# General Population Mortality Adjustment in Survival Extrapolation of Cancer Trials: Exploring Plausibility and Implications for Cost-Effectiveness Analyses in HER2-positive breast cancer in Sweden

*Kun Kim[1,2], Michael Sweeting[3], Nils Wilking[4], Linus Jönsson[1]

**MSR112**

- **Uncertainty in the long-term survival extrapolation is a challenging problem in economic evaluations of oncology medicines.**
- **Excess hazard methods that incorporate background mortality rates in HER2-positive breast cancer patients provided more accurate estimates and significantly reduced between-model variance.**
- **This novel method may be preferred to reduce uncertainty in health economic modelling and enhance the application of evidence-based healthcare decision-making.**

Disclosures
KK and MS are employees and/or shareholders of AstraZeneca PLC.

## Background

In economic evaluations of novel therapies, assessing lifetime effects based on trial data often necessitates survival extrapolation, with the choice of model impacting outcomes. The aim was to assess accuracy and variability between alternative approaches to survival extrapolation.

## Method

Data on HER2-positive breast cancer patients from the Swedish National Breast Cancer Register[1] was used to fit standard parametric distribution (SPD) models and excess hazard (EH) models adjusting the survival projections based on general population mortality (GPM). Models were fitted using 6-year data for stage I and II, 4-year data for stage III, and 2-year data for stage IV cancer reflecting typical trial data cut-off for these stages while maintaining sufficient events for comparison of model estimates with actual long-term outcomes. We compared model projections of 15-year survival and restricted mean survival time (RMST) to 15-year registry data and explored variability between models in extrapolations of long-term survival.

## Results

Of 12,345 patients with invasive HER2-positive breast cancer, 11,224 of treatment-naïve patients were included after excluding those with unknown status for mortality or cancer stage, previous treatments for breast cancer or other cancers before their primary diagnosis, or male patients. The cancer severity was defined with cancer stage I – IV.

The 15-year RMST from the registry was 12.7, 11.4, 9.3, and 4.8 for stages I to IV, respectively. Compared to the registry estimates, across the disease stages the AIC-averaged projections varied as follows: -8.2% to +5.3% for SPD models, -4.9% to +5.2% for EH models without a cure assumption, and -19.3% to -0.2% for EH models with a cure assumption.

**Table 1: Restricted mean survival time at 50-years in stage II HER2+ breast cancer**

| | SPD models | EH no cure model | EH cure model |
|---|---|---|---|
| RMST (95% CI) | | | |
| Exponential | 24.4 (23.5 - 25.3) | 21.4 (20.9 - 22.0) | 21.5 (20.8 - 22.2) |
| Weibull | 23.0 (21.7 - 24.4) | 20.3 (19.4 - 21.1) | 23.8 (23.5 - 24.2) |
| Gompertz | 25.4 (22.5 - 28.7) | 20.5 (18.8 - 22.3) | 23.4 (23.0 - 23.8) |
| Gamma | 23.1 (21.9 - 24.3) | 20.3 (19.6 - 21.1) | 23.2 (22.7 - 23.7) |
| Log-logistic | 25.9 (24.8 - 27.0) | 20.7 (20.0 - 21.4) | 23.4 (23.0 - 23.7) |
| Log-normal | 28.2 (27.2 - 29.3) | 21.3 (20.7 - 21.9) | 22.9 (22.2 - 23.6) |
| Generalized gamma | 26.0 (24.6 - 27.6) | 20.6 (19.9 - 21.3) | 22.9 (22.0 - 23.8) |
| Mean (SD) | 25.2 (1.8) | 20.7 (0.5) | 23.0 (0.7) |
| Min - Max | 23.0 - 28.2 | 20.3 - 21.4 | 21.5 - 23.8 |
| Between-model variance | 3.36 | 0.21 | 0.56 |

*EH: excess hazard, SPD: standard parametric distribution

Fig 1 presents survival extrapolations based on immature data with early data cut-off compared to the mid-term KM data for stage II. Comparisons for other cancer stages are presented elsewhere (Kim et al., Med Decis Making. 2024 Oct;44(7)).

