ISPOR EU 2025 MSR220 Poster: Supplementary Appendix.

Title: What About a Latent Cure Model? Assessing Cure Models' Performance in Paediatric Acute Lymphoblastic Leukaemia Treated with Tisagenlecleucel.

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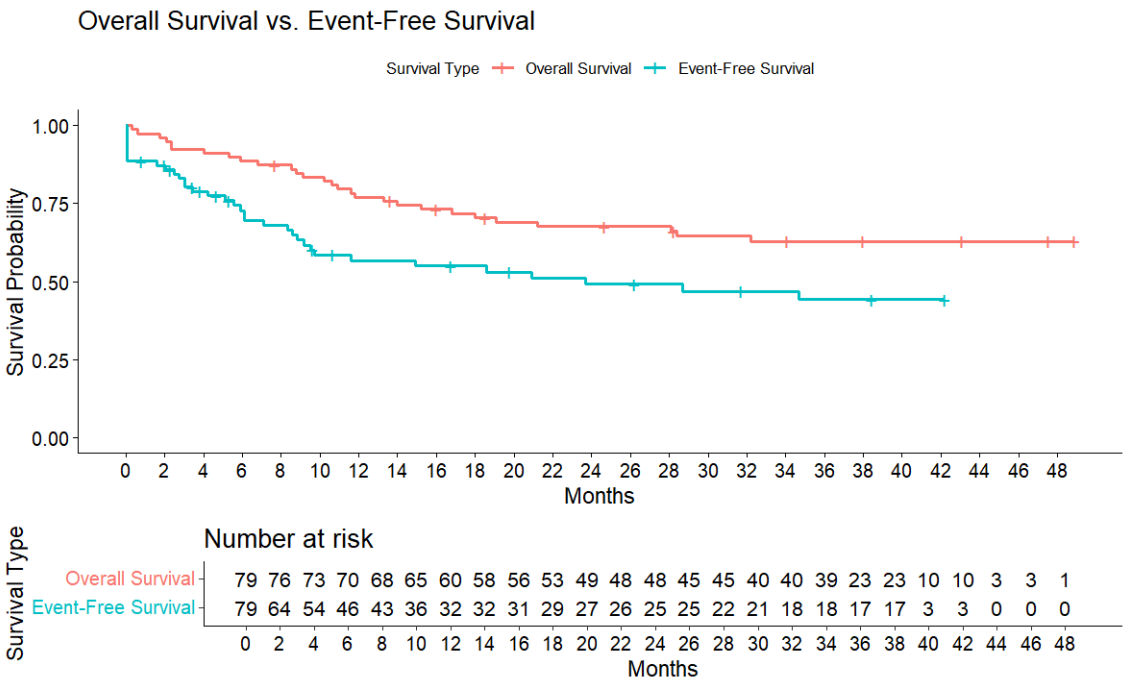
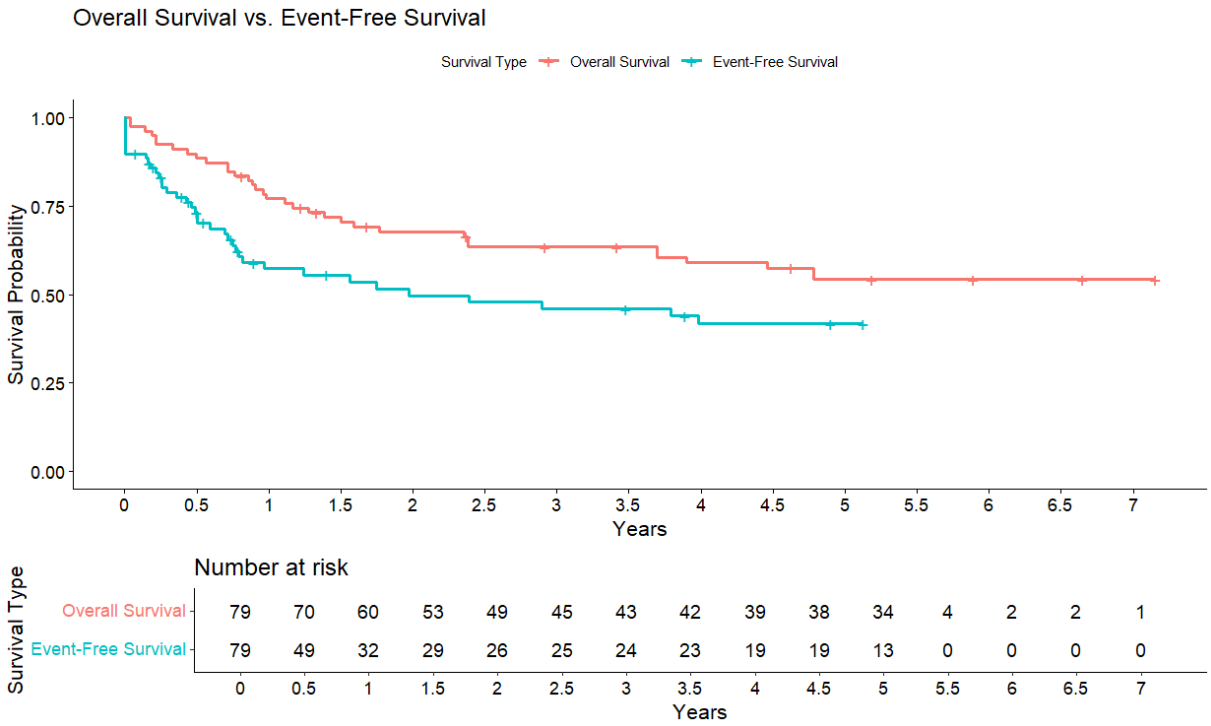
Clinical trial data

