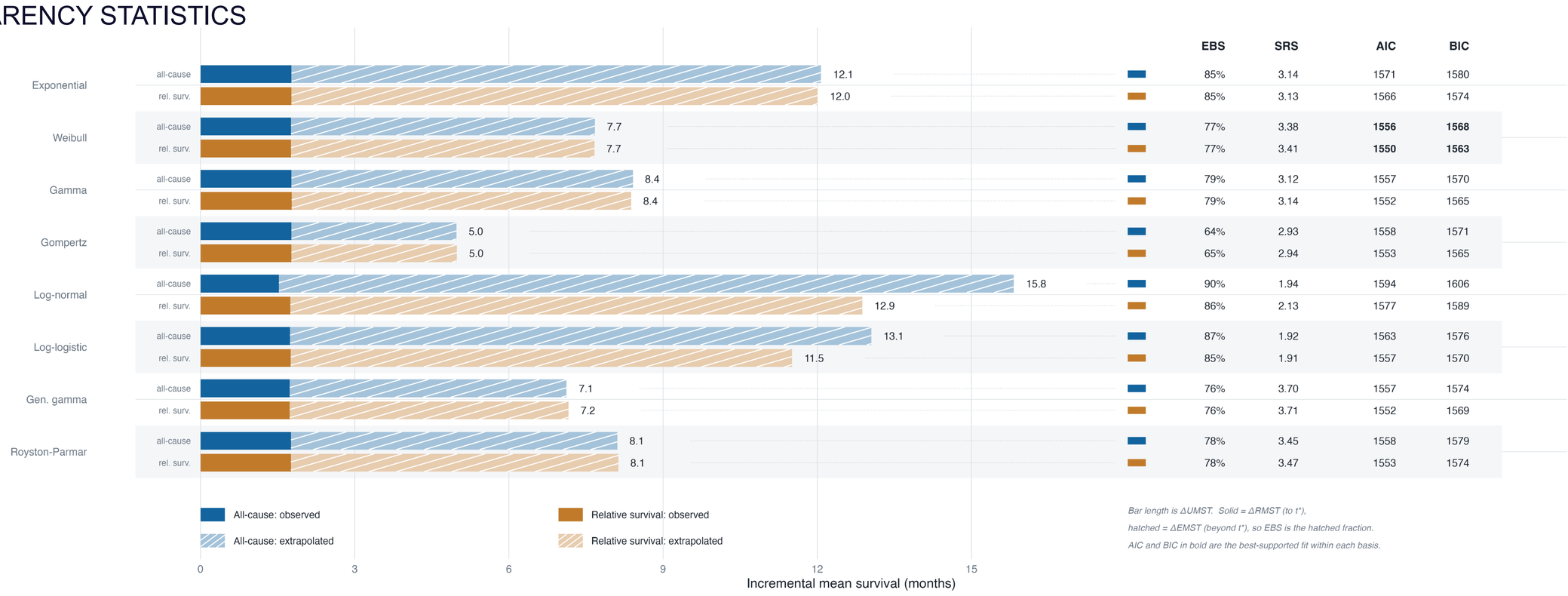
- **EBS** = ΔEMST / ΔUMST — the share of the incremental gain arising beyond the observed data.
- **SRS** = $(EMST_T/EMST_C) / (RMST_T/RMST_C)$ — above 1, the gain is concentrated in the extrapolated tail.

THE EXTRAPOLATION



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

TRANSPARENCY STATISTICS



		EBS	SRS	AIC	BIC
Exponential	all-cause	85%	3.14	1571	1580
	rel. surv.	85%	3.13	1566	1574
Weibull	all-cause	77%	3.38	**1556**	**1568**
	rel. surv.	77%	3.41	**1550**	**1563**
Gamma	all-cause	79%	3.12	1557	1570
	rel. surv.	79%	3.14	1552	1565
Gompertz	all-cause	64%	2.93	1558	1571
	rel. surv.	65%	2.94	1553	1565
Log-normal	all-cause	90%	1.94	1594	1606
	rel. surv.	86%	2.13	1577	1589
Log-logistic	all-cause	87%	1.92	1563	1576
	rel. surv.	85%	1.91	1557	1570
Gen. gamma	all-cause	76%	3.70	1557	1574
	rel. surv.	76%	3.71	1552	1569
Royston-Parmar	all-cause	78%	3.45	1558	1579
	rel. surv.	78%	3.47	1553	1574

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

The advantage is loaded into the tail under every distribution; only its size is open.

Both information criteria select the Weibull. Its lifetime gain is 7.7 months. All eight put 1.7–1.8 months of that gain inside the observed period and differ only in what follows, which ranges 3.2–11.1 months, so EBS runs 65–86% and SRS 1.9–3.7 — the highest in the series, where the lowest value here is about the highest on any other poster. An SRS of 3.4 means the treated-to-control ratio of mean survival is more than three times larger beyond the data than within them. The criteria are not silent: the two long-tailed fits rank sixth and eighth of the eight on AIC and track the observed curves about half as closely, so the data lean towards the persisting camp without settling the size. The population-mortality floor barely touches any of it, because excess mortality dominates background mortality in this disease — the persist-versus-fade choice is left where it started, with the clinician rather than the criteria.

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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.