HOW LONG IS LONG-ENOUGH? AN INVESTIGATION INTO THE RELATIONSHIP BETWEEN TRIAL MATURITY AND UNCERTAINTY IN COST-EFFECTIVENESS, THE CASE OF THE FIRST COMMERCIALLY AVAILABLE CAR T-CELL THERAPY: AXICABTAGENE CILOLEUCEL

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Introduction

Chimeric antigen receptor (CAR) T-cell therapies have been studied in multiple haematological malignancies, with survival curves exhibiting what has been commonly described as a 'cure fraction' – i.e., a proportion of patients that achieve a 'statistical cure'. To enable patient access to these therapies in the UK and other European markets, it is necessary to undertake a health technology assessment (HTA) to ascertain the clinical and cost-effectiveness of the CAR T-cell therapy versus the established standard of care.

Recent trends indicate that HTA submissions are being made on earlier data, necessitating a trade-off between data maturity, plausibility of cost-effectiveness (CE) results, and avoiding unnecessary delays to access. In this study, we explore the value of extended follow-up data from the ZUMA-1 clinical trial[1] (NCT02348216) of axicabtagene ciloleucel (axi-cel) for the treatment of adult patients with refractory aggressive non-Hodgkin lymphoma, and the impact of these additional data on the results of a CE model.

Methods

Data from the ZUMA-1 trial were used to fit standard parametric, spline, and mixture-cure models (MCMs). The statistical analysis software package *R*[2] was used to perform all analyses described below. Models were fitted to 12-, 24-, 36-, 48-, and 60-month datacuts, and were then implemented within a CE model closely resembling the model used in the first European HTA submission of a CAR T-cell therapy (NICE TA559 of axi-cel)[3].

The CE model adopts a partitioned-survival analysis (PartSA) structure commonly used[4] in HTAs of life-extending cancer therapies. We report a range of analyses to quantify the relationship between follow-up and certainty of results, focusing on the range of modelled life-year gains (LYG) versus standard care (i.e., mean increase in life expectancy associated with axi-cel vs SCHOLAR-1).

Standard parametric models
Six 'standard' parametric models were fitted in line with standard practice in HTA: Exponential, generalised gamma, Gompertz, lognormal, log-logistic, and Weibull models. Models were fitted using the *flexsurv*[5] package.

Spline models
Fitted with 1, 2, or 3 internal knots; with three different functional forms: 'hazard', 'odds', and 'normal' (flexible extensions of the Weibull, log-logistic, and lognormal standard parametric models, respectively). Models were fitted using the *flexsurv*[5] package.

Mixture-cure models
Fitted using the same distributions considered in the standard parametric models, but specifically including a 'cure fraction' (π) to capture a differential long-term survival profile for long-term survivors, via the flexsurvcure[6] package.

Results

Findings from the authors earlier research (Vadgama *et al.*, 2022[7]) were aligned with the findings of this analysis – that MCMs were identified to provide the most plausible long-term extrapolations. Consequently, we focus our results on the MCM models, which are presented in Figure 1. When fitted to the 12-month datacut, a broad range of LYG was estimated across the MCM models with a total range of 7.17 years (i.e, 6.29 minus -0.87 years), which reduced substantially for the 24-month datacut (range: 0.70). The LYG range was similar for all later datacuts (36-month: 0.45, 48-month: 0.40, 60-month: 0.32 years).

The difference in the Incremental Cost-Effectiveness Ratio (ICER, a commonly used metric of cost-effectiveness) based on models fitted to the 24-, 36-, and 48-month datacuts, versus those using the latest 60-month datacut were compared (Figure 2). These results illustrate that the MCMs produce similar ICERs based on the earlier data to those achieved when fitting to the 60-month datacut, whereas the standard and spline models were capable of yielding ICERs that were more than double the ICERs obtained from the 60-month datacut.

Figure 1: Range of life-years gained (LYG) for models fitted to each datacut from ZUMA-1