In the ELIANA trial, EFS was defined as the time from date of tisa-cel infusion to the earliest of death, relapse or treatment failure, and OS was defined as the time from date of tisa-cel infusion to the date of death due to any reason (1).

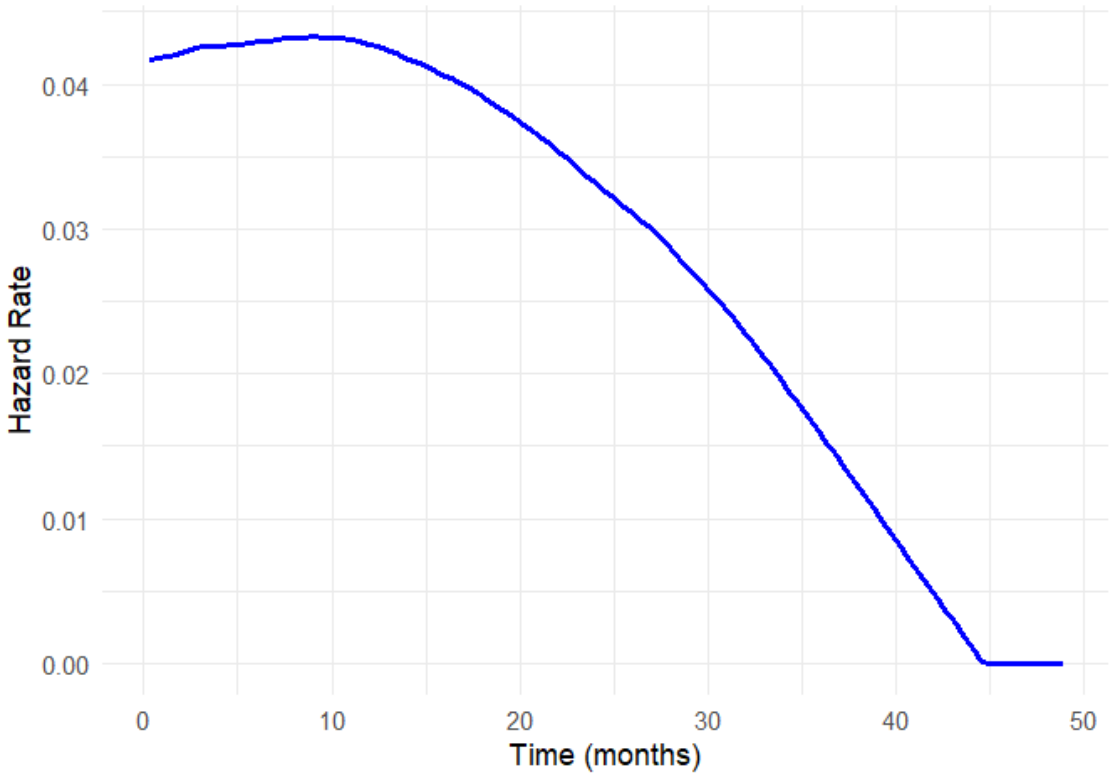
Tisa-cel's EFS and OS on first DCO



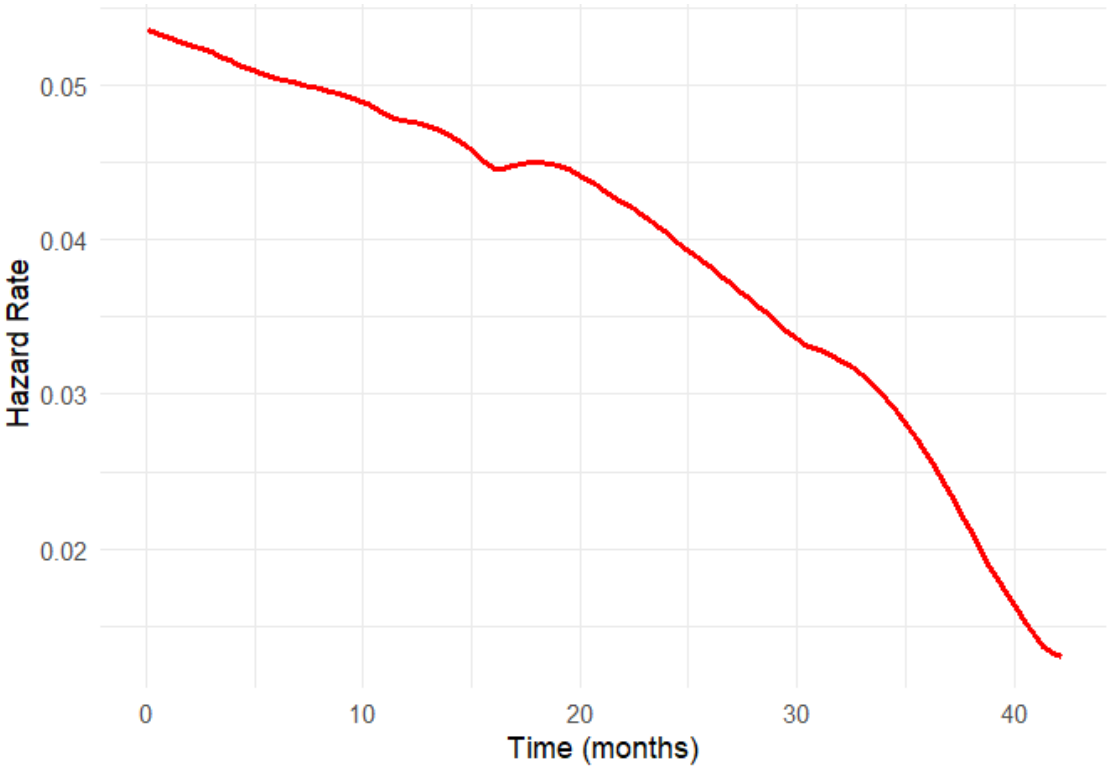
Tisa-cel's EFS and OS on second DCO



Tisa-cel's OS smoothed hazard function (1st DCO)



Tisa-cel's EFS smoothed hazard function (1st DCO)



Survival analysis

Cure models

In the present analysis, cure models were fitted using a relative survival framework. When using this framework, general mortality rates are directly used and these are allowed to govern the long-term survival function (2–5).

