Abstract 7555: Quality-adjusted Time without Symptoms or Toxicities (Q-TWiST) Analysis of ZUMA-7, A Randomized Controlled Trial of Axicabtagene Ciloleucel versus Standard of Care for Second-Line Large B-Cell Lymphoma

Authors: Marie José Kersten,[1] Yao Qiao,[2] Ruchit Shah,[2] Caitlyn Solem,[2] Julia Thornton Snider,[3] Christina To,[3] Paul Cheng,[3] Clare Spooner,[3] Miguel-Angel Perales[4,5]
Affiliations: 1. Amsterdam University Medical Center, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands; 2. OPEN Health, Bethesda, MD, USA;
3. Kite, A Gilead Company, Santa Monica, CA, USA; 4. Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 5. Department of Medicine, Weill Cornell Medical College, New York, NY, USA

Background/Methods

- **Background**
  - High-dose chemotherapy with autologous stem-cell transplantation (HDT-ASCT) has been the standard of care (SOC) for relapsed or refractory large B-cell lymphoma (R/R LBCL) in the second-line setting for those with response to salvage chemoimmunotherapy.[1,2]
  - The United States (US) Food and Drug Administration (FDA) recently approved axicabtagene ciloleucel (axi-cel) as a second-line therapy for adult patients with R/R LBCL,[3] based on ZUMA-7, the first randomized, global, multicenter Phase 3 study of axi-cel versus SOC as second-line treatment in patients with R/R LBCL.[4]
  - In ZUMA 7,[4] axi-cel significantly improved event-free survival (EFS) compared with second-line SOC in R/R LBCL. Grade 3 or higher adverse events (AEs) occurred in 91% and 83% of patients in the axi-cel and SOC arms, respectively.
  - Quality-adjusted time without symptoms or toxicity (Q-TWiST) method provides a comprehensive framework for treatment comparison.[5]
    - Taking into consideration both quantity and quality of survival time.
    - Accounting for patient preference with time spent in each state.
- **Objective:** To compare the quality-adjusted survival time between R/R LBCL patients receiving axi-cel and those treated with SOC in the second-line setting.
- **Methods**
  - Data source: patient-level data from the phase 3 ZUMA-7 trial (axi-cel n=180; SOC n=179).[4]
  - Statistical analyses: Q-TWiST assesses the overall quantity and quality of survival based on the amount of restricted mean time spent in each health state, defined using Kaplan-Meier curves (**Table 1)**
  - Mean Q-TWiST: utility-weighted sum of time in each state

$$\text{Q-TWiST} = U_{TWiST} \times \text{TWiST} + U_{TOX} \times \text{TOX} + U_{REL} \times \text{REL}$$

