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Quality-Adjusted Survival Analysis of Neurologic Events With Ciltacabtagene Autoleucel vs Standard of Care in Patients With Lenalidomide-Refractory Multiple Myeloma Who Received 1–3 Prior Lines of Therapy: CARTITUDE-4 Trial Population

Surbhi Sidana[1], Leyla Shune[2], Luciano J Costa[3], Roberto Mina[4], Rafal Slowik[5], Jianming He[5], João Mendes[5], Jackie Kwong[5], Maren Gaudig[5], Seina Lee[5], Mukta Sharma[5], Rakesh Popat[6], Cyrille Touzeau[7]

[1]Stanford University School of Medicine, Stanford, CA, USA; [2]The University of Kansas Medical Center, Kansas City, KS, USA; [3]University of Alabama at Birmingham, Birmingham, AL, USA; [4]University of Torino and Azienda Ospedaliero-Universitaria (A.O.U.) Città della Salute e della Scienza di Torino, Torino, Italy; [5]Johnson & Johnson, Raritan, NJ, USA; [6]University College London Hospitals, NHS Foundation Trust, London, UK; [7]Service d'Hématologie, Centre Hospitalier Universitaire (CHU) Hotel Dieu, Nantes, France

Key Takeaway

Cilta-cel showed a statistically significant and clinically meaningful gain in quality-adjusted time without grade 3/4 neurologic AEs vs SOC, consistent with previous Q-TWiST results based on all grade 3/4 AEs,[4] further supporting its favorable benefit-risk profile

Conclusions

- Patients treated with cilta-cel (ITT or as-treated populations) experienced a Q-TWiST gain of +9 to 13 months vs SOC, representing a 34.6–52.3% relative improvement in time without grade 3/4 neurologic AEs
- The relative improvement exceeded 10–15% threshold generally considered clinically meaningful, with higher gains (52.3%) seen in the cilta-cel as-treated population
- The observed benefit with cilta-cel vs SOC was maintained despite a short relative duration of time spent with grade 3/4 CAR-T–related neurologic AEs in the analysis, supporting the patient-centric benefit of cilta-cel

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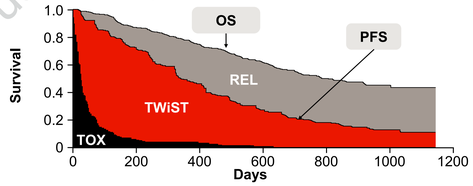
Introduction

- In CARTITUDE-4, a single ciltacabtagene autoleucel (cilta-cel) infusion significantly prolonged progression-free survival (PFS) and overall survival (OS) vs standard of care (SOC) in patients with lenalidomide-refractory multiple myeloma after 1–3 prior lines of therapy[1,2]
  - At a median follow-up of 33.6 months, cilta-cel reduced the risk of death by 45% vs SOC (P=0.0009)[3]
- A previously reported Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWiST) analysis using CARTITUDE-4 data showed a 32.1–49.2% relative gain in time without grade 3/4 adverse events (AEs) with cilta-cel vs SOC based on all grade 3/4 AEs,[4] including neurologic AEs (an infrequent but recognized risk with chimeric antigen receptor [CAR]-T cell therapies)[5]
- Here, we report a focused Q-TWiST analysis of CARTITUDE-4, assessing the impact of neurologic AEs on the quality-adjusted survival benefit of cilta-cel vs SOC

Methods

- As of the May 1, 2024, data cut-off, the Q-TWiST analysis included the intent-to-treat (ITT; cilta-cel [N=208]; SOC [N=211]) and the as-treated (ie, received cilta-cel as study treatment; cilta-cel, [N=176]; SOC, [N=208]) populations from CARTITUDE-4 with a maximum follow-up of 45 months
- The base case analysis in ITT and as-treated populations covered all grade 3/4 neurologic AEs (treatment-emergent and non–treatment-emergent), including CAR-T–related events, such as immune effector cell–associated neurotoxicity syndrome (ICANS) and ICANS-associated symptoms
  - A subanalysis in the cilta-cel arm evaluated PFS time with grade 3/4 CAR-T–related neurologic AEs (excluding ICANS and ICANS-associated symptoms)
- OS was partitioned into 3 distinct health states (**Figure 1**): PFS time with grade 3/4 neurologic AEs (TOX), PFS time without grade 3/4 neurologic AEs (TWiST), and time after disease progression (REL)
- Conventional utilities were used for each health state: TWiST (1.0), TOX (0.5), and REL (0.5) (**Figure 2**)
- A 10–15% relative Q-TWiST gain was considered as a clinically important difference based on previous recommendations[6]

Figure 1: Partitioned OS curve with progression and toxicity states (TWiST, TOX, and REL)[a]



[a]Illustrative example using hypothetical data to show partitioning of OS into TOX, TWIST, and REL.