Cure models were fitted to the pseudo-IPD in R using the packages *cuRe* and *rstpm2* (5–7). Spanish general population mortality rates were taken from the publicly available human mortality database (8).

Mixture cure models

For both OS and EFS, mixture cure models (MCM) were fitted to the first DCO of the ELIANA trial modelling the survival of the non-cured patients with the following distributions: exponential, Weibull, Weibull-Weibull, Weibull-Exponential, and generalised modified Weibull. The cure proportion was estimated using logistic functions. The background mortality hazard was informed from the Spanish general population mortality data, adjusted with the SMR of 4. Other standard parametric distributions could not be considered as they are not supported by the cuRe package (7).

Generalised mixture cure models

Five different generalised mixture cure models with natural cubic splines were fitted for both EFS and OS, modelling the survival of the uncured proportion using splines with one to five degrees of freedom (i.e., 0 to 4 interior knots) (5). The position of the internal knots was determined automatically based on quantiles of the distribution of the non-censored event times. These were assumed to be able to represent different levels of flexibility without necessarily overfitting to the data. By default, a boundary knot was set at the 95% quantile of the uncensored follow-up times (4). All other parameters were equal to the ones specified for MCMs.

Latent cure models

When using standard parametric models to model the survival of the uncured, estimates of MCMs and non-mixture cure models (NCMs) will typically be similar (2). In order to avoid overcomplicating the analysis with repetitive estimates, only NMCs estimated with natural cubic splines (i.e., latent cure models) were fitted (5).

For OS, nine latent cure models were fitted to the 1st DCO of the ELIANA trial, varying the position of the last boundary knot (at 5, 7, or 10 years) and the number of internal knots (1, 2, or 3). The position of the last boundary knot allowed to determine when cure would occur in the latent cure models. Based on the smoothed hazard function, when using only one internal knot, this was set at 9 months where there is a clear turning point in the hazard. When using two knots, these were set at 9 months and at 24 months, where the rate of the hazard seems to change. Lastly, when using three knots, the last interior knot was set at 39 months in order to maintain equidistance between the three knots.

For EFS, twelve latent cure models were fitted to the 1st DCO of the ELIANA trial, varying the position of the last boundary knot (at 5, 7, or 10 years) and the number of internal knots (2, 3, 4, or 5). Again, the position of the last boundary knot determined when cure occurred. Based on the smoothed hazard function, when using two knots these were set at 16 and 30 months, corresponding to the time points where the most pronounced declines in the hazard function were observed. When using three knots, the third knot was set at 18 months, where there is a turning point in the hazard function. For the fourth knot, this was set at 35 months, where an accelerated decrease in the hazard function is observed. Finally, the fifth knot was set at 11 months, in order to provide more flexibility in the initial hazard function.

For both OS and EFS, the same additional parameters as described for MCMs were considered.

It is important to note that while the position of the internal knots was specified for the latent cure models but not for the generalised mixture cure models, this is due

to technical reasons. By specifying when cure occurred in the latent cure models, the position of the internal knots also had to be determined. This was not considered a problem, given that the number of knots is generally more relevant compared to their positioning (9).

Spline-based models

Spline-based models with natural cubic splines were fitted in R using the *rstpm2* package (5,6). For OS, five different spline-based models were fitted from 2 to 6 degrees of freedom (i.e., 1 to 5 internal knots). In the same fashion as for the generalised mixture cure models, the positioning of the knots was done automatically according to quantiles of the distribution of the non-censored event times. This range of models was assumed to be able to represent different levels of flexibility without necessarily overfitting the data. Again, by default a boundary knot was set at the 95% quantile of the uncensored follow-up times (4).

References

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