Survival Estimates Using Hazard Ratios Derived from Network Meta-Analyses: Exploratory Recommendations for Reference Curves

Kloska T,[1] Fox HL,[2] Kaiser E,[2] van Hest N[1]
[1]Costello Medical, London, UK; [2]Costello Medical, Boston, MA, USA

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OBJECTIVE

- To investigate how choice of reference treatment when using (NMA)-derived hazard ratios to obtain survival estimates affects the appropriateness of survival estimates for decision-making.

BACKGROUND

- Survival estimates used in cost-effectiveness analyses are often generated by applying network meta-analysis (NMA)-derived hazard ratios (HRs) to extrapolated trial data for a chosen 'reference' treatment.
- Limited guidance is available for selecting this reference treatment.[1]
- Previous research has demonstrated that survival estimates generated by applying a HR to a chosen 'reference' treatment are sensitive to the choice of reference, with variations of up to 28% of mean progression-free survival (PFS).[2]
- Resulting HR-derived survival outcomes can also differ considerably from the estimates obtained from direct extrapolation.[2]

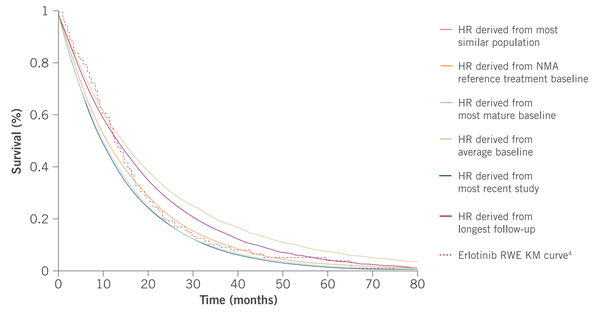
METHODS

- A published NMA for non-small cell lung cancer served as a case study to estimate PFS for erlotinib.[3]
- Survival functions that meet the proportional hazards assumption (exponential, Weibull, Gompertz) were fitted to PFS data from each relevant trial to derive reference curves.
- The NMA-derived HRs were applied to each reference curve option to estimate PFS for erlotinib (**Figure 1**). HR-derived PFS estimates for erlotinib were validated against a real-world study, from the FLATIRON database.[4]
- Different reference treatments were chosen from trials in the NMA based on the following: most aligned population (chosen based on most similar patient characteristics to the RWE [Real world evidence] study), longest follow-up, data maturity (chosen from the study with the most mature data with the largest absolute number of events observed), NMA reference treatment, and most recent data (**Table 1**).

RESULTS

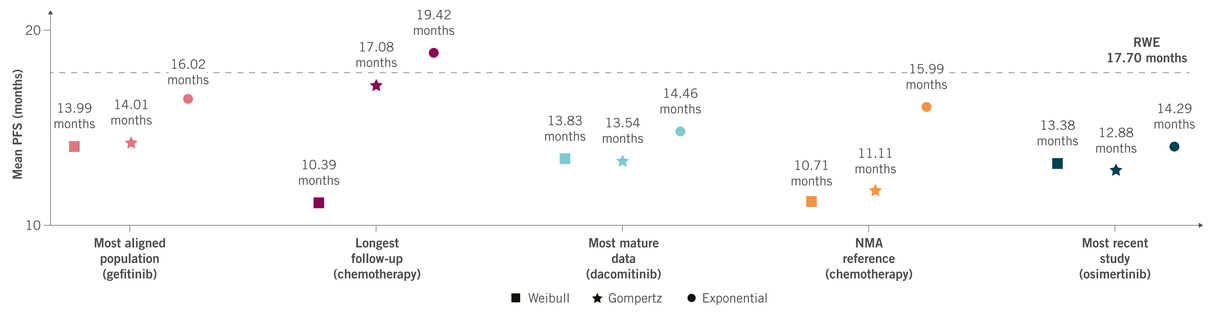
- Across the survival functions, the reference treatment with the most aligned population (gefitinib) produced mean PFS estimates closest to RWE (1.68–3.71 month [3.03 month average] deviation from the RWE) (**Figure 2**).
- The NMA reference treatment (chemotherapy) had the poorest estimate (1.71–6.99 month [5.10 month average] deviation from the RWE), with a maximum deviation of 6.99 months (39.5%) when using the Weibull baseline curve to estimate erlotinib survival.
- Data maturity (dacomitinib) estimated the most consistent results across survival functions (range of 0.93 months [13.54–14.46 months]), however, was less consistent with RWE (3.24–4.16 month [3.76 month average] deviation from the RWE).
- Survival estimates using the most recent study (osimertinib) and the trial with the longest follow-up (chemotherapy) had 3.41–4.82 month (4.19 month average) and 0.62–7.31 month (3.22 month average) deviations from the RWE, respectively.

