Assessing The Impact Of Survival Data Maturity In Cost-effectiveness Estimates In Advanced Non-small Cell Lung Cancer

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Objectives

A requirement in health technology assessment (HTA) concerns extrapolation of outcomes beyond randomized clinical trial (RCT) duration which is a source of uncertainty in cost-effectiveness results. We investigate the **impact of data maturity on the estimation of survival and cost-effectiveness outcomes** by examining RCT data from patients with non-small cell lung cancer (NSCLC) undergoing second or subsequent lines of treatment (2L+).

Methods

A targeted review was conducted in IQVIA's HTA accelerator® to identify two-arm, phase 3 clinical trials in 2L+ NSCLC that reported results for at least two data cuts.

Overall survival (OS) and progression-free survival (PFS) data were reconstructed using published Kaplan Meier (KM) curves with Guyot's algorithm[1].

The data from two data cuts of each arm were fitted in standard parametric and flexible parametric models (i.e. *Exponential, Weibull, Log-normal, Log-logistic, Gompertz, Generalized Gamma and Normal and hazard splines with one knot)* in R using the flexsurv package[2].

Model selection included statistical fit in terms of Akaike Information criterion (AIC), clinical plausibility (mean OS not higher than mean PFS) and comparability of extrapolations with long-term real-world data.

The OS and PFS data were used in a **partitioned survival model.**

The cost effectiveness model was further populated with published cost[3,4,5] and utility[6] data. Drug acquisition, administration, treatment initiation, disease management and terminal care costs, but also treatment stopping rules were implemented in the model.

The comparison of data cuts was conducted on **two distinct levels**. Initially, we examined how data maturity affected **long-term extrapolations** and which survival models were more appropriate for model selection. We then assessed how the **cost-effectiveness estimates** were influenced by differences in survival outcomes between data cuts, and different extrapolation models.

Same model was chosen for both treatment arms and data cuts for consistency. The cost-effectiveness analysis was conducted under a base case for the best survival model according to all model selection criteria, as stated above, and a scenario analysis for the second-best survival model.

Results

Four RCTs were identified, CheckMate 017&057 (nivolumab vs docetaxel), KEYNOTE 010 (pembrolizumab vs docetaxel), LUX – lung - 8 (afatinib vs erlotinib) and OAK (atezolizumab vs docetaxel).

Mean OS and PFS, based on all statistical models fitted, **were mostly increased** using data from the second data cut but there were exceptions, depending on the model selection, suggesting the absence of a definitive trend *(Figure 1*). The between data cut difference in extrapolation results was **higher in immunotherapies** compared to chemotherapies and targeted therapies based on the mean OS difference across all statistical models fitted (*Figure 2*).

Based on the model selection criteria **normal spline had the best performance** in the long-term data and was selected in approximately half of the analyses (*Figure 3*)

Across all RCTs, **the ICER increased in the second data** cut under different survival models (*Table 1*). Even though in most scenarios survival outcomes were higher in the second data cut (10 out of 16 or OS and 13 out of 16 for PFS), the incremental estimates were decreased in three out of four trials resulting in an increased ICER.

Figure 1. Percentage change in mean OS and PFS between data cuts

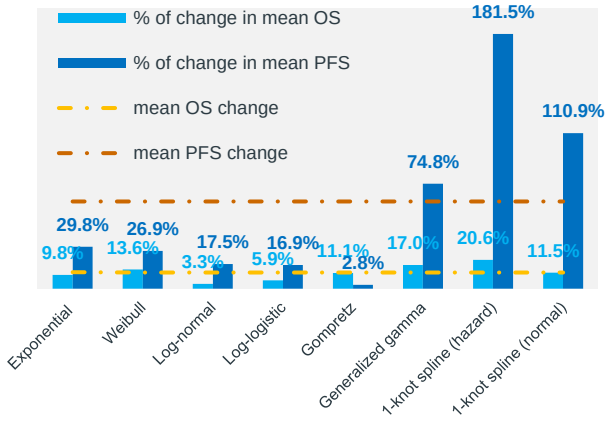


Figure 2. Mean OS difference in 5-years and 10 years extrapolations

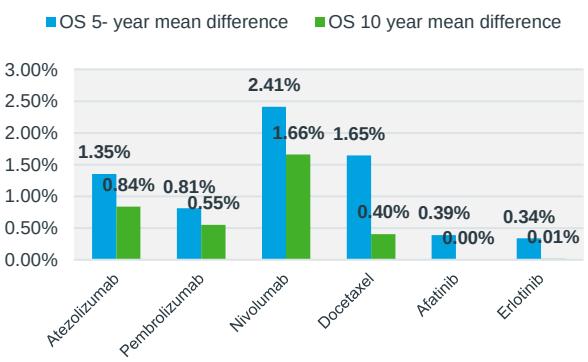
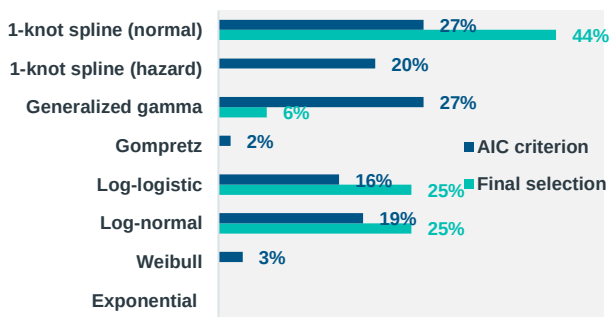


Figure 3. Model selection percentage in terms of AIC and in terms of all criteria combined for OS and PFS



These findings warrant **further investigation** to uncover an underlying relationship between data maturity and ICER, as the increase was not consistent between scenarios. The impact of treatment switching, adverse events, time to treatment discontinuation data and indirect comparisons with relevant real-world comparators were not considered in the cost-effectiveness results.

Table 1. Difference in cost effectiveness estimates between the data cuts

Trial	Analysis	Model fitted for OS	Model fitted for PFS	Difference in incr. LYs	Difference in incr. QALYs	Difference in incr. costs (£)	Difference in ICER
CheckMate 017&057	Base case	1-knot spline (normal)	Log-logistic	+0.26 ↑	+ 0.18 ↑	+ 17,333 ↑	+ 11,423 ↑
	Scenario	Log-normal	Log-logistic	+0.17 ↑	+ 0.13 ↑	+ 17,430 ↑	+ 16, 148 ↑
KEYNOTE 010	Base case	1-knot spline (normal)	Log-normal	-0.15 ↓	- 0.09 ↓	+ 2,412 ↑	+12,2445 ↑
	Scenario	Log-normal	Log-normal	-0.01 ↓	0.00	+ 2,730 ↑	+4,055 ↑
LUX-lung 8	Base case	Log logistic	Gen. gamma	-0.06 ↓	- 0.04 ↓	- 2,126 ↓	+ 25,910 ↑
	Scenario	1-knot spline (normal)	1-knot spline (normal)	-0,01 ↓	- 0.01 ↓	+ 473 ↑	+14,720 ↑
OAK	Base case	Log logistic	1-knot spline (normal)	-0.18 ↓	- 0.11 ↓	- 1,413 ↓	+ 12,673 ↑
	Scenario	1-knot spline (normal)	1-knot spline (normal)	-0.22 ↓	- 0.13 ↓	- 1,338 ↓	+ 16,208 ↑

Conclusion

More mature data resulted in increased ICERs in the identified RCTs for 2L+ NSCLC. The generalizability of these findings warrants further investigation due to the small sample of studies assessed.

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