# Novel Methodology in Network Meta-analysis of Time-to-event Data using Blended Survival Curves

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## INTRODUCTION

Due to the absence of head-to-head evidence, network meta-analysis (NMA) of parametric survival curves are frequently used to inform the extrapolation of relative treatment effects for multiple interventions while the follow-up of trials are limited. However, conventional methods mainly assume constant treatment effect over time that is implausible, especially in heavily censored data. This study develops a new extrapolation technique called blended survival curves into the NMA setting for evidence synthesis.

## METHODOLOGY

The basic idea of blended survival curves is to mix a flexible model to fit as well as possible the observed data $S_{obs}$ and a parametric model encoding assumptions on the expected behaviour of underlying long-term survival $S_{ext}$.

The "blended" survival curve is obtained as

$$S_{ble}(t|\boldsymbol{\theta}) = S_{obs}(t|\boldsymbol{\theta}_{obs})^{1-\pi(t;\alpha,\beta,a,b)} \times S_{ext}(t|\boldsymbol{\theta}_{ext})^{\pi(t;\alpha,\beta,a,b)}$$

- where: $\pi(t;\alpha,\beta,a,b) = \Pr\left(T \le \frac{t-a}{b-a}\Big|\alpha,\beta\right) = F_{Beta}(\frac{t-a}{b-a}|\alpha,\beta)$
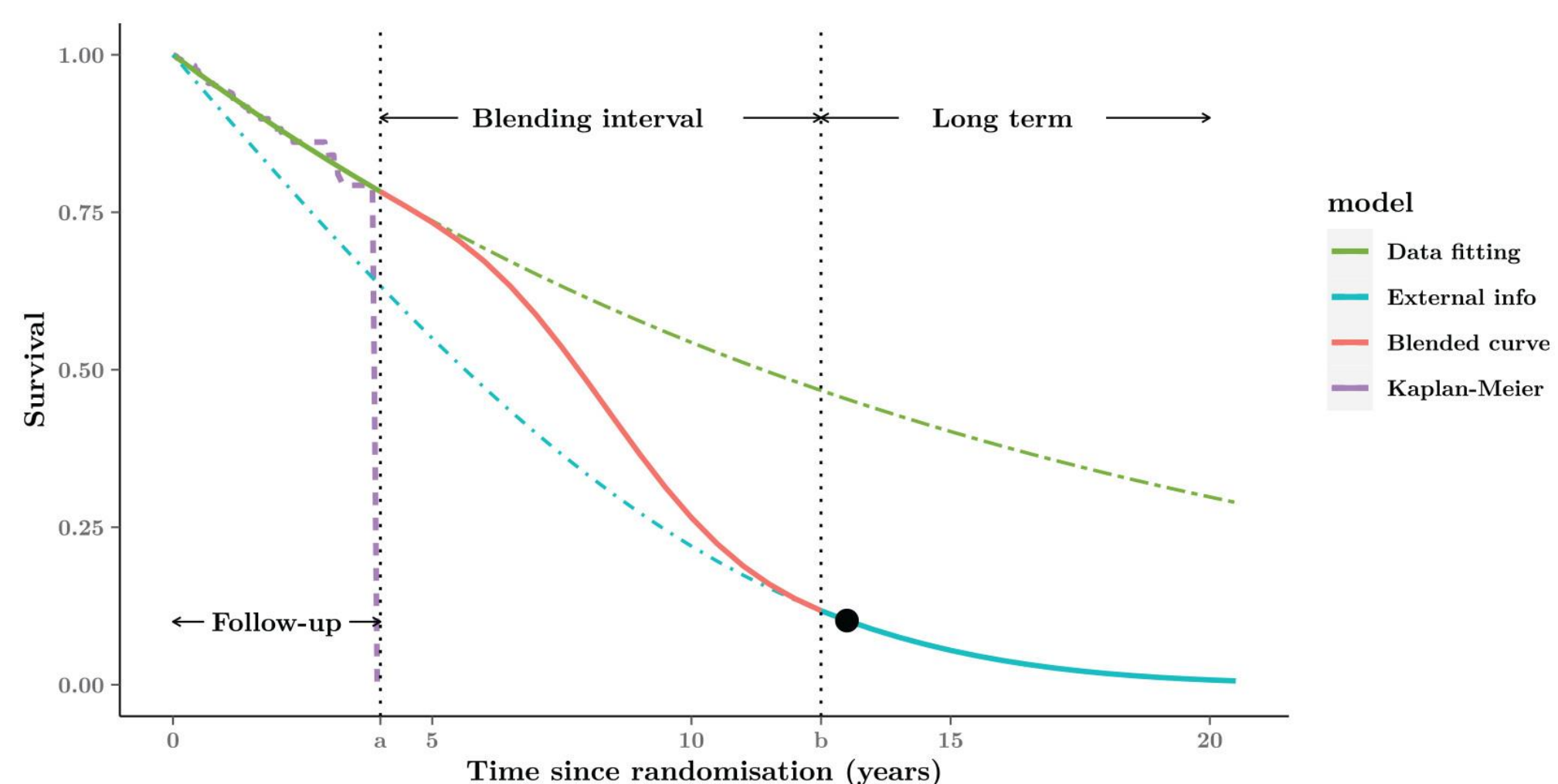