1 Erlotinib survival curves



HR: hazard ratio; **NMA:** network meta-analysis.

2 HR-derived mean PFS outcomes for erlotinib broken down by choice of reference treatment



HR: hazard ratio; **NMA:** network meta-analysis; **PFS:** progression-free survival; **RWE:** real-world evidence.

1 Comparison of available trial data from the NMA to inform reference treatment options

Study (trial)	Treatment	Sample size EGFR patients	Median PFS in months	Length of follow-up in months	Survival at end of follow-up (non-censored events)	Reference treatment selection basis
Fukuoka 2011 (IPASS)[5]	Gefintinib	132	9.5	21	0% (72.9%)	
	Chemotherapy (carboplatin/paclitaxel)	129	6.3	21	0% (84.0%)	
Han 2012 (First-SIGNAL)[6]	Gefintinib	26	8.0	29	0% (92.3%)	
	Chemotherapy (gemcitabine and cisplatin)	16	6.3	49	0% (93.8%)	Longest follow-up
Maemondo 2010 (NEJ002)[7]	Gefintinib	114	10.8	27	5% (NR)	
	Chemotherapy (carboplatin/paclitaxel)	110	5.4	22	NR	NMA reference treatment
Park 2016 (Lux-Lung 7)[8]	Afatinib	160	1.1	37	10% (NR)	
	Gefintinib	159	10.9	40	5% (NR)	
Sequist 2013 (Lux-Lung 3)[9]	Afatinib	230	11.1	25	NR	Most aligned population
	Chemotherapy (cisplatin plus pemetrexed)	115	6.9	22	10% (NR)	
Soria 2018 (FLAURA)[10]	Osimertinib	279	18.9	25	25% (NR)	Most recent study
	1st Gen TKIs (gefitinib/erlotinib)	277	10.2	26	10% (NR)	
Wu 2017 (ARCHER 1050)[11]	Dacomitinib	227	14.7	35	0% (59.9%)	Most mature data
	Gefintinib	225	9.2	34	10% (79.6%)	

For ease of comparison, the survival curves and outcomes in Figure 1 and Figure 2 have been color coordinated to the relevant reference treatment options in this table).

EGFR: epidermal growth factor receptor; **GEN:** generation **NMA:** network meta-analysis; **NR:** not reported; **PFS:** progression-free survival; **TKI:** tyrosine kinase inhibitor.

CONCLUSIONS

- There are several factors to consider when choosing the most appropriate reference treatment for deriving survival estimates using NMA-derived HRs.
- Similarity in patient population is expected to be an important factor. Importantly, the reference treatment of an NMA might not be the most appropriate reference treatment for extrapolation, and data maturity can minimize uncertainty in extrapolations but not necessarily have external validity. However, this research considered only one NMA and RWE validation as a case study, limiting generalizability of findings.
- Furthermore, conclusions might be endpoint specific. For example, data recency might be a more important factor for overall survival (OS) compared to PFS, as it becomes relevant to consider which treatment patients receive after progression, and whether that aligns with current standard of care.

References

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