To the Editor:

Kallam and Vose have presented a very extensive landscape of the current information on the efficacy and safety of treatment with chimeric antigen receptor T-cell (CAR-T) in patients with non-Hodgkin lymphoma. As regards efficacy, we have carried out a comparison of overall survival between patients treated with tisagenlecleucel and a large sample of historical controls given a standard treatment. Our objective was to offer a quantitative estimate of the survival gain resulting from CAR-T compared with standard treatment. This estimate was based on the restricted mean survival time (RMST).

In the past years, an extensive literature has accumulated on the use of RMST in the interpretation of survival curves. In comparison with traditional analyses based on hazard ratio (HR) and medians, the RMST has important advantages because it examines the entire survival curve (like the HR) and expresses the survival outcomes using time as unit of measurement (like medians). Most previous experiences on the application of RMST are focused on oncology (eg, see Trinquart et al, 20162 and Royston and Parmar, 20113). Quite recently, the application of RMST has been investigated in cardiovascular4 and infectious diseases. Briefly, the RMST combines the main advantages of HR and medians without possessing their disadvantages.

From a practical point of view, the RMST is characterized by a high mathematical complexity of its statistical calculations. However, 2 recent papers4-5 have suggested an original method of calculation, drawn from the field of pharmacokinetics, that allows for an extreme simplification of RMST estimation.

In the present study focused on the treatment of diffuse large B-cell lymphoma, we assessed the survival gain derived from CAR-T treatment (experimental group) in comparison with previous treatments not involving any gene manipulations (control group).

The controls included in our analysis were obtained from an article published by Crump et al (SCHOLAR-1 study8). The experimental group (CAR-T group; CAR-T = tisagenlecleucel) was obtained from the patient series published by Schuster et al (JULIET trial9). These 2 populations of patients (experimental arm, N = 48; controls, N = 603) were identified through a simple PubMed search. Their disease consisted of diffuse large B-cell lymphoma including transformed follicular lymphoma and primary mediastinal B-cell lymphoma. All patients had received at least 2 previous lines of treatment. When they received their salvage treatment, they met specific criteria of either relapse or refractory. Twenty-nine (60.4%) of 48 patients and 118 (19.6%) of 603 patients were in relapse in the experimental and in the control groups, respectively. Autologous transplantation had been performed in 49% of patients in the experimental group and in 19.6% of the SCHOLAR-1 patients. Further details on these 2 populations can be found in the original studies.8,9

Despite the indirect nature of the comparison described herein, one advantage of our analysis lies in the attempt to estimate for the first time the survival improvement related to the use of CAR-T under specific circumstances. No direct comparison is in fact available on this issue.

The values of model-independent RMST were 13.46 months for CAR-T and 10.81 for the controls. Both values were based on a “milestone” set at 22 months of follow-up; the milestone is the time point in the follow-up at which the area under the survival curve (AUC) is truncated. The 2 AUCs are shown in Figure 1. The survival gain estimated from the comparison of the 2 curves was 2.65 months per patient in favor of the CAR-T group.

The main result expected from our indirect comparison was to demonstrate a survival gain for CAR-T compared with a standard therapeutic approach and to estimate the magnitude of this benefit. A difference in overall survival was found from our analysis. Apart
from the level of statistical significance of this difference (which is anyhow questionable in such an imbalanced indirect comparison, 48 vs. 603 patients), the survival gain in favor of CART-T was quite small. This lack of a clinically relevant incremental efficacy for CART-T at 22 months is the main finding of our analysis.

The availability of the SCHOLAR-1 study including patients not given a CAR-T was the main reason that led us to undertake this analysis. In the comparison between our experimental group given CART-T versus the controls, the RMST had the methodological advantage of taking into account the entire shape of the 2 survival curves.

More importantly, another consideration is that, at the end of the follow-up of 22 months, the patients given CAR-T might have, in future perspective, a longer life expectancy than those not given CAR-T. This hypothesis will need to be verified through a further follow-up for the patients of the JULIET trial (ie, beyond 22 months). Fortunately, the SCHOLAR-1 patients already have a very long follow-up (up to 180 months), and so these controls will remain comparable with CAR-T patients when, in the future, the further follow-up of these patients will allow to set a milestone at more than 22 months. The obvious hypothesis is that, with a longer follow-up, the AUC for CAR-T patients could become much greater than that of the controls, but this demonstration is presently lacking.

Were the 2 populations studied in our analysis comparable? In our view, they were sufficiently comparable. Furthermore, it should be recalled that the information about the efficacy of CART-T is still limited, and so the comparison presented herein seems the only one that currently can be made.

Two conclusions are suggested by our study. Firstly, the RMST is confirmed to be a suitable parameter for managing the survival data of lymphoma patients receiving a CAR-T.10 Secondly, the RMST analysis based on the outcomes currently available does not demonstrate any breakthrough survival advantage for tisagenlecleucel in comparison with treatments not involving any gene manipulations. Hence, our analysis provides a quantitative confirmation of the statement by Kallam and Vose1 that "despite the promising results from the large multicenter trials, the efficacy of CAR-T cells in non-Hodgkin lymphoma is limited."

References