# QoL data in CAR-T CEA in France: What to use?

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## Background and objective

CEAs assessing CAR-T cell therapies are required by the French HTA because of the eligibility criteria of financial revenue threshold and their innovative character. Selection of QoL data considered in the CEAs submitted has been challenging and the level of acceptability evolving over time. The objectives of this analysis were to review choices made to document QoL in the previously assessed CEAs and to trace the evolution of choices made and their level of acceptability over time.

## Methods

Available French efficiency opinions of CAR-T cell therapies in oncology were reviewed. Approaches to document QoL were identified and enriched with French HTA requests. Evolution of approaches changing and acceptability level over time were tracked.

## Results

Nine efficiency opinions assessing CAR-T cell therapies have been released in France since January 2019. QoL data were generally documented using data collected during pivot clinical trials. The review showed the following trends: while mapping QoL data using foreigner tariffs used to be accepted, only French tariffs are currently accepted; use of QoL data estimated in clinical trials did not raise major reservations, even when lacking robustness being estimated on very small sample sizes; utility scores estimated using EQ-5D-3L questionnaire were lower and therefore consistent with the general population's utility scores, whereas those estimated using EQ-5D-5L questionnaire were almost those of the general population's; and the importance of assigning utility decrements to CAR-T specific adverse events is increasing.

The efficiency opinions that were retained are presented in **Table 1.** The specificities of each opinion are presented in **Table 2.**

Chronologic evolution of reservations raised is presented in **Figure 1.**

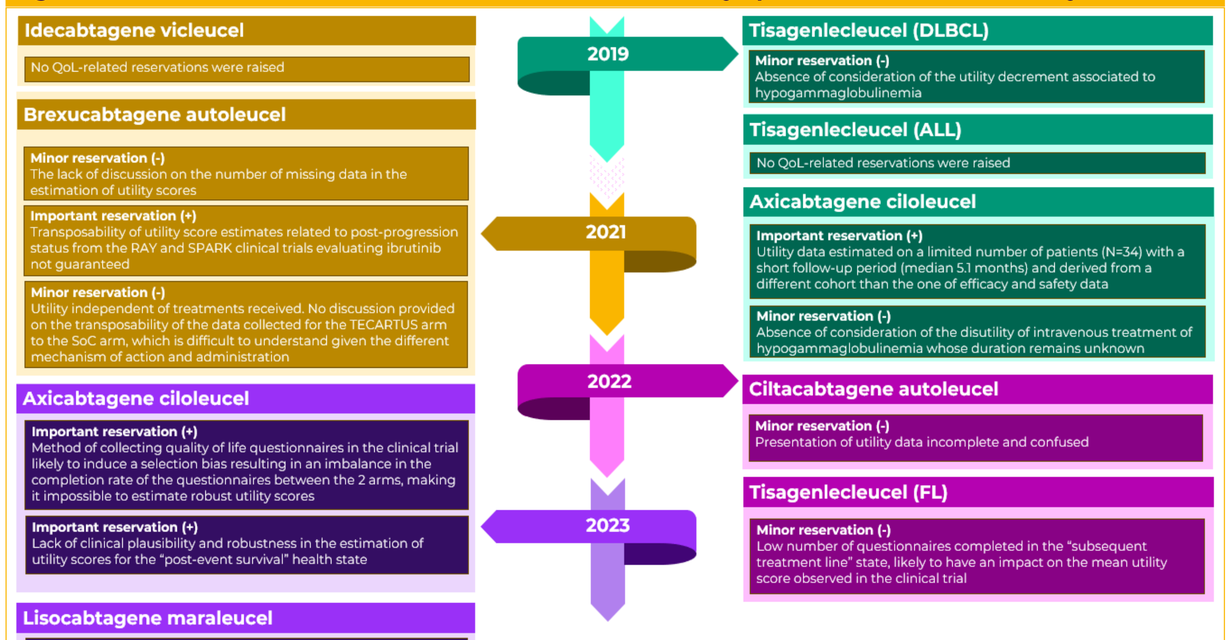
**Table 1. Efficiency opinions retained in the analysis**

| # | CID | Indication | CEESP opinion release date |
|---|---|---|---|
| 1 | Tisagenlecleucel (1) | Adults with R/R DLBCL after ≥2 lines of systemic therapy | 15 January 2019 |
| 2 | Tisagenlecleucel (2) | Children and young adults aged ≤25 years with refractory B-cell ALL, B-cell ALL relapsed after transplant, or B-cell ALL after second or subsequent relapse | 15 January 2019 |
| 3 | Axicabtagene ciloleucel (3) | Adults with R/R DLBCL and PMBCL after ≥2 lines of systemic therapy | 15 January 2019 |
| 4 | Brexucabtagene autoleucel (4) | Adults with MCL refractory or relapsed after ≥2 lines of systemic treatment, including treatment with a BTK inhibitor | 8 June 2021 |
| 5 | Idecabtagene vicleucel (5) | Adults with R/R MM with ≥3 previous treatments, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, whose disease progressed during the last treatment | 23 November 2021 |
| 6 | Ciltacabtagene autoleucel (6) | Treatment of adult patients with R/R MM who received ≥3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, whose disease progressed during the last therapy | 13 December 2022 |
| 7 | Tisagenlecleucel (7) | Adults with R/R FL after ≥2 lines of systemic therapy | 13 December 2022 |
| 8 | Axicabtagene ciloleucel (8) | Treatment of adult patients with R/R DLBCL and HGBCL within 12 months of completion of first-line chemoimmunotherapy | 29 August 2023 |
| 9 | Lisocabtagene maraleucel (9) | Treatment of relapsed DLBCL, HGBCL, PMBCL, or FL3B within 12 months of completion of first-line immunochemotherapy or refractory to first-line treatment | 19 December 2023 |

**Table 2. Specificities of each efficiency opinion retained in the analysis and associated outcomes**