Truncating Time-to-Event Data for Methodological Investigation

Harper S[1], Hansell N[1], Bromilow T[1], Butler K[1]

[1] **York Health Economics Consortium**

INTRODUCTION

Clinical trials often need to run for several years before mature data are available to be published. However, pharmaceutical companies face time-sensitive pressures which mean that immature data (data lacking sufficient duration or sample size) is often used as a key source of evidence in dossier submission. Using this immature data poses substantial challenges for health technology assessment because it requires extrapolation from earlier timepoints, with a limited number of events observed, amounting to increased uncertainty in subsequent analysis. This can lead to trends and conclusions seen in immature data differing to those seen in end-of-trial publications.

Publications that report early Kaplan Meier (KM) from a clinical trial are useful for understanding how accurate trends seen in immature data are to that of end-of-trial publications. However, this immature data may not be reported or available to use. Hence this research aimed to develop of a method to recreate early trial data from published mature KM. This methodology could then be used to adjust trial evidence to reflect an earlier timepoint, allowing for before and after comparisons, so that analysts can observe predictive data trends and characteristics.

METHODS

Published five-year KM from the ZUMA-1 trial[1] for axicabtagene ciloleucel (axi-cel) CAR-T therapy in diffuse large B-cell lymphoma (DLBCL) was digitised and pseudo individual participant data (IPD) was generated using the Guyot algorithm[2]. The full dataset is called FDS1 in this analysis. The aim was to produce IPD that reflected earlier data cuts. These earlier, less mature datasets are often associated with a high degree of censoring earlier in the KM, relative to mature datasets, as a by-product of less events taking place at the time of data cut. Three artificially selected timepoints were selected to truncate the KM curves. 12-months, 18-months and 24-months were used as minimum follow-up times, to align approximately with prior interim publications of the ZUMA-1 clinical trial[3-4].

Censoring proportions were based on these early publications[3-4]. The proportion censored at ~10 to 11 months[3] was approximately 70%, which was then used as the proportion censored in DC1A, the 12-months minimum follow-up data cut. At month 23, approximately 50% were censored [4,] approximately 50% were censored, which was used to for 'DC1C', the data cut at 24 months minimum follow-up. DC1B (18-month follow-up) marked the mid-point between DC1A and DC1C. It was assumed that the proportion censored would be 60%, the mid-point between DC1A (50%) and DC1C (70%).

All analysis was conducted in R Studio. All proportions are shown in Table 1. The censoring indicator was changed until the desired proportion censored was reached, starting with the latest reported events in the five-year dataset. A truncated normal distribution was assumed when assigning the relevant follow-up time for the newly censored points. Generated early datasets were plotted and summary statistics produced, which were compared to equivalent outputs of early ZUMA-1 publications.

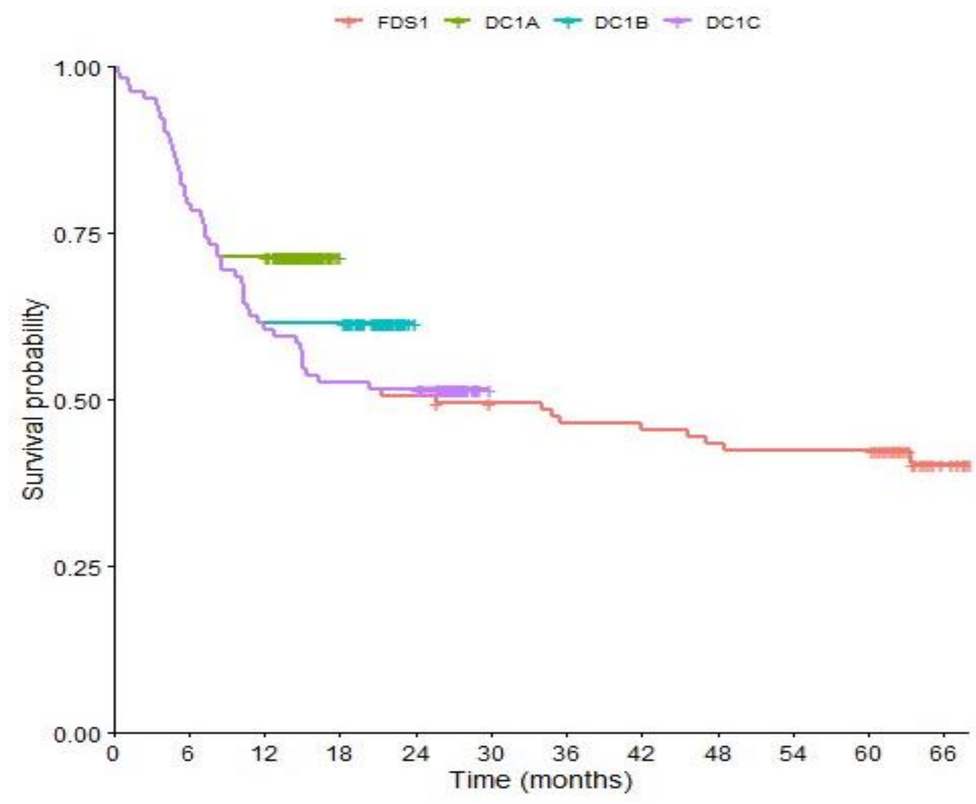
Table 1: Summary of the pseudo early data cuts

