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When the tail wags the dog I:

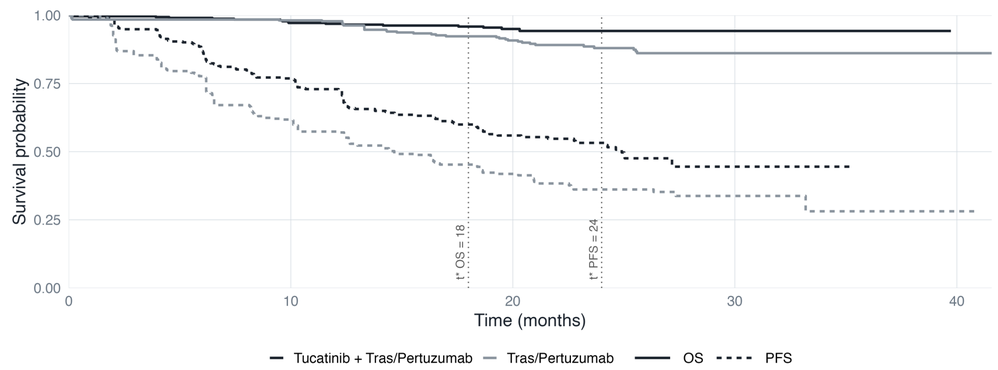
a within-trial demonstration of extrapolation transparency and relative survival (HER2CLIMB-05)

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]).

HER2CLIMB-05

- Women with HER2-positive metastatic breast cancer whose disease had not progressed after induction therapy; median age 54 years, all female.
- **Tucatinib** added to trastuzumab / pertuzumab maintenance, against **placebo** added to the same maintenance.
- **Overall survival** — published hazard ratio 0.539 (95% CI 0.303–0.957), neither median reached. 51 deaths in total among 326 and 328 patients.
- **Progression-free survival** — published hazard ratio 0.641 (95% CI 0.514–0.799), medians 24.9 against 16.3 months. 141 and 191 progression events in the same patients.
- The contrast is the whole case study: about seven times as many progression events as deaths, in the same patients over the same follow-up.
- Diéras V, et al. *J Clin Oncol.* 2025;44(17):1597–1607. PMID 41369677.



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

WHY THIS CASE STUDY

HER2CLIMB-05 has the least mature overall-survival data in the series. Neither median was reached, only 4.0% and 7.3% of patients had died by 18 months, and the two curves were still at 0.96 and 0.92 where the observed period ends — barely separated. Progression-free survival, in the same patients over the same follow-up, separates within ten months and stays apart. This is the common pattern in good-prognosis cancers: the trial is powered on the surrogate endpoint and is not long enough for overall survival to mature.

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

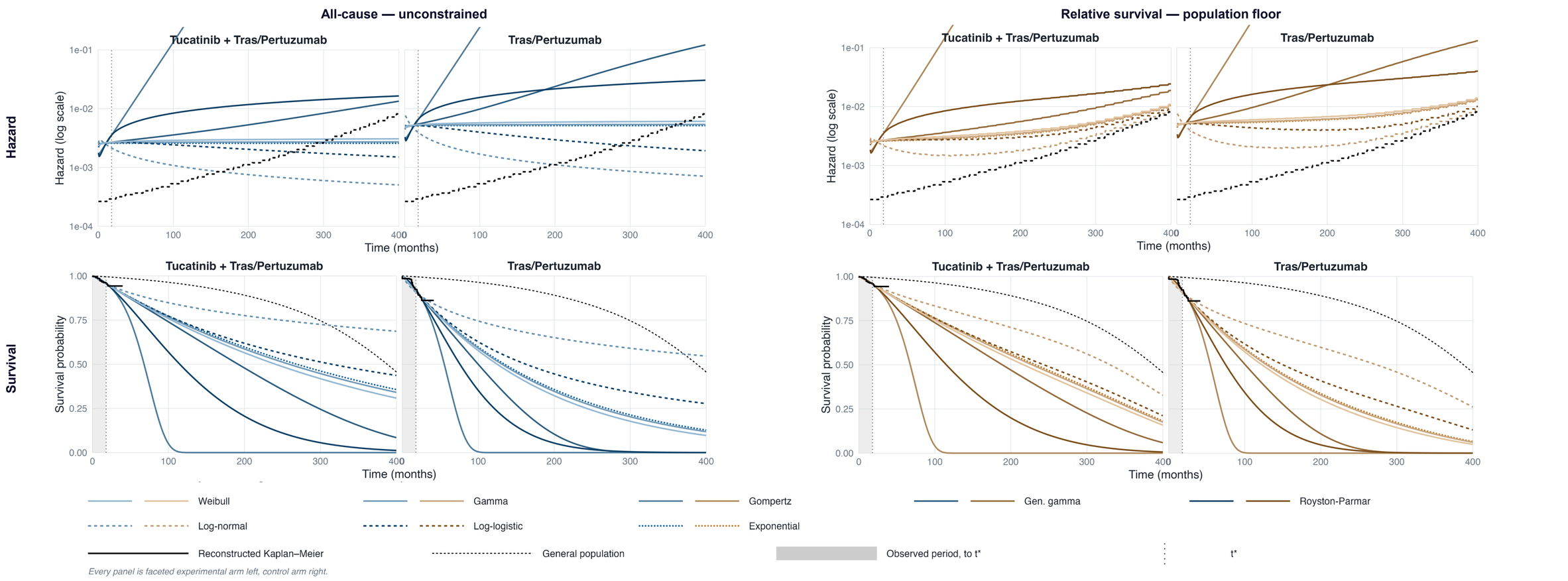
The area under each survival curve up to t* is the Restricted Mean Survival Time (RMST) and the period beyond t* is the Extrapolated Mean Survival Time (EMST). Added together they give the Unrestricted Mean Survival Time (UMST), which is the quantity that is compared between arms in an HTA / cost-effectiveness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