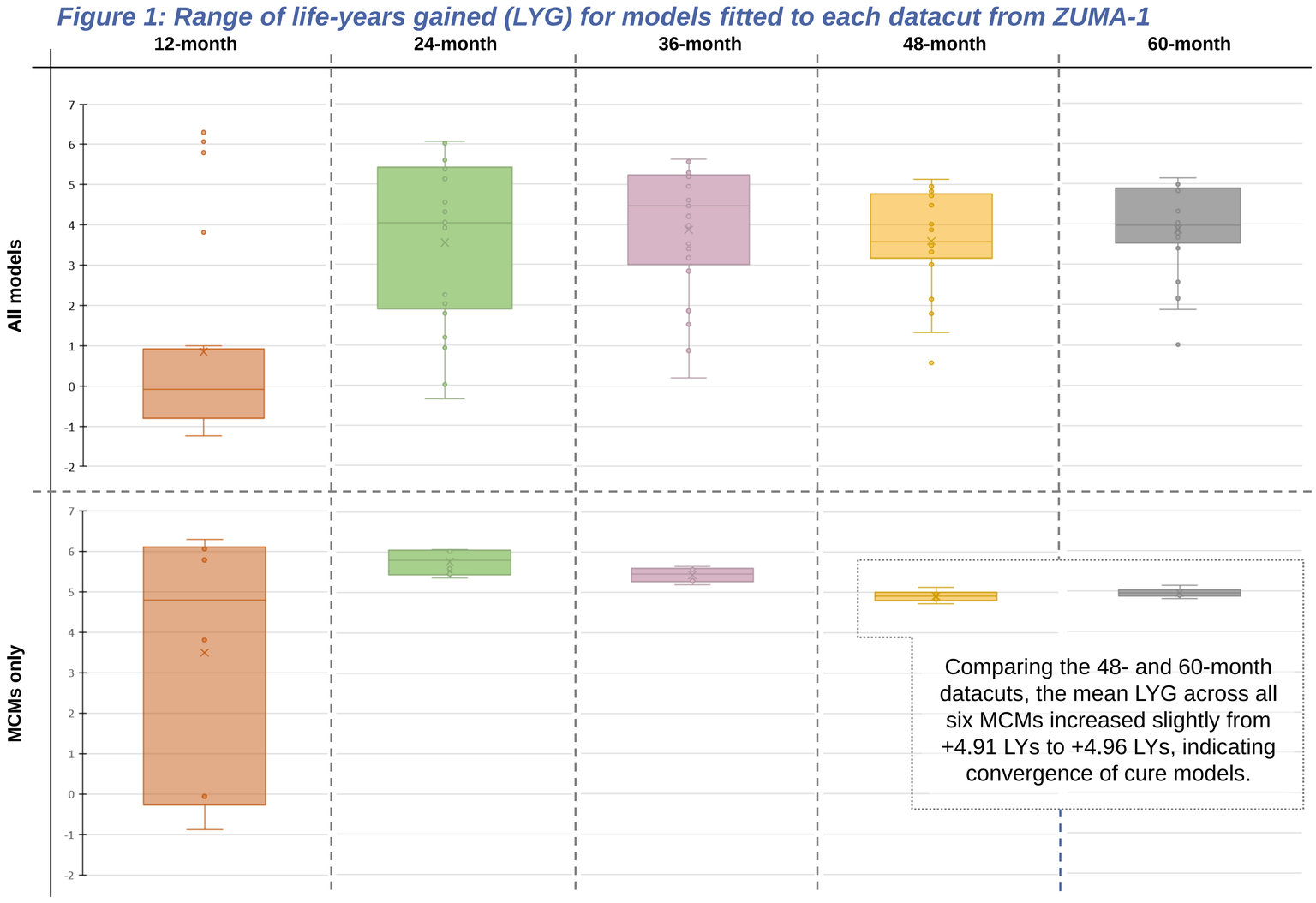
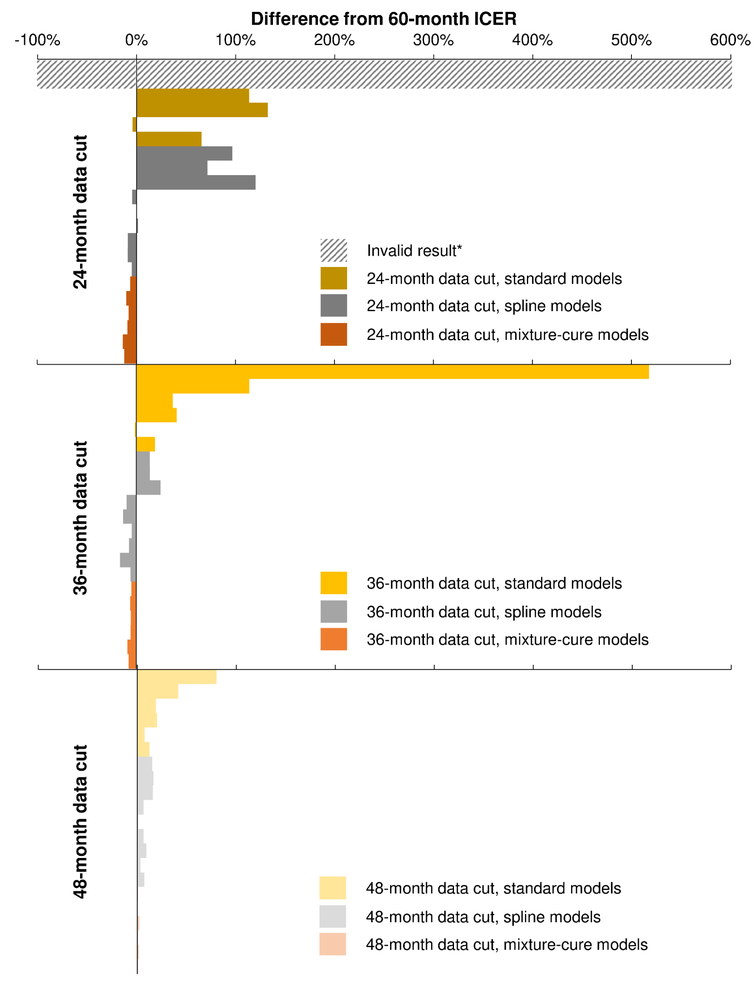


Figure 2: Difference in ICER for models fitted to each datacut from ZUMA-1 (smaller is better)



***Note:** *Result not valid as extrapolation predicting higher survival in BSC versus axi-cel.*

Discussion

Utilising long-term data from the pivotal ZUMA-1 study, we show that results were substantially more certain with ≥24 months follow-up, reducing a key uncertainty for decision making. Beyond 24 months results were consistent for axi-cel, indicating that delaying HTA decisions in anticipation of further data would not substantially reduce uncertainty driven by survival. However, findings should be interpreted with caution when considering other CAR T-cell therapies and/or cancers, given varied results seen in other studies.

References

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