Long-Term Survival Projections of Loncastuximab Tesirine–Treated Patients in Relapsed or Refractory Diffuse Large B-cell Lymphoma

ABCL-334

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CONTEXT

- Loncastuximab tesirine (loncastuximab tesirine-lpyl; Lonca) is a Food and Drug Administration (FDA)-approved CD19-directed antibody-drug conjugate for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) supported by the pivotal LOTIS-2 clinical trial.
- The LOTIS-2 study (NCT03589469) was a single-arm, open-label, phase 2 study of 145 adults with R/R DLBCL after ≥ 2 prior treatments. Intravenous Lonca (150 µg/kg for 2 cycles, 75 µg/kg thereafter) was given for up to 1 year or until disease relapse/progression.
- Based on the primary data cut from the LOTIS-2 trial (6 April 2020), overall response rate was 48.3% and median overall survival (OS) was 9.9 months. The OS Kaplan-Meier (KM) plot[1] displayed a survival plateau suggesting presence of long-term survivors (LTSs).

OBJECTIVE

- The objective of this study was to estimate the percentage of LTSs and expected lifetime survival (mean OS) for Lonca-treated patients via extrapolation of data collected in the LOTIS-2 trial.
- Results of an analysis based on the data cut of 1 March 2021 with a median follow-up of 1.7 years (81% follow-up completeness at median) was submitted. Following abstract acceptance, the most recent LOTIS-2 data cut (1 March 2022) with a median follow-up of 2.6 years (85% follow-up completeness at median) became available. We provide additional results using the most recent data cut.

DESIGN

Consistent with studies of other R/R DLBCL treatments identified through a literature review, survival analyses including parametric, flexible cubic spline, mixture cure, and non-mixture cure models were fit using multiple distributions. Flexible cubic splines used the hazard scale, and models were fit with 1, 2, and 3 knots. Parametric, mixture cure, and non-mixture cure models were fit using the gamma, generalized gamma, Gompertz, log-logistic, log-normal, and Weibull (accelerated failure time parametrization) distributions.

A hybrid model, following the best-fit parametric/spline model to a defined timepoint and switching to general population mortality, was also constructed.

All analyses were carried out in R v4.2.0 with the packages flexsurv and flexsurvcure.

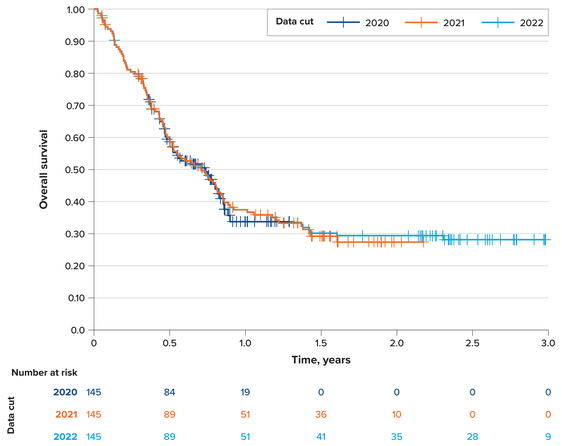
Age- and gender-matched United States life table[2] hazards were used in mixture and non-mixture cure models to incorporate background mortality; they were also used in the generation of long-term survival projections to ensure modeled hazards were not less than general population at the corresponding average age.

Best-fit models were determined through fit statistics (e.g., Akaike's information criterion [AIC]), KM and fitted curve overlays, and clinical plausibility. The best-fit model from each method was selected to be considered for overall best fit.

RESULTS

- The OS KM plot comparing the primary (2020) and 2 more mature data cuts (2021 and 2022) showed that a survival plateau begins to appear between 1 and 2.5 years of follow-up and remains constant between data cuts with additional follow-up, indicating a pronounced survival plateau (Figure 1).
- Overall, mixture cure, non-mixture cure, and hybrid models with a 2-year switch point were consistent in OS predictions (6.11-6.69 years) in both data cuts. Parametric and spline analyses from the 2022 data cut aligned, as well (Table 1).
- Mixture cure models with gamma distribution and non-mixture cure models with Weibull distribution fit the observed data well (lowest AICs) in both 2021 and 2022 data cuts. LTS percentage was estimated to be 24%-26% from the 2021 data cut and 29% from the 2022 data cut. Mean OS from the mixture and non-mixture cure models was estimated to be 6.11-6.64 years.
- Parametric and spline models did not fit the observed data well in the 2021 data cut (highest AIC). With the longer follow-up, the parametric and spline models in the 2022 data cut analyses were consistent with the mixture cure, non-mixture cure, and hybrid models of both data cuts. Parametric and spline models from the 2022 data cut resulted in OS projections of 6.34-6.47 years.
- Due to better fit than parametric models, spline models with 2 and 3 knots were used in the hybrid model with a 2-year switch point as the base case in both data cuts. The hybrid models aligned with the mixture and non-mixture cure models in both data cuts with OS projections of 6.23-6.69 years. A sensitivity analysis of a hybrid model with a 3-year switch point in the 2022 data cut estimated similar survival (6.32 years).
- Figures 2 and 3 show the KM and statistical model overlays of the more recent data cuts (2021 and 2022, respectively).