Table 1. Definition and estimation of time spent in each health state

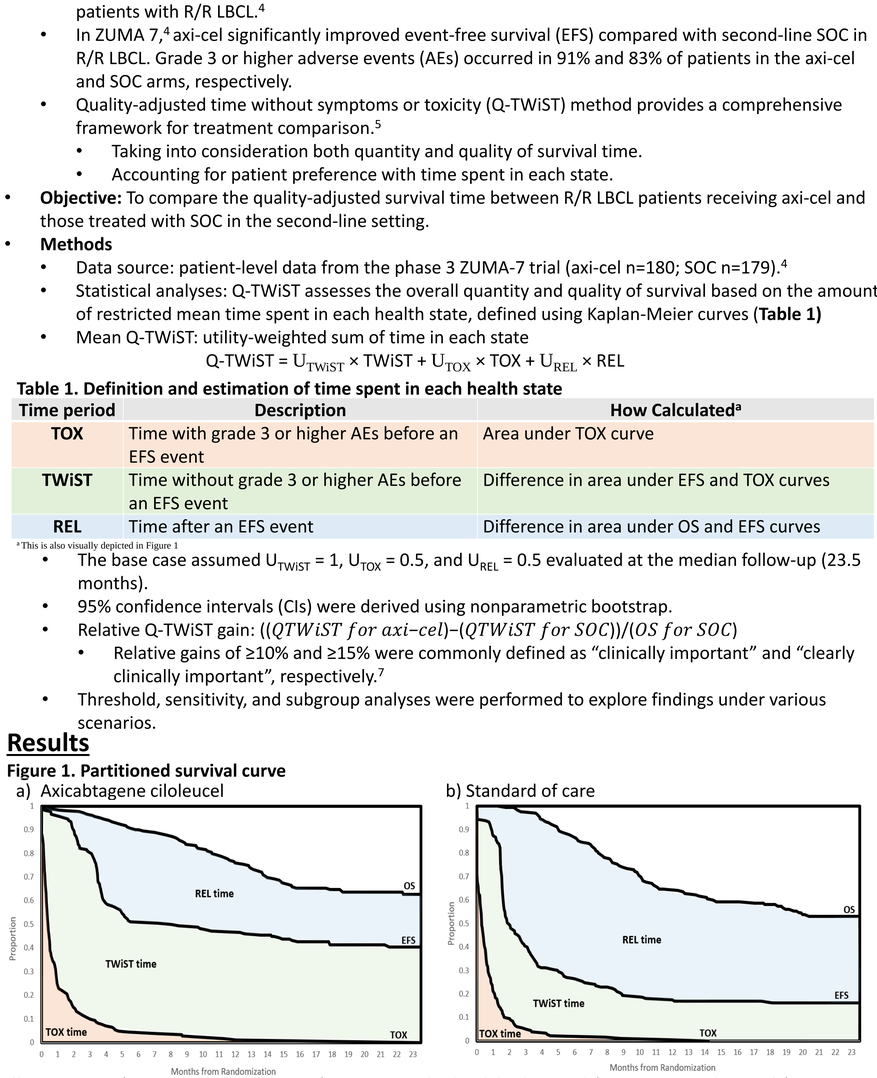
Time period	Description	How Calculated[a]
TOX	Time with grade 3 or higher AEs before an EFS event	Area under TOX curve
TWiST	Time without grade 3 or higher AEs before an EFS event	Difference in area under EFS and TOX curves
REL	Time after an EFS event	Difference in area under OS and EFS curves

[a]This is also visually depicted in Figure 1

  - The base case assumed U_{TWiST} = 1, U_{TOX} = 0.5, and U_{REL} = 0.5 evaluated at the median follow-up (23.5 months).
  - 95% confidence intervals (CIs) were derived using nonparametric bootstrap.
  - Relative Q-TWiST gain: $((QTWiST\ for\ axi\text{–}cel)\text{–}(QTWiST\ for\ SOC))/(OS\ for\ SOC)$
    - Relative gains of ≥10% and ≥15% were commonly defined as "clinically important" and "clearly clinically important", respectively.[7]
  - Threshold, sensitivity, and subgroup analyses were performed to explore findings under various scenarios.

Results

Figure 1. Partitioned survival curve



Abbreviations: EFS, event-free survival; OS, overall survival; REL, time after event; TOX, time with grade 3 or higher adverse events before event; TWiST, time without toxicity before an event.

Conclusions

Axicabtagene ciloleucel, compared with standard of care, demonstrated a **clinically meaningful difference in quality-adjusted survival** supporting the use of axi-cel as a second-line therapy for patients with R/R LBCL

- Compared with published results summarized in a systematic review and benchmarking study of Q-TWiST analyses, the relative Q-TWiST gain associated with axi-cel was higher than approximately 89% of published results for cancer treatment.[5]
- The results were robust to various QoL utility values, different durations of follow-up, and subgroups by age and relapse/refractory status.

Correspondence: Dr. Marie José Kersten at m.j.kersten@amsterdamumc.nl

Results (continued)

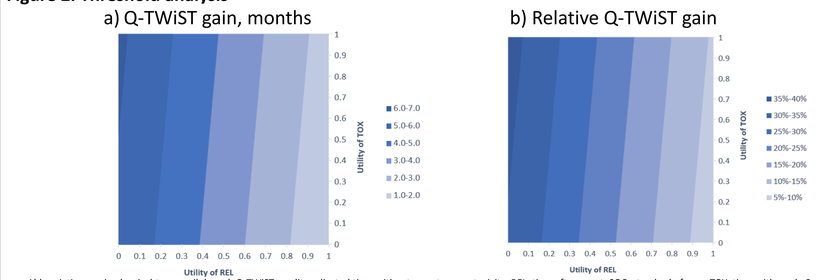
- Compared with patients receiving SOC, those receiving axi-cel had significantly longer time in TWiST, a health state considered to have the highest QoL (**Figure 1, Table 2**); patients receiving axi-cel had slightly longer TOX and shorter REL.
- Patients receiving axi-cel showed a significant gain in quality-adjusted survival of 3.7 months (**Table 2**); the relative Q-TWiST gain was estimated to be 21.9%, representing a "clearly clinically important" gain.

