Survival Estimates Using Hazard Ratios Derived From Network Meta-Analyses: Is More Guidance Needed?

Kloska T,[1] Ip S,[1] van Hest N[1]

[1]Costello Medical, London, UK

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OBJECTIVES

- Network meta-analyses (NMAs) are often used to derive hazard ratios (HRs) of relative treatment effect when modelling survival estimates in cost-effectiveness analyses (CEAs).
- A 'reference' treatment, for which Kaplan-Meier (KM) data are available, is selected and survival estimates for remaining treatments are generated by applying NMA-derived HRs.
- Limited guidance exists for choosing this 'reference' treatment when using NMA-derived HRs in CEAs. Therefore, this research investigated the impact of the choice of reference treatment on survival estimates.

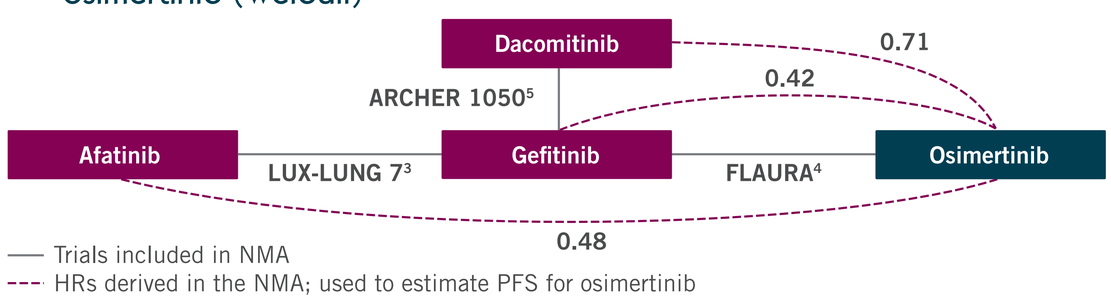
BACKGROUND

- Evaluating the cost-effectiveness of a new intervention requires assessment of comparative effectiveness between relevant comparator treatments.
- One method for deriving estimates of relative treatment effect between relevant comparators is an NMA, in which the relative treatment effect can take the form of an HR.
- Using one treatment's extrapolated survival curve as the 'reference', the NMA-derived HRs can be applied to generate relative survival curves for all other comparators.
- While guidance on conducting NMAs is available from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) technical support document (TSD) 2 – including specific guidance for choosing the reference treatment within the NMA itself – there is limited guidance on which 'reference' treatment should be selected to calculate relative survival estimates for comparators when extrapolating trial data for use in CEAs.[1]