Figure 1: Graphical representation of the blended curve method

The blending hazard function is described as

$$h_{ble}(t) = \left(1-\pi(t)\right) \times h_{obs}(t) + \pi(t) \times h_{ext}(t)$$
$$+ \frac{f_{Beta}(\frac{t-a}{b-a})}{b-a} \times (H_{ext}(t) - H_{obs}(t))$$
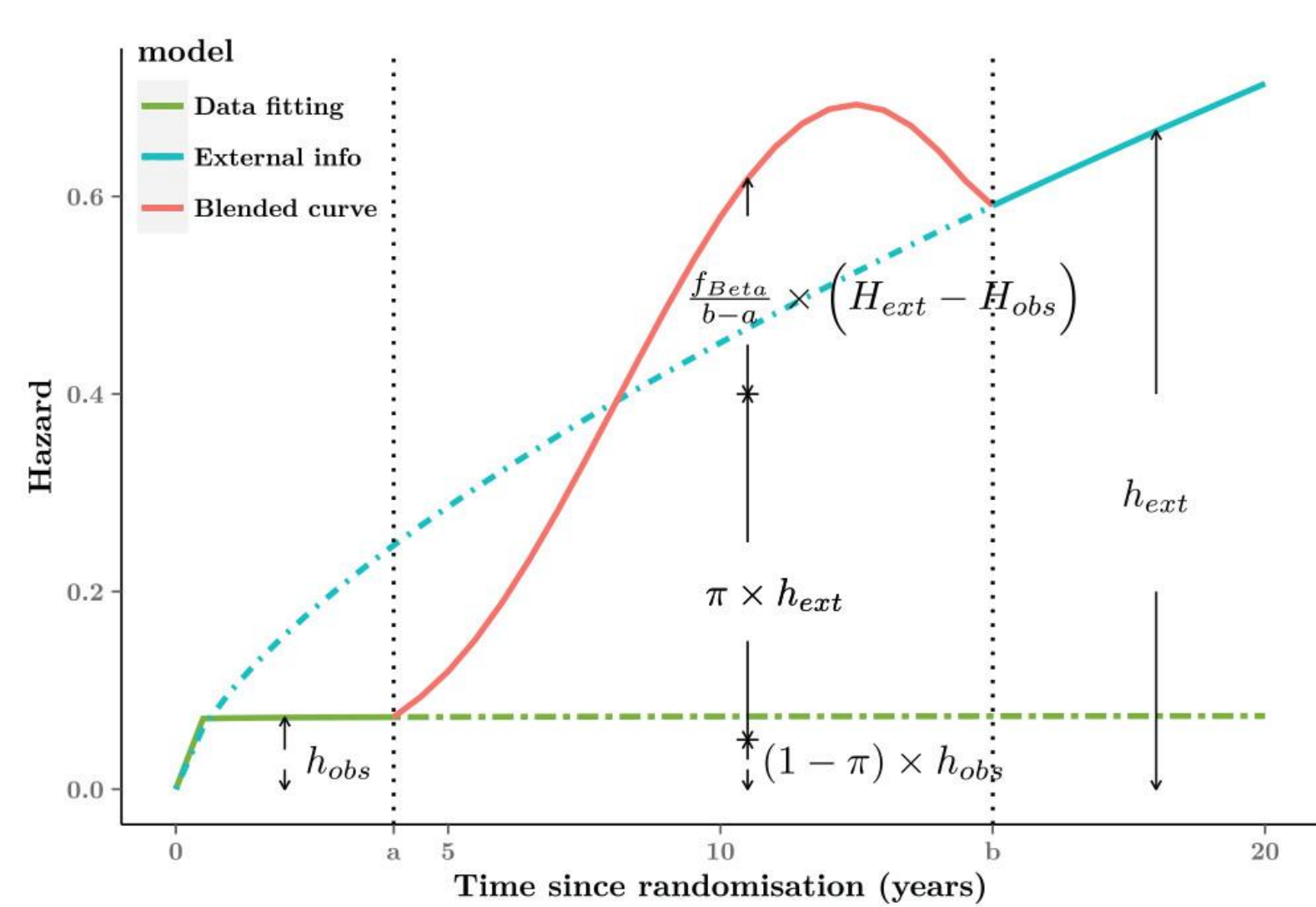


Figure 2: Graphical representation of the blended hazard

While extending the blended method to NMA framework, it has three components: 1) standard NMA for the short-term data; 2) long-term estimate using external evidence; 3) blended process combing two curves.
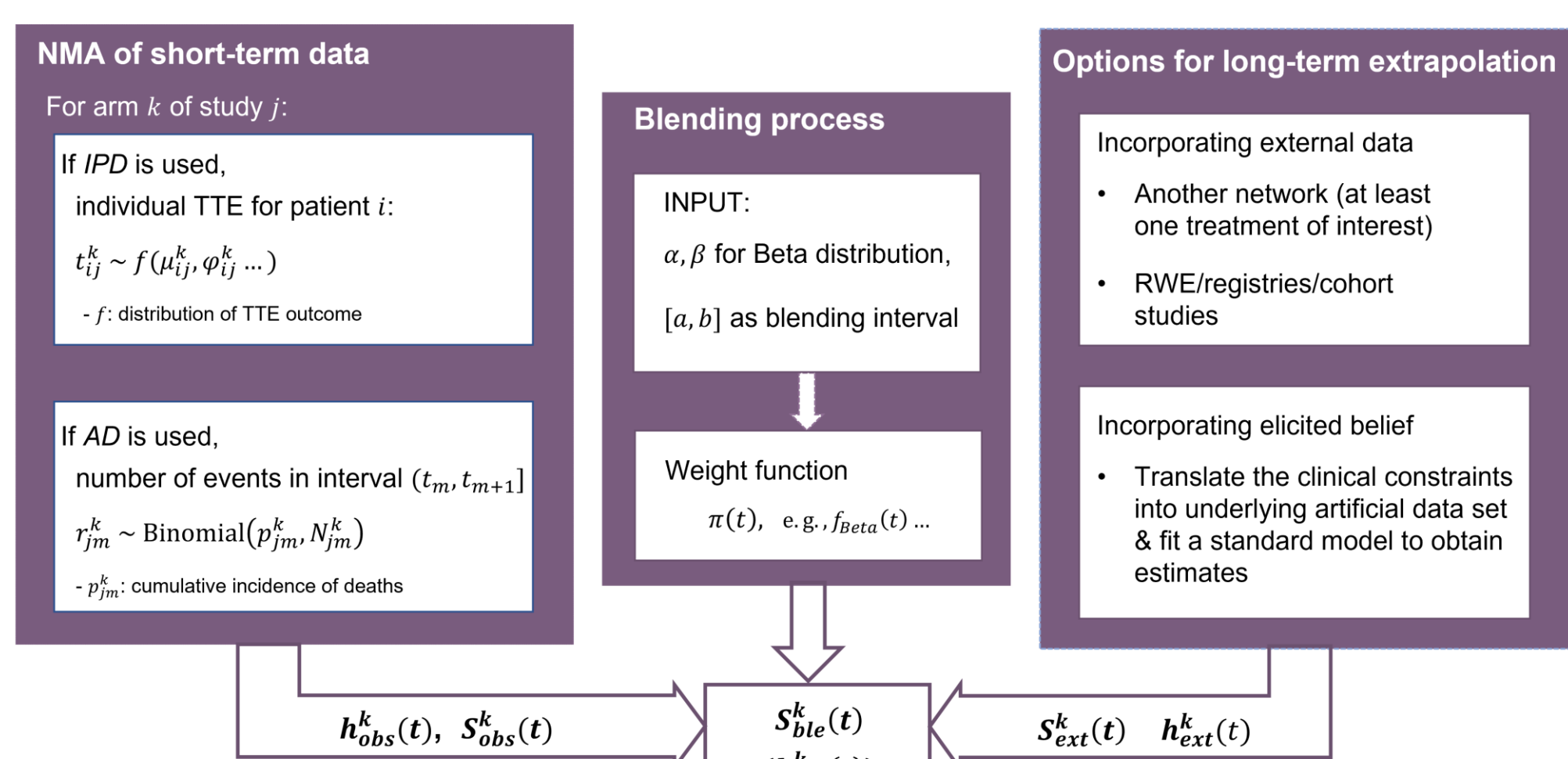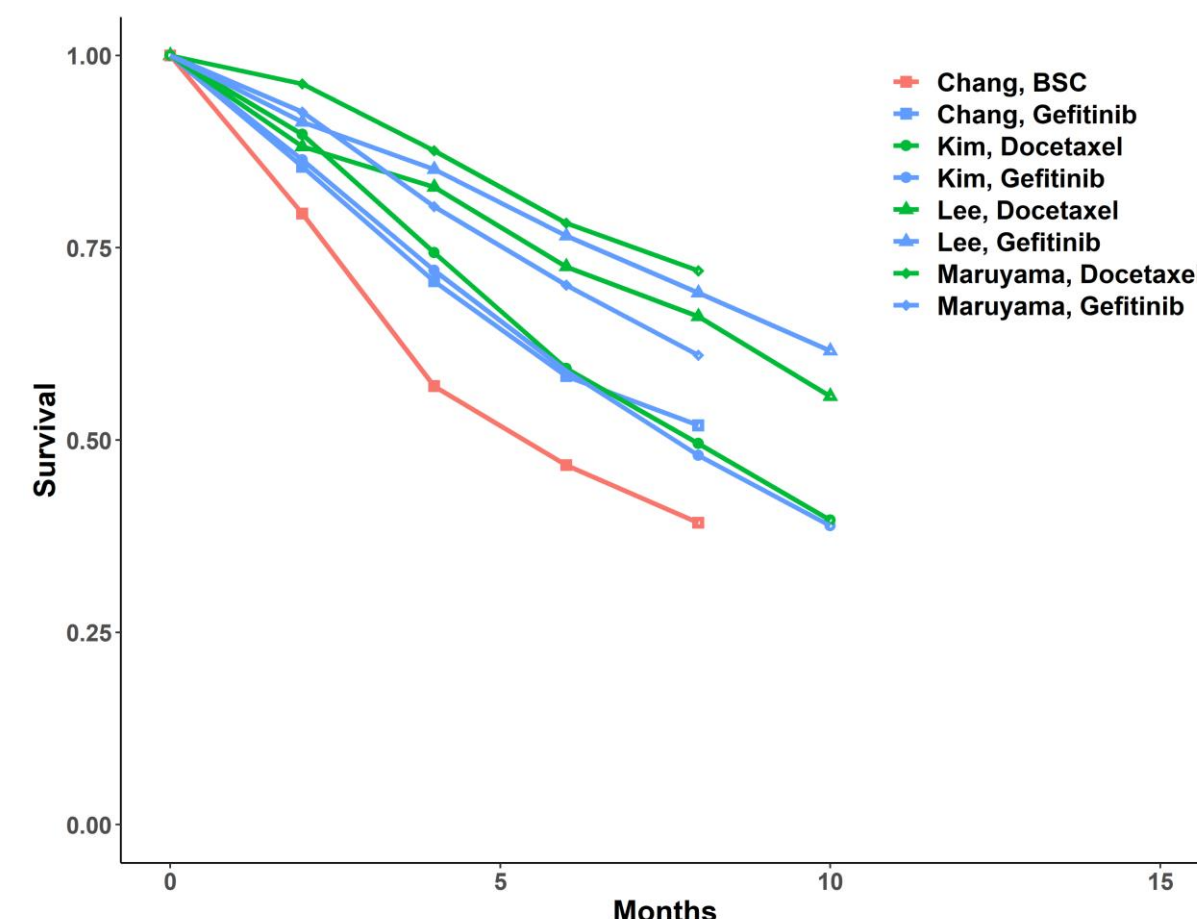