Figure 1. Loncastuximab Overall Survival Kaplan-Meier Plot



Source: LOTIS-2 2020, 2021, and 2022 data cuts.

Figure 2. Overlay of Overall Survival Kaplan-Meier Plot and Fitted Statistical Models: 2021 Data Cut

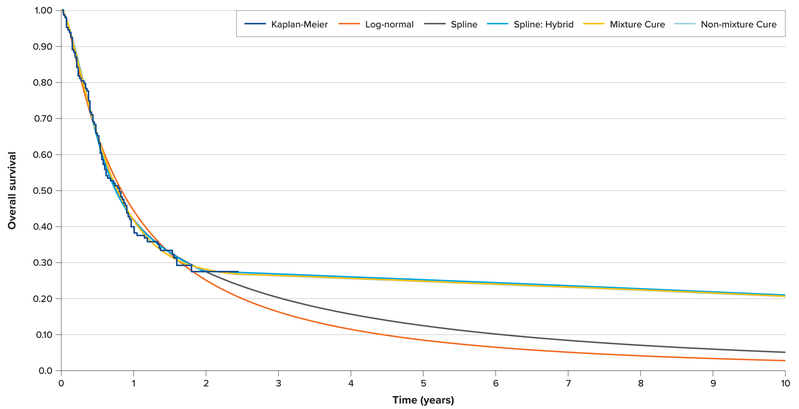


Figure 3. Overlay of Overall Survival Kaplan-Meier Plot and Fitted Statistical Models: 2022 Data Cut

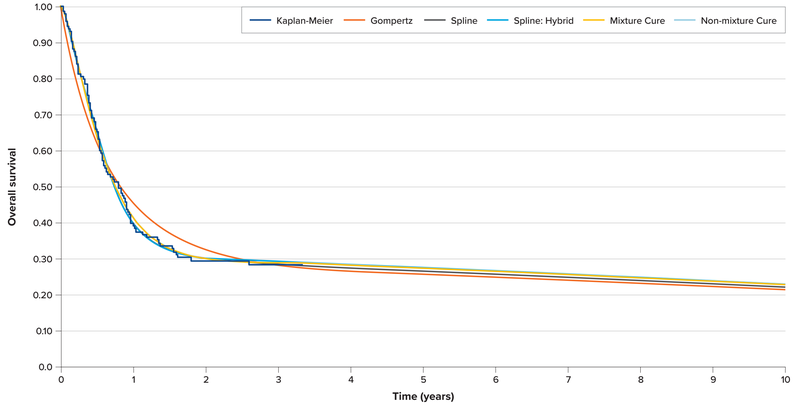


Table 1. Lifetime Survival Projections

Method	Data cut	Best-fit distribution	Mean survival, years	AIC[a]
Parametric	2021	Log-normal	1.97	238.69
	2022	Gompertz	6.34	264.44
Flexible cubic splines	2021	Hazard, 2 knots	2.39	240.18
	2022	Hazard, 3 knots	6.47	254.05
Hybrid model with spline until year 2	2021	Hazard, 2 knots	6.23	–
	2022	Hazard, 3 knots	6.69	–
Mixture cure	2021	Gamma	6.13	236.71
	2022	Gamma	6.62	249.37
Non-mixture cure	2021	Weibull	6.11	236.80
	2022	Weibull	6.64	249.56

[a] AIC cannot be compared between analyses (i.e., data cuts), only within analyses.

CONCLUSIONS

The observed survival plateau of the OS KM plot suggests that Lonca-treated patients may include LTSs with additional follow-up showing a more pronounced and consistent plateau. Multiple statistical methods—including parametric, mixture and non-mixture cure, and hybrid models—fit the trial data well and align on survival projections across the 2 most recent data cuts. LTSs were estimated to be as high as 29%, and statistical models from the most recent data cut (2022) resulted in mean OS estimates over 6 years.

REFERENCES

1. Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, Hamadani M, Hess B, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2021 Jun;22(6):790-800. doi: 10.1016/S1470-2045(21)00139-X.
2. Arias E, Xu JQ. United States life tables, 2018. National Vital Statistics Reports. Vol. 69, no. 12. National Center for Health Statistics: Hyattsville, MD; 2020.

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