- **ΔUMST** = ΔRMST + ΔEMST

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

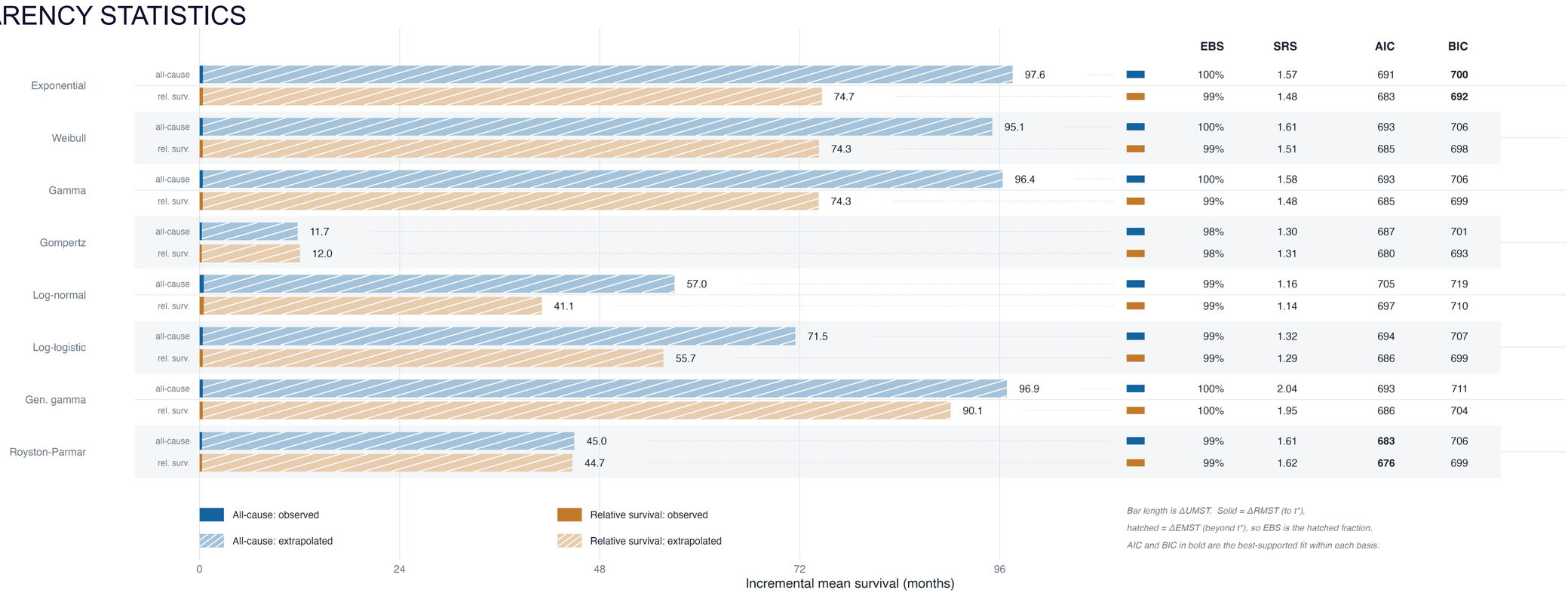
- **EBS** = ΔEMST / ΔUMST — the share of the incremental gain arising beyond the observed data.
- **SRS** = $(EMST_T/EMST_C) / (RMST_T/RMST_C)$ — above 1, the gain is concentrated in the extrapolated tail.

THE EXTRAPOLATION



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

TRANSPARENCY STATISTICS



		EBS	SRS	AIC	BIC
Exponential	all-cause	100%	1.57	691	**700**
	rel. surv.	99%	1.48	683	**692**
Weibull	all-cause	100%	1.61	693	706
	rel. surv.	99%	1.51	685	698
Gamma	all-cause	100%	1.58	693	706
	rel. surv.	99%	1.48	685	699
Gompertz	all-cause	98%	1.30	687	701
	rel. surv.	98%	1.31	680	693
Log-normal	all-cause	99%	1.16	705	719
	rel. surv.	99%	1.14	697	710
Log-logistic	all-cause	99%	1.32	694	707
	rel. surv.	99%	1.29	686	699
Gen. gamma	all-cause	100%	2.04	693	711
	rel. surv.	100%	1.95	686	704
Royston-Parmar	all-cause	99%	1.61	**683**	706
	rel. surv.	99%	1.62	**676**	699

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 immature survival data, the lifetime gain becomes a choice, but relative survival helps define that choice by asking whether the long-term hazard remains above the background or tends towards it.

AIC selects the Royston-Parmar spline and BIC the exponential. Their lifetime gains are 44.7 months and 74.7. EBS puts at least 98% of the gain after the data end whichever is chosen, and across the eight distributions the gain ranges from 12–90 months with SRS of 1.1–2.0. The selection is weaker than it looks: BIC separates the exponential from the Gompertz by 1.0 units, and those two imply 74.7 months and 12.0. The fit that tracks the observed curves most closely is the log-normal, at 41.1 months. The population-mortality floor disciplines the most optimistic fits without resolving that immaturity.

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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.