BEYOND THE TRIAL: EVALUATING PARAMETRIC MODELS FOR LONG-TERM ONCOLOGY PROJECTIONS OF OVERALL SURVIVAL

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Introduction

Due to time and budget constraints, as well as the increasing efficacy of novel therapies, clinical trials for cancer treatments often present immature overall survival (OS) data.[1] Consequently, when making regulatory and reimbursement decisions, regulatory bodies commonly rely on extrapolation methods to evaluate survival benefits of cancer drugs beyond trial follow-up.[2]

Despite several parametric and semi-parametric models are available for this purpose,[3] none of them is exempt from uncertainty, and the appropriateness and plausibility of the results they produce is often debated.[2] In this context, selecting a reliable extrapolation model is crucial for accurately projecting long-term data,[3] enabling regulatory bodies to properly assess the expected survival benefits of new technologies and ensure timely patient access to novel therapeutic options.[1,2]

This study aims at investigating the reliability of six different parametric models in extrapolating long-term survival projections from immature OS data, for the five deadliest cancers in Italy.

Methods

Phase 3 clinical trials having OS as primary endpoint and reporting mature Kaplan-Meier (KM) survival data for drugs indicated and reimbursed in Italy in the last three years (2021-2023) for the five deadliest cancers in Italy[4] (breast cancer, colorectal cancer, gastric cancer, lung cancer or pancreatic cancer) were identified through an IQVIA proprietary database on Italian negotiation dynamics.
To assess parametric models' validity in extrapolating long-term OS projections, each trial's survival data were analyzed through the following four steps:

1. The mature OS curve reported in the study was digitized with the publicly available WebPlotDigitizer online software to retrieve the KM data. Then, an immature version of the same curve was derived by cutting the mature KM dataset at two different data points, depending on whether the trial referred to a first-line (1L) indication (cut at 24 months) or a subsequent line (2L+) indication (cut at 12 months);
2. Both the immature and mature KM datasets were extrapolated over a 10-year horizon using the six standard parametric models[3,5,6] (exponential, generalized gamma, Gompertz, loglogistic, lognormal and Weibull distributions);
3. Each model's goodness of fit was evaluated by assessing the sum of the Akaike and Bayesian Information Criteria (AIC+BIC),[6] for both the immature and mature KM datasets. The model reporting the lowest AIC+BIC value was considered to be the fittest;
4. Lastly, the reliability of each distribution was quantified by calculating a proxy of the model's capability of producing similar projections when based on either immature or mature data. In particular, the curves extrapolated from the two datasets using the same model were compared by measuring the mean squared error (MSE) between each corresponding point of the two curves. The models showing an MSE<0.0005 were considered to be reliable.