METHODS

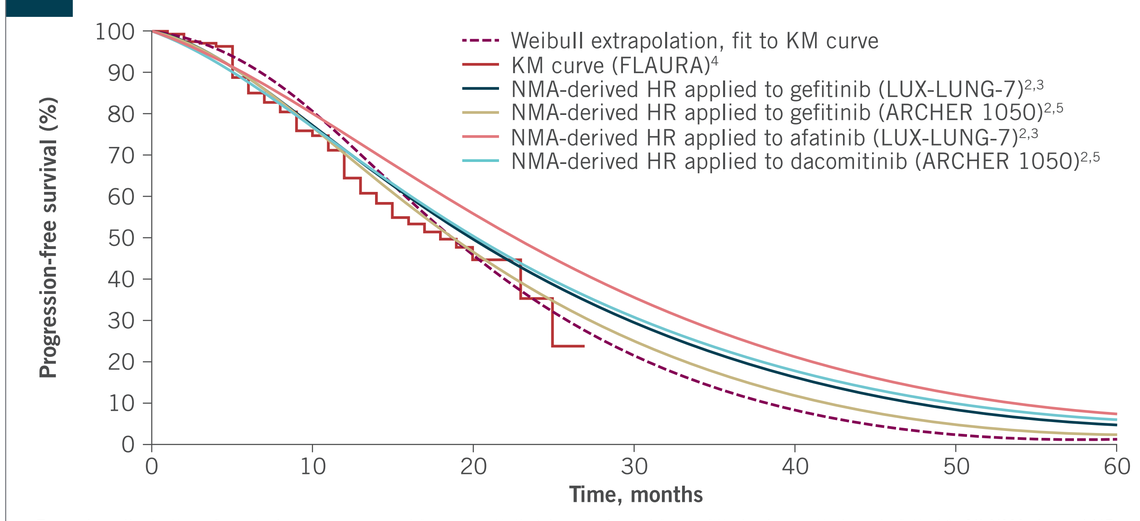
- A published NMA containing several treatments for non-small cell lung cancer (afatinib, dacomitinib, gefitinib, osimertinib), each with published KM curves, was used as a case study (an illustration of the NMA network is given in **Figure 1**, with HRs for osimertinib relative to each other treatment highlighted as an example).[2–5]
- Based on the maturity of the KM data, the progression-free survival (PFS) data were chosen over the overall survival data for this analysis.
- KM curves for each treatment were extracted from the original publications using the metaDigitise package in R;[6] the KM curves were then converted into pseudo individual patient data (IPD) using the Guyot algorithm.[7]
- Survival models were fitted to the pseudo IPD, using the survival functions recommended by the DSU in TSD 14 for which the proportional hazard assumption holds – exponential, Weibull, and Gompertz.[8]
- The HRs derived in the NMA were applied to each extrapolated reference treatment to derive a complete set of HR-derived and extrapolated PFS curves for each treatment (all curves for osimertinib are illustrated in **Figure 2**, as an example).
- For each treatment, the mean PFS was calculated for the directly extrapolated KM data and for each survival profile generated via application of the NMA-derived HRs to each reference treatment. The mean PFS was calculated using the complete PFS curve until PFS reached 0.
- The range of HR-derived mean PFS estimates for each treatment was compared to the mean PFS obtained when directly extrapolating the KM data. To contextualise the range, it was also calculated as a proportion of its extrapolated mean PFS, with a lower percentage representing a smaller relative range.

1 Partial presentation of network; including the NMA-derived HRs for osimertinib (Weibull)



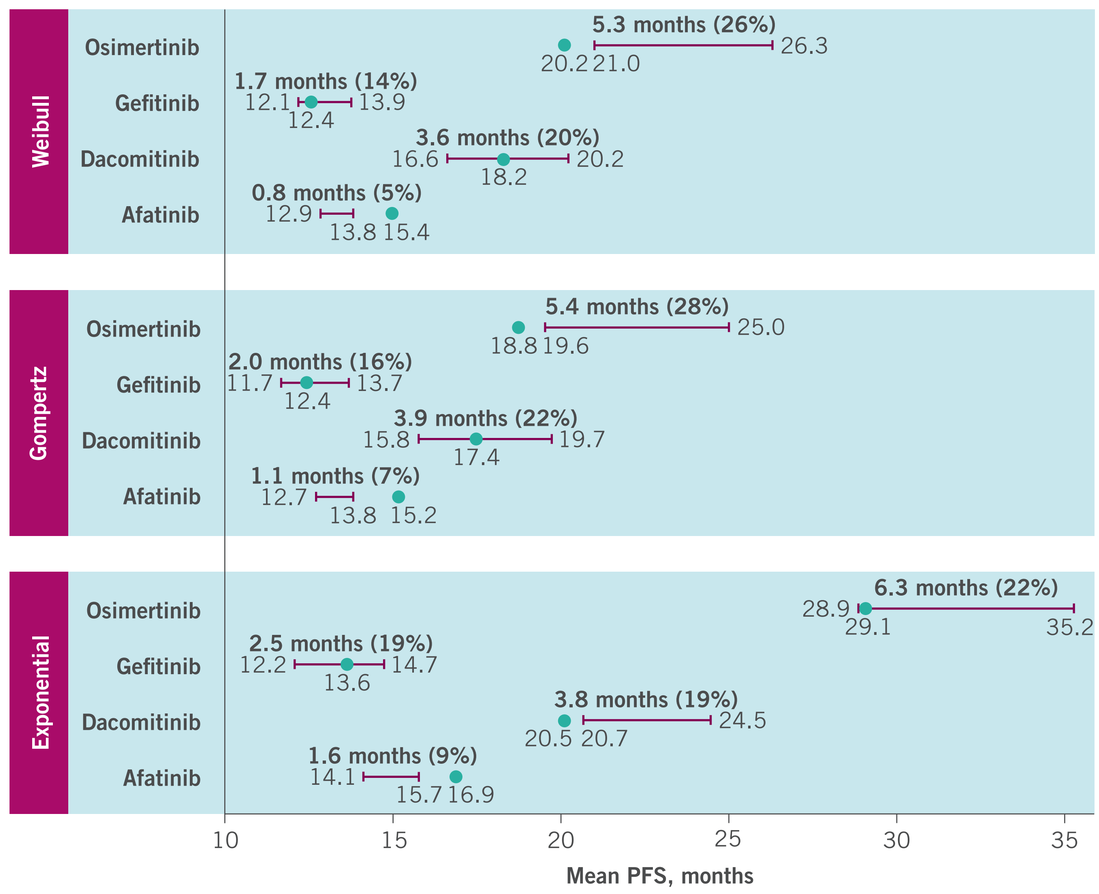
This figure presents a partial representation of the complete published network[2] focussing on tyrosine kinase inhibitors (TKIs) as used in this study. As an example, the osimertinib PFS HRs derived from the complete NMA are presented (osimertinib versus treatment).
Abbreviations: HR: hazard ratio; NMA: network-meta analysis; PFS: progression-free survival.