Table 2. Mean duration (95% CI) of each health state and Q-TWiST, months

Time period	Axi-cel	SOC	Difference (Axi-cel – SOC)
TOX	1.16 (0.83, 1.48)	0.74 (0.51, 0.94)	0.42 (0.04, 0.82)
TWiST	11.18 (9.73, 12.61)	5.39 (4.21, 6.56)	5.79 (4.07, 7.62)
REL	6.02 (4.9, 7.15)	10.66 (9.42, 11.93)	-4.64 (-6.39, -3.09)
Q-TWiST	14.8 (13.6, 15.9)	11.1 (10, 12.1)	3.7 (2.3, 5.2)

Abbreviations: axi-cel, axicabtagene ciloleucel; CI, confidence interval; Q-TWiST, quality-adjusted time without symptoms or toxicity; REL, time after event; SOC, standard of care; TOX, time with grade 3 or higher adverse events before event; TWiST, time without toxicity before an event.

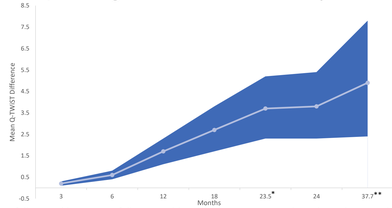
Figure 2. Threshold analysis



Abbreviations: axi-cel, axicabtagene ciloleucel; Q-TWiST, quality-adjusted time without symptoms or toxicity; REL, time after event; SOC, standard of care; TOX, time with grade 3 or higher adverse events before event.

- Regardless of the patient's relative preferences for avoiding AEs and EFS events, axi-cel would give a greater Q-TWiST time and would be preferred (**Figure 2**). Q-TWiST gain was the greatest (6.2 months; 37.0%) for patients not bothered by AEs (U_{TOX}=1) but with a strong preference to avoid EFS events (U_{REL}=0); the gain was smaller but still positive (1.2 months; 6.9%) for those with a strong preference to avoid AEs (U_{TOX}=0) but not bothered by EFS events (U_{REL}=1).

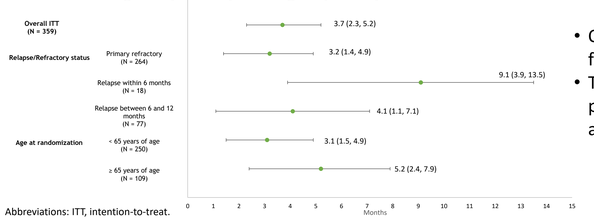
Figure 3. Q-TWiST gains at different follow-up times



- Q-TWiST gain from axi-cel was significant across durations of follow-up (**Figure 3**).
- The gain increased with longer duration of follow-up.

*Median follow-up **Maximum follow-up. Abbreviations: Q-TWiST, quality-adjusted time without symptoms or toxicity.

Figure 4. Q-TWiST gains (95% CI) in subgroup analysis



Abbreviations: ITT, intention-to-treat.

- Q-TWiST gain was significant for all subgroups (**Figure 4**).
- The gain was higher among patients ≥65 years than among those <65 years.

References: 1. Crump M, et al. Blood. 2018;131(5):587-588. 2. Philip T, et al. N Engl J Med. 1995;333(23):1540-1545. 3. Gilead. 2022. 4. Locke FL, et al. N Engl J Med. 2022;386(7):640-654. 5. Solem CT, et al. Expert Rev Pharmacoecon Outcomes Res. 2018;18(3):245-253. 6. Cheson BD, et al. J Clin Oncol. 2014;32(27):3059-3068. 7. Revicki DA, et al. Qual Life Res. 2006;15(3):411-423.