Results

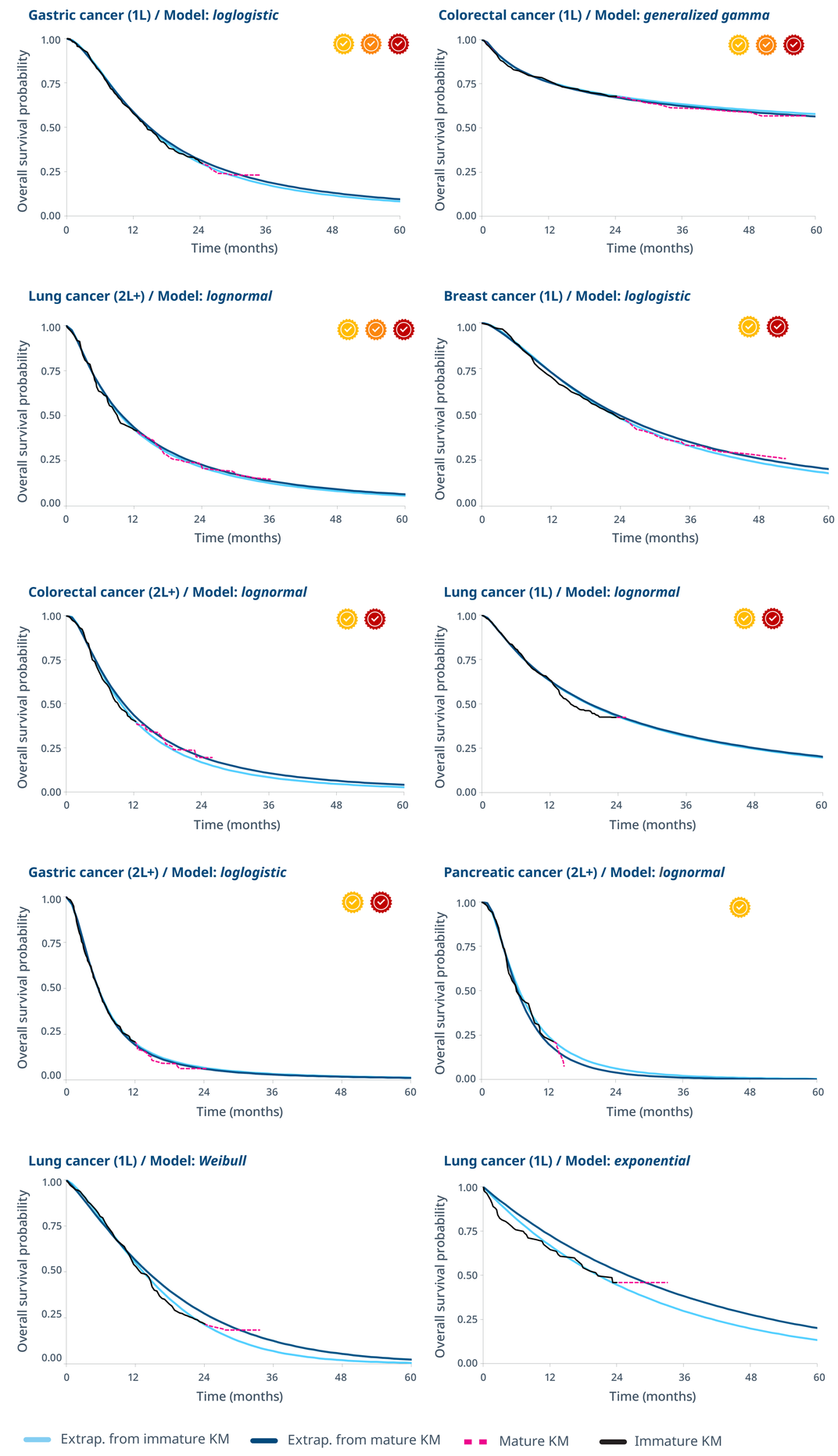
Ten clinical trials were included in the study, four on lung cancer, two on gastric and colorectal cancers, and one for breast and pancreatic cancer. Overall, six trials pertained to indication for the 1L treatment of these cancers and four to indications for 2L+ treatment. Average survival at data cut-off for immature data was 38.2%, ranging from 21.0% to 68.0% among all observations.
The main results of the analysis are presented in *Figure 1* and *Table 1*:

- In terms of model fitness and reliability, the fittest model for immature data was also reliable (MSE<0.0005) in 8 cases out of 10, reporting the lowest MSE among all six extrapolations in 3 occurrences (*Figure 1*). Furthermore, in 7 out of these 8 cases, the fittest model for the immature dataset was also the fittest when applied to mature data *(Table 1)*, highlighting that parametric extrapolations might be appropriate for long-term extrapolations even when data is available for a shorter follow-up period;
- Analyzing the performance of each parametric model, the lognormal distribution emerged to be the fittest for immature data in most cases (4 out of 10), followed by the loglogistic distribution in 3 cases, and the exponential, generalized gamma and Weibull distributions in only 1 case each. The lognormal, loglogistic and generalized gamma models consistently proved to be also reliable when applied to mature data, while in contrast, the exponential and Weibull distributions were neither reliable nor fittest for mature data (*Table 1*). The high performance of the loglogistic and lognormal distributions is aligned with the wide use of models from the log-location-scale family in medical studies.[7]

Conclusions

This study showed that in the setting of interest long-term extrapolations of immature OS data might be appropriate, in particular when using the lognormal and loglogistic parametric distributions.
The two models, while yielding the best values to fit immature KM data, were also consistent and reliable when applied to mature data.

Figure 1. ***Extrapolations of immature and mature KM data with fittest model for immature data***



Note: although being extrapolated over a 10-year horizon, graphs report data over a 5-year horizon to allow readability and interpretability of results.
Acronyms: 1L = First-line; 2L+ = Subsequent line; MSE = Mean Squared Error; KM = Kaplan-Meier

Table 1. ***Fitness and reliability, by parametric model***

Parametric model	Fittest model for immature data (N of observations)	Reliable with respect to mature data (N of observations)	Not reliable with respect to mature data (N of observations)	Fittest model for both immature and mature data (N of observations)
Exponential	1	-	1	-
Generalized gamma	1	1	-	1
Gompertz	-	-	-	-
Loglogistic	3	3	-	3
Lognormal	4	4	-	3
Weibull	1	-	1	-
Total	**10**	**8**	**2**	**7**

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