Early data cut	DC1A	DC1B	DC1C
Minimum follow-up	12 months	18 months	24 months
Censoring proportion	70%	60%	50%

RESULTS

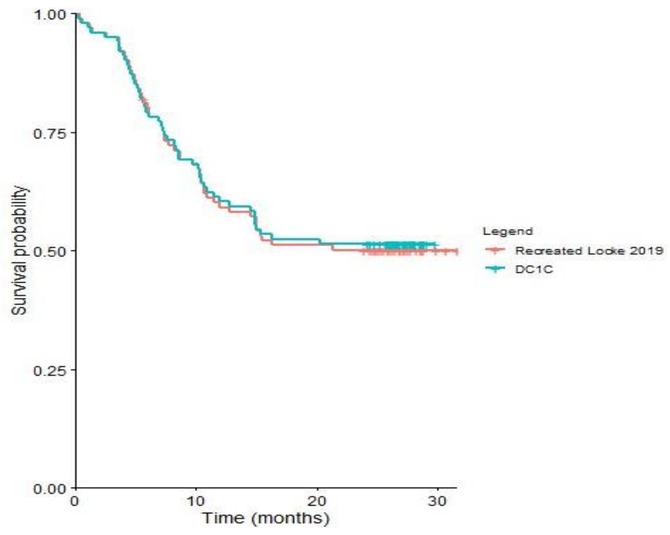
The early data cuts are overlayed with the full data cut in Figure 1. Median survival was not met in either dataset, though this was expected because the median survival for full data cut is 26 and the final early data cut DC1C is truncated at 24 months. The total number of events is 49 in the generated truncated 24-months minimum follow-up dataset and 50 in the ZUMA-1 publication with 27-month median follow-up. The generated truncated datasets resulted in KM that visually matched the KM reported in early ZUMA-1 publications (Figure 2).

Figure 1: Each early data cut overlayed with the full data cut



Each early data cut matched the full dataset (FDS1) until the censoring was applied, at which point each curve flattened. The earliest censoring points in FDS1 matched the cut-off time in DC1C. The DC1A and DC1B curves plateaued earlier than FDS1, and more events were missed due to the high level of censoring. The 24-month minimum follow-up data cut (DC1C) aligned more closely with FDS1 after the minimum follow-up is reached.

Figure 2: Truncated data-cut compared with published KM



CONCLUSIONS

DC1A and DC1B appeared to exaggerate the plateauing of the curves. However, DC1C did reflect (visually and statistically) those of the published interim data. All early data cuts followed the same KM curve as FDS1 until the timepoint where events are censored. The increased variation, characterised by fluctuations rather than a steady decline, and the wide confidence intervals displayed in the earlier data-cuts hazard relative to the more mature datasets is noteworthy. This effect is expected when few events have occurred and at an inconsistent rate, reflecting inherent uncertainty.

Overall, the early pseudo data cuts are a good match and appropriate for survival analysis. Publications reporting mature trial KM can be truncated to recreate earlier datasets to a reasonably accurate degree. A key feature of the published KM that allowed for this truncation was the small range from minimum to maximum follow-up timepoint, as to narrow the applied censoring to a more accurate range.

REFERENCES

1. Neelapu *et al.* Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood, J AmSoc of Hem. 2023.
2. Guyot *et al*. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC med res meth. 2012.
3. Neelapu *et al.* Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. New Eng J Med. 2017.
4. Locke *et al.* Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. Lancet onc. 2019

CONTACT US

samuel.harper@york.ac.uk

+44 1904 326476

York Health Economics Consortium

www.yhec.co.uk

Providing Consultancy & Research in Health Economics

UNIVERSITY of York

INVESTORS IN PEOPLE® We invest in people Gold

YHEC York Health Economics Consortium