Figure 3: Framework of NMA modelling structure

## ILLUSTRATIVE EXAMPLE

To test blended method, four NSCLC trials were used comparing gefitinib with best-supportive care (BSC) (1 study) and gefitinib with docetaxel (3 studies).



### Incorporating external information

- *External data:* Other trials were identified (BSC: 1 study; docetaxel: 2 studies) with relatively longer follow-up until 20 months.

- *Expert judgement:* clinical opinion is assumed for arm gefitinib, that 10% of the cohort would be alive beyond 20 months.
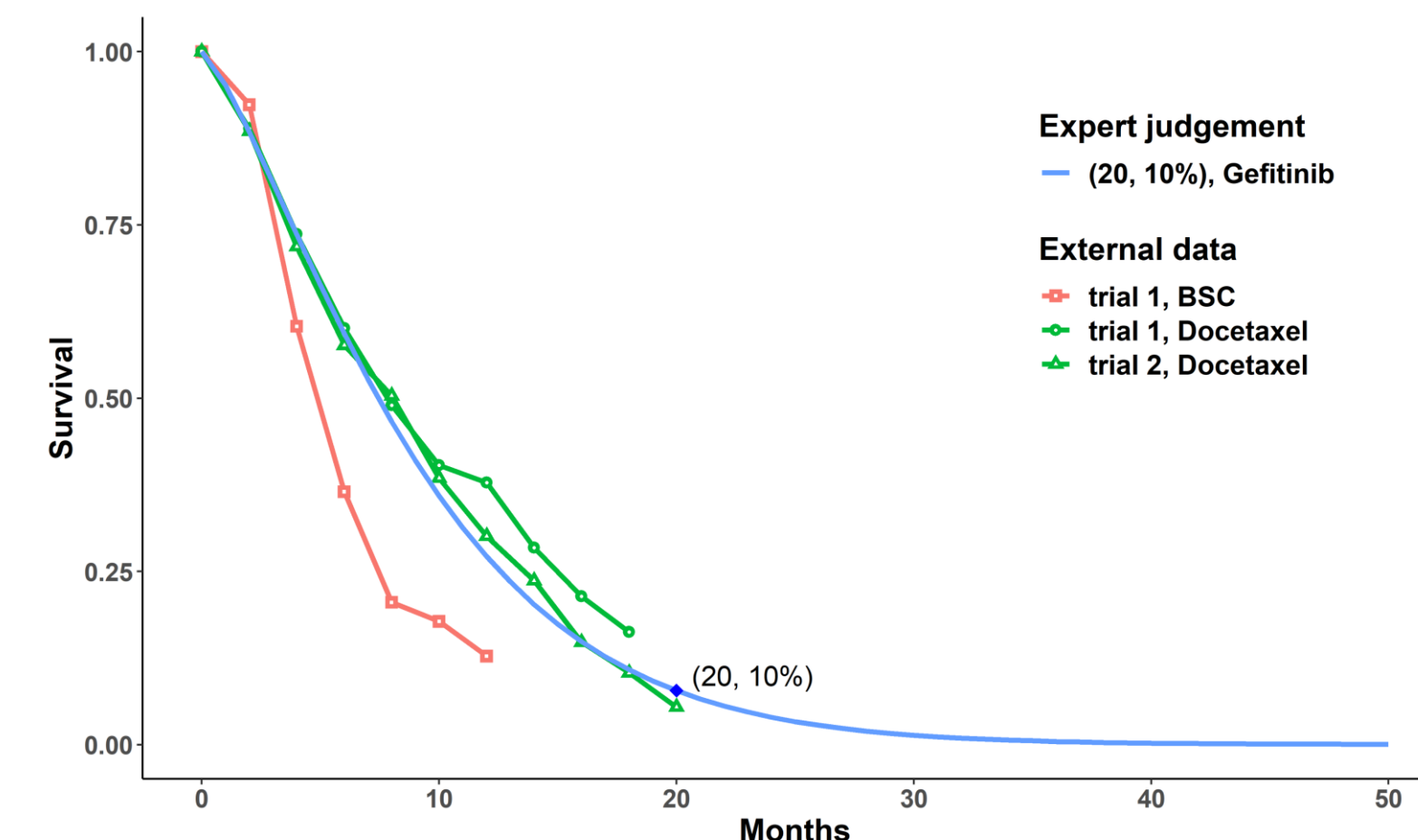


## RESULTS

- **Observed period:** ***Best*** **fit to the network**

  There is no restriction to the models used in the NMA, but in this example, the Weibull distribution provides the best fit according to goodness-of-fit criteria.
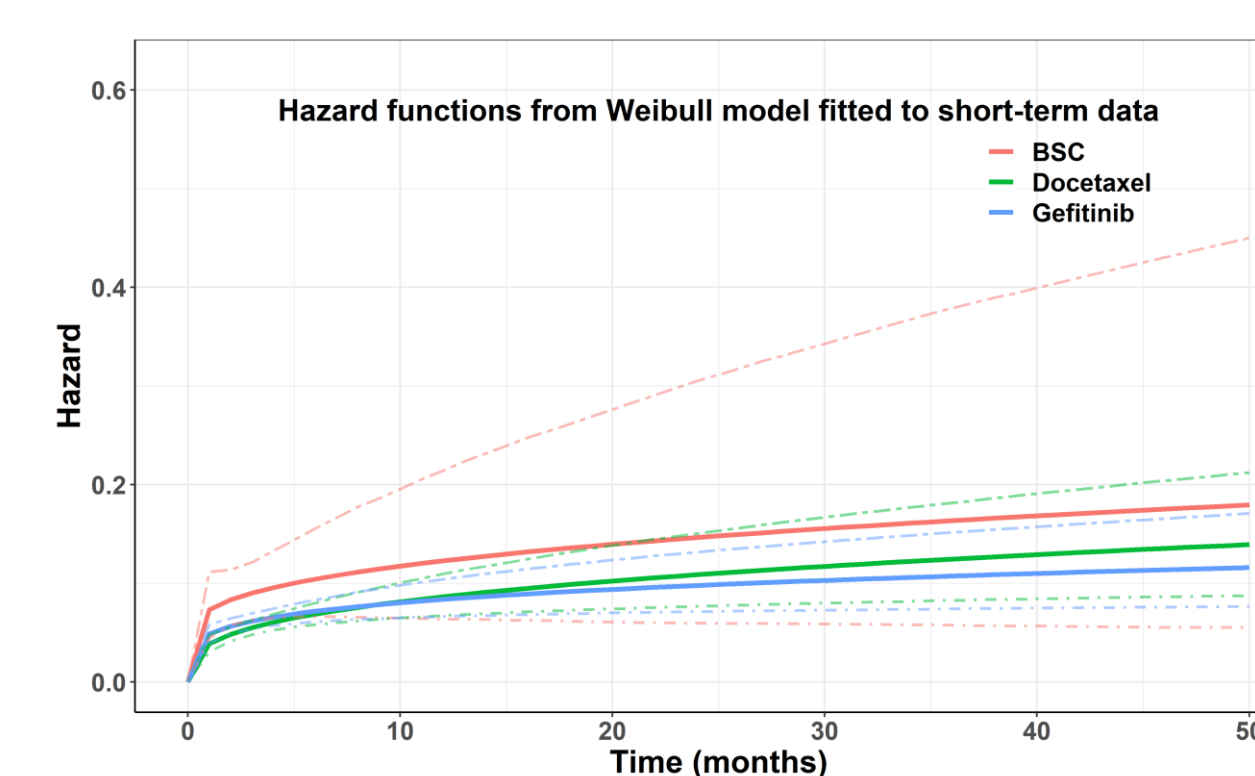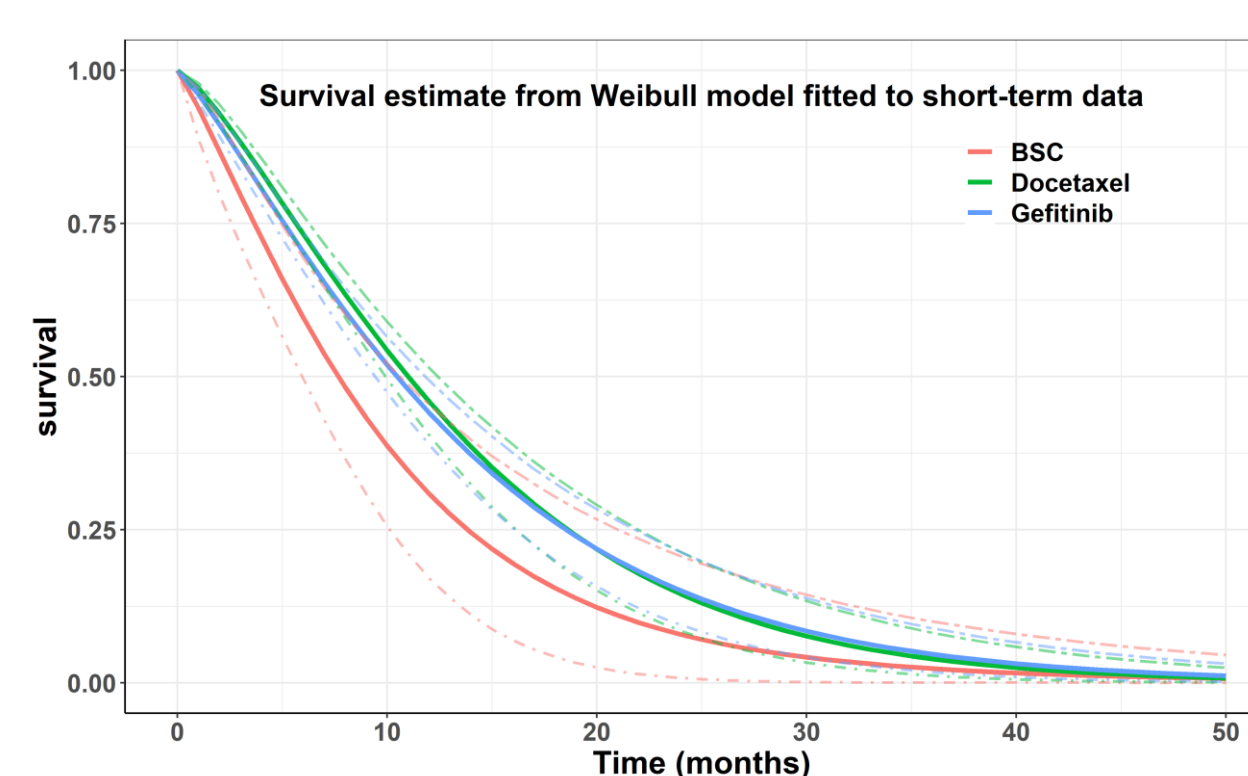


- **Extrapolated period: using external evidence**

  For the arm docetaxel and BSC, a piecewise constant hazard model is fitted to the external reconstructed patient-level data. In terms of gefitinib, we translate the clinical constraints into appropriate estimate of survival.
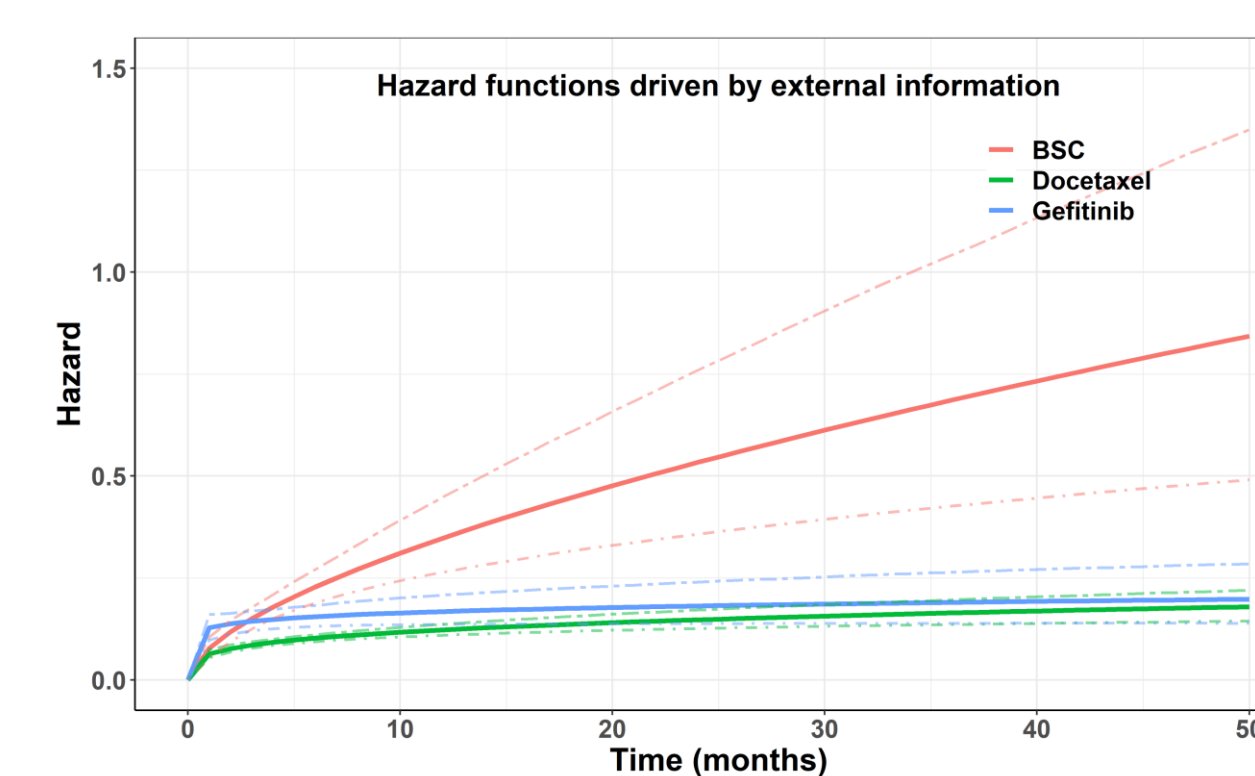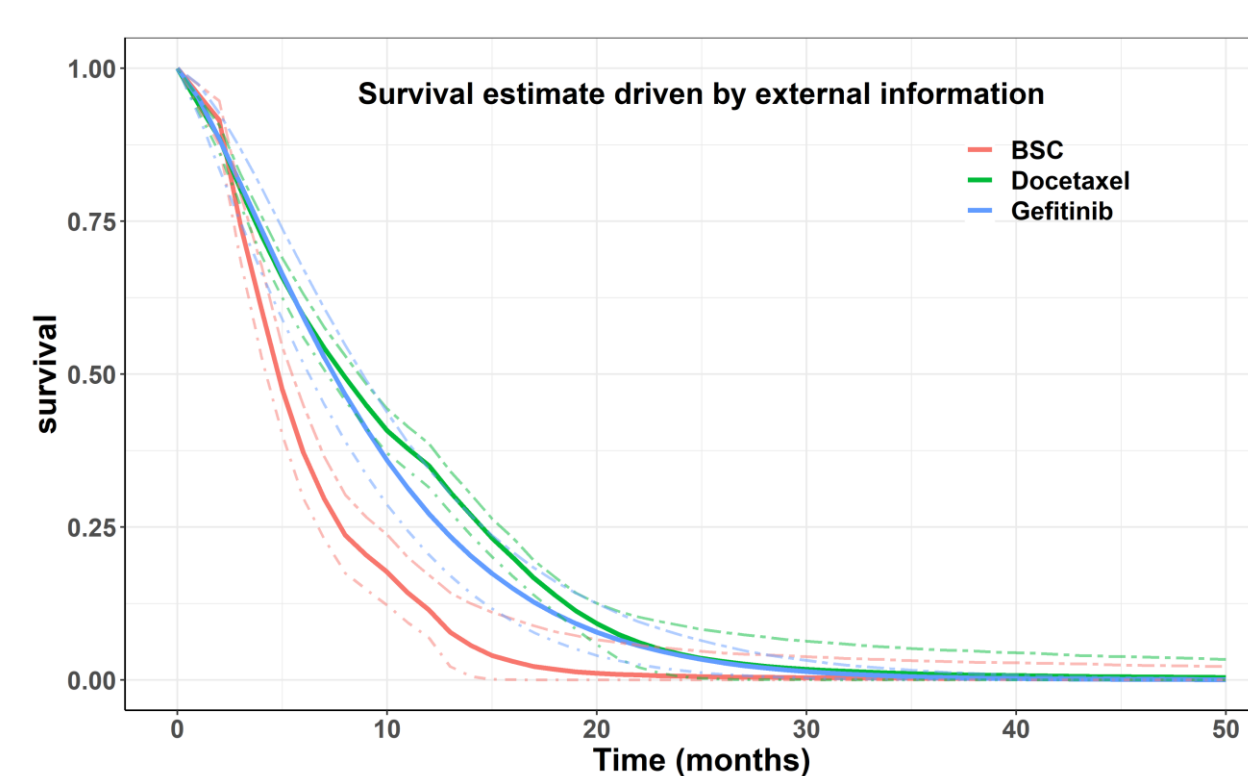