In stage II, both SPD and EH no cure models underestimated survival by year 15, whereas EH cure models provided a closer match to the mid-term KM data. A similar pattern was observed in stage I and III. In stage IV, where the cure assumption is less plausible, the AIC-averaged EH no cure models delivered the mid-term projections, most closely aligning with the KM data.

Based on these models, long-term survival was projected across the cancer stages. Fig 2 presents, for stage II, that although SPD models displayed small between-model variance up to mid-term survival, the deviation continued to increase, resulting in large deviations by the end of the projection. Meanwhile, EH models effectively reduced between-model variance. This pattern was similarly observed for other cancer stages.

EH models, regardless of assuming cure, tended to predict lower RMST compared to SPD models. Notably, in early stage cancer, SPD models overestimated RMST, as the mean RMST was 32.5 years for stage I, which exceeded the expected RMST of 26.0 years in the general population over a 50-year time horizon.

## Conclusion

- Survival extrapolation with EH models may be preferred to SPD models to reduce uncertainty in economic evaluations when the study population is adequately matched with the general population.
- Our findings suggest that the most plausible scenarios with survival extrapolations are provided by EH models with or without a cure assumption depending on the stage of disease and plausibility of cure.
- EH cure models may be considered for patients with a favourable prognosis while EH models may be considered for patients with a poor prognosis.

Fig 1: Survival extrapolations for stage II HER2+ breast cancer with data cut-off at 6-years, comparing to 14-year registry data

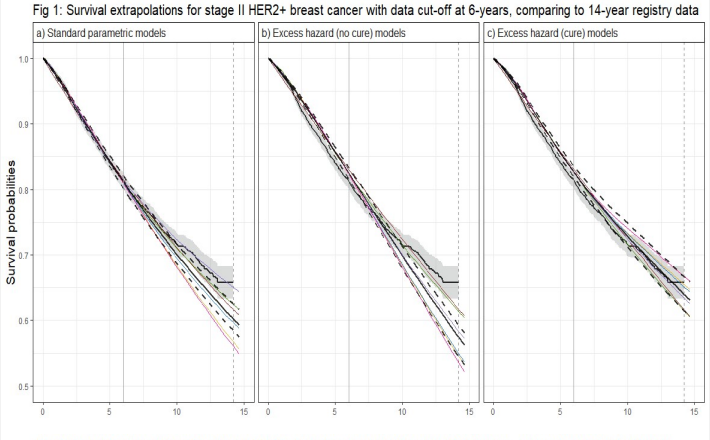
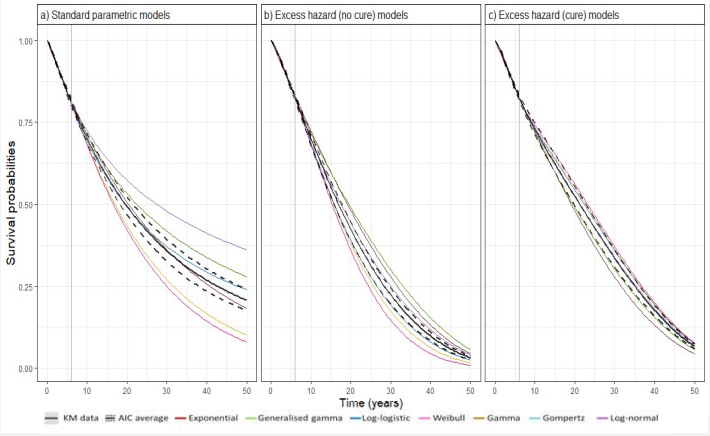



Fig 2: Survival extrapolations for stage II HER2+ breast cancer with data cut-off at 6-years, with extrapolation to 50-year




[1]Karolinska Institutet, Department of Neurobiology, Care Sciences and Society; [2]AstraZeneca Nordic AB, Health Economics; [3]AstraZeneca UK, Statistical Innovation, Oncology Biometrics; [4]Karolinska Institutet, Department of Oncology-Pathology
*Corresponding author: Kun Kim, PhD student, BioClinicum J9:20, Visionsgatan 4, 17164 Solna, Sweden, kun.kim@ki.se

'Predictive extrapolation - a framework to reduce uncertainty around long-term treatment effects in immuno-oncology' is our mission.

Karolinska Institutet