Figure 2: Q-TWiST formula with utility weights across health states

Utility value at each health state

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

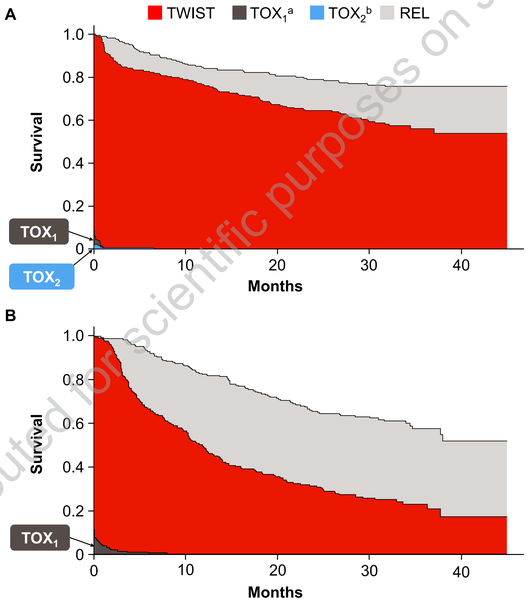
U, utility value assigned to each health state.

Results

Base case analysis

- A greater proportion of time was spent progression free and without grade 3/4 neurologic AEs in the cilta-cel arm compared with SOC (**Figure 3A, 3B**)
  - In the cilta-cel arm, overlaying time with grade 3/4 CAR-T–related neurologic AEs (TOX_2) on the broader grade 3/4 neurologic AE profile (TOX_1) showed that time with CAR-T–related AEs (excluding ICANS and ICANS-associated symptoms) was low relative to overall neurologic AE time (**Figure 3A**)
- Cilta-cel was associated with a longer duration of PFS without grade 3/4 neurologic AEs vs SOC across populations (**Table**)
  - In the ITT population, mean PFS time without grade 3/4 neurologic AEs was 30.4 months for cilta-cel and 17.7 months for SOC
  - In the as-treated population, mean PFS time without grade 3/4 neurologic AEs was 35.7 months for cilta-cel and 17.7 months for SOC

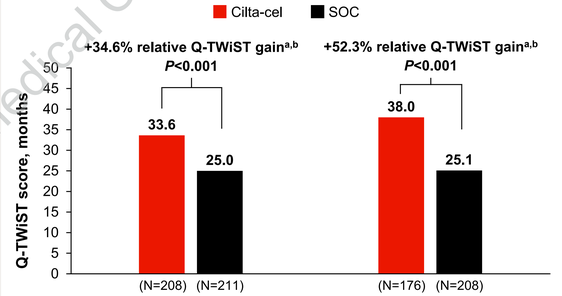
Figure 3: Time spent in 3 health states (TOX,[a,b] TWiST, and REL) in the ITT population for (A) cilta-cel and (B) SOC



[a]TOX_1, PFS time with grade 3/4 neurologic AEs. [b]TOX_2, PFS time with grade 3/4 CAR-T–related neurologic AEs, excluding ICANS and ICANS-associated symptoms. Base case includes grade 3/4 neurologic AEs (both treatment-emergent and non–treatment-emergent). Utility weights applied were 1.0 for TWiST and 0.5 for both TOX and REL.

- Cilta-cel vs SOC demonstrated a statistically significant improvement in the total Q-TWiST scores in both the ITT and as-treated populations (**Figure 4**)
  - In the ITT population, cilta-cel showed a +34.6% relative Q-TWiST gain vs SOC (+8.7 months, 95% CI, 5.7–11.6; P<0.001)
  - In the as-treated population, the relative Q-TWiST gain was 52.3% in favor of cilta-cel (+13.1 months, 95% CI, 10.4–15.7; P<0.001)

Figure 4: Q-TWiST scores for cilta-cel vs SOC in the base case (ITT and as-treated populations)



[a]Relative gain reflects the percentage increase in Q-TWiST value with cilta-cel vs SOC. [b]P<0.001. Utility weights applied were 1.0 for TWiST and 0.5 for both TOX and REL.