2 Osimertinib PFS curves (KM, extrapolated and HR-derived)



Exemplary illustration of survival curves compared for osimertinib (also conducted for: gefitinib, dacomitinib and afatinib). All NMA-derived HRs were applied to each respective specified reference treatment's Weibull extrapolation, and the analysis repeated for exponential and Gompertz extrapolations. **Abbreviations:** HR: hazard ratio; KM: Kaplan-Meier; NMA: network-meta analysis; PFS: progression-free survival.

3 Extrapolated and HR-derived mean PFS, by reference curve and treatment



The range (in months) between the minimum and maximum estimated PFS from NMA-derived HRs is presented above each bar. The percentage reflects this range as a proportion of the treatment's extrapolated mean PFS, with a lower percentage representing a smaller relative range. Reported ranges may not exactly match with reported upper and lower HR-derived mean PFS results due to rounding.
Abbreviations: HR: hazard ratio; KM: Kaplan-Meier; NMA: network-meta analysis; PFS: progression-free survival.

RESULTS

- Based on the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), Weibull was the best fitting extrapolation for all treatments.
- Using the Weibull extrapolation for each reference treatment, the mean PFS estimates derived by the NMA-derived HRs varied between 5% (afatinib) and 26% (osimertinib) of the directly extrapolated mean PFS (**Figure 3**).
- To demonstrate that the observed results were not an artefact of the choice of extrapolation (Weibull), survival estimates were also calculated using the Gompertz and exponential extrapolations. The mean PFS estimates based on the other extrapolations demonstrated similar trends:
  - Using Gompertz extrapolations for each reference treatment, the mean PFS estimates derived by applying the NMA-derived HRs varied between 7% (afatinib) and 28% (osimertinib) (**Figure 3**)
  - Using exponential extrapolations for each reference treatment, the mean PFS estimates derived by applying the NMA-derived HRs varied between 9% (afatinib) and 22% (osimertinib) (**Figure 3**)
- Notably, half (n=6) the extrapolated mean PFS estimates fell outside the range of the HR-derived mean PFS estimates (**Figure 3:** all afatinib extrapolations, the osimertinib Weibull and Gompertz extrapolations, and the dacomitinib exponential extrapolation). This quantitatively highlights the considerable sensitivity of the mean PFS to the choice of reference treatment.

CONCLUSIONS

- This research quantitatively demonstrates that survival estimates generated using HRs are sensitive to the choice of reference treatment included in an NMA, and their resulting PFS estimates can differ considerably to the estimates obtained from direct extrapolation.
- This research investigated the choice of reference treatment on absolute survival outcomes which could have unforeseen consequences for health technology assessments; for example, results of CEAs or NICE's new severity modifier calculation.
- Typical CEA results are driven by the incremental differences between treatment outcomes. Therefore, as further research, the impact of using different reference treatments on incremental survival outcomes should be investigated. This could further demonstrate a need for clear guidance on selecting the reference treatment when using NMA-derived HRs to derive survival estimates in CEAs.

References

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