- **Blended curves**

  The short-term and long-term estimates are blended over time interval $(a=8, b=30)$ based on the weight function with $\alpha = \beta = 3$.
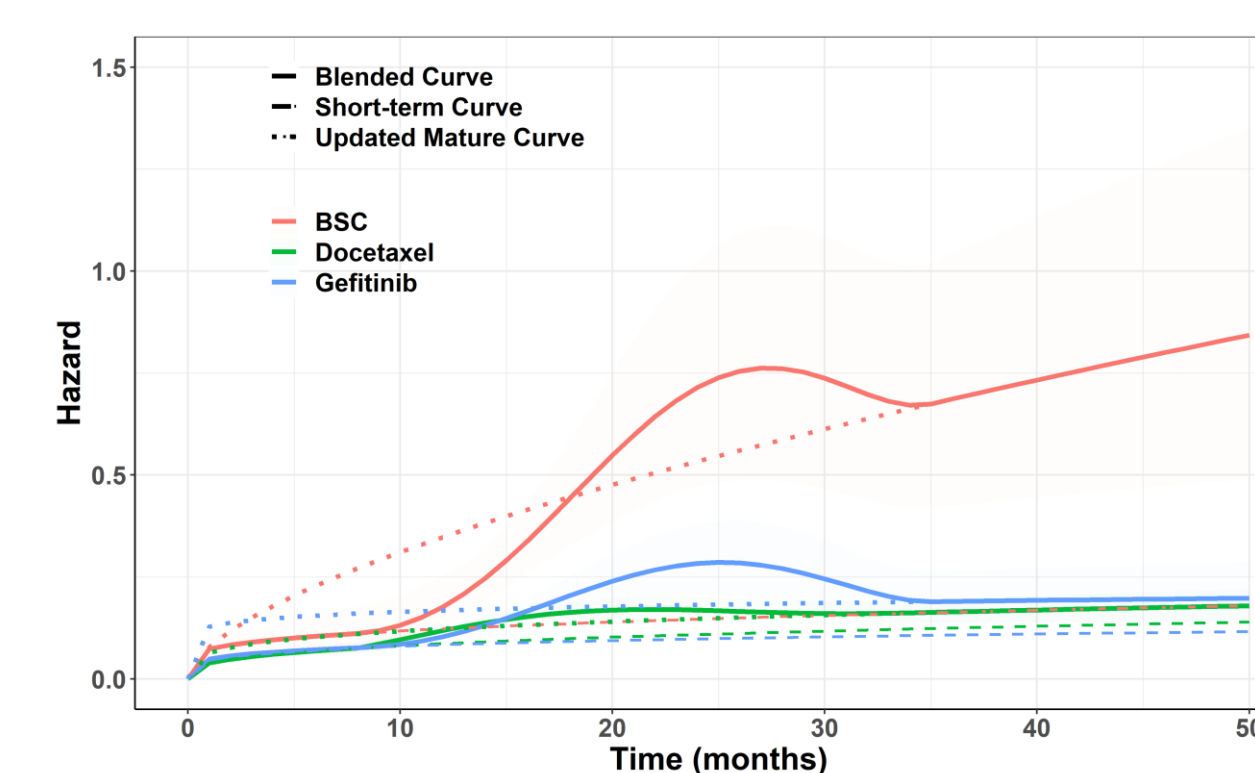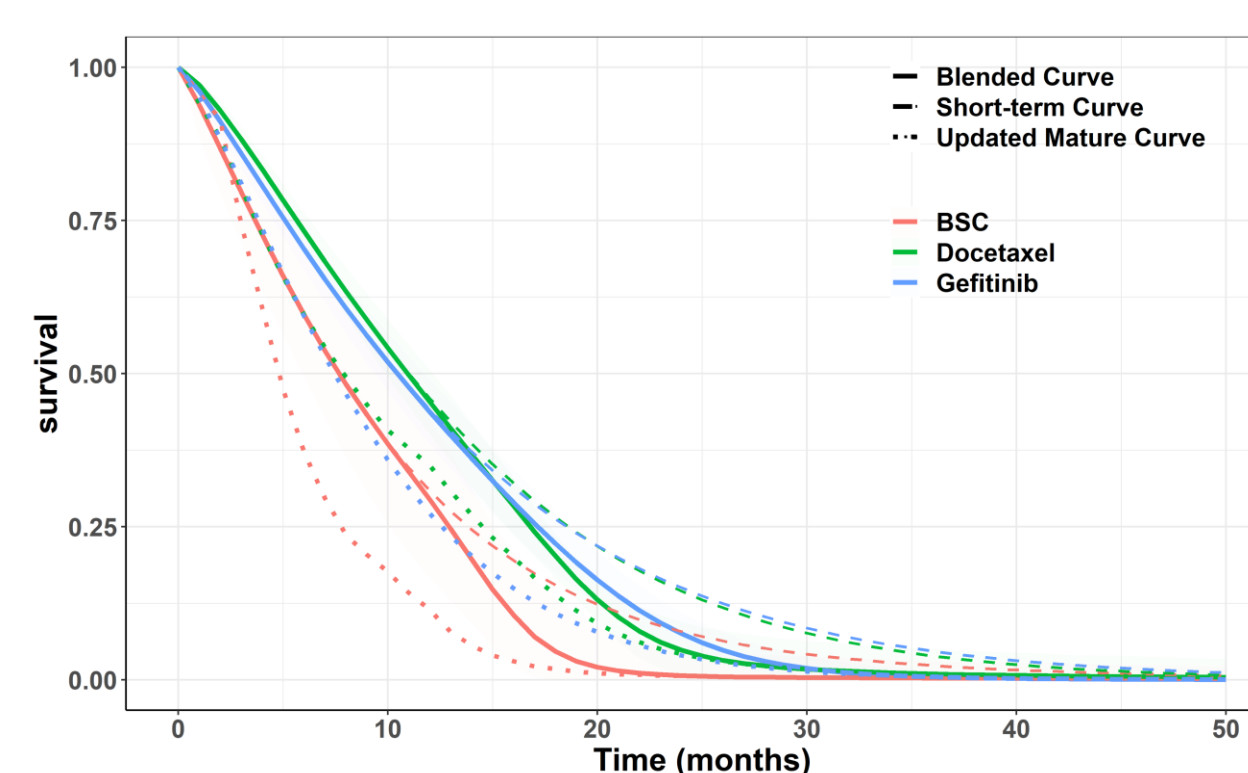


## CONCLUSION

The blended NMA method provides flexibility and allows the extrapolation taking advantage of external knowledge that manufacturers might have in form of hard data or elicited belief. A range of assumptions for treatment effect can be carefully considered.

## REFERENCES

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https://github.com/StatisticsHealthEconomics/blendR

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