Table: Quality-adjusted estimates for TOX, TWiST, and REL in the ITT and as-treated populations

	Cilta-cel	SOC	Cilta-cel vs SOC	
	Restricted mean (95% CI)	Restricted mean (95% CI)	Restricted mean (95% CI)	P value
ITT population				
PFS time with grade 3/4 neurologic AEs, months	0.07 (0, 0.13)	0.15 (0.04, 0.26)	–0.09 (–0.21, 0.04)	0.169
PFS time without grade 3/4 neurologic AEs, months	30.4 (28.0, 32.9)	17.7 (15.4, 20.1)	12.7 (9.4, 16.0)	<0.001
Time after disease progression, months	6.4 (4.8, 8.0)	14.3 (12.2, 16.5)	–8.0 (–10.6, –5.3)	<0.001
Q-TWiST, months	**33.6 (31.5, 35.8)**	**25.0 (22.9, 27.0)**	**8.7 (5.7, 11.6)**	<0.001
As-treated population				
PFS time with grade 3/4 neurologic AEs, months	0.07 (0, 0.14)	0.16 (0.04, 0.28)	–0.08 (–0.23, 0.06)	0.243
PFS time without grade 3/4 neurologic AEs, months	35.7 (33.6, 37.7)	17.7 (15.4, 20.1)	17.9 (14.9, 21.0)	<0.001
Time after disease progression, months	4.7 (3.3, 6.0)	14.3 (12.2, 16.5)	–9.7 (–12.2, –7.1)	<0.001
Q-TWiST, months	**38.0 (36.3, 39.8)**	**25.0 (23.0, 27.0)**	**13.1 (10.4, 15.7)**	<0.001

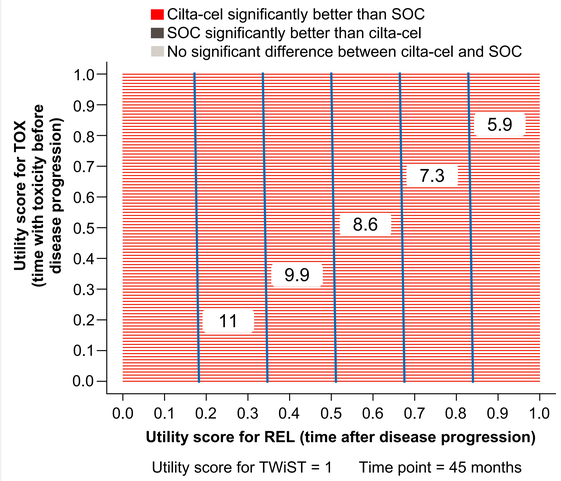
Utility weights applied were 1.0 for TWiST and 0.5 for both TOX and REL. Base case includes grade 3/4 neurologic AEs (both treatment-emergent and non–treatment-emergent).

- Q-TWiST remained higher for cilta-cel vs SOC in all scenarios when the full range of utility values (0–1) for TOX and REL health states was tested over the maximum follow-up of 45 months (**Figure 5**)

Strengths and limitations

- The Q-TWiST method offers a comprehensive, patient-centric approach to assess treatment benefit by integrating survival, toxicity, and progression, while accounting for the impact of treatment-related toxicities on quality of life
- A key limitation of the Q-TWIST methodology is the assumption that all grade 3/4 AEs have equal impact on quality of life; this may be addressed by refining TOX-state definitions using subsets of AEs with known quality-of-life impact
  - This Q-TWiST analysis focused on neurologic AEs to explore their contribution to the overall benefit-risk profile of cilta-cel, addressing physician and patient concerns about neurologic risks observed with CAR-T therapies[5]
- The analysis used predefined, fixed-utility values originally suggested by Gelber et al. (1995) when introducing the Q-TWiST method[7,8]
  - Validating results using patient-derived utility data from clinical trials or real-world settings would further strengthen generalizability
- Results are based on a single data cut-off (May 1, 2024; maximum follow-up, 45 months)

Figure 5: Q-TWiST estimates for utility values of TOX and REL in the base case analysis[a]



[a]Numbers shown are Q-TWiST gain over follow-up time of 45 months in the ITT population.

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Multiple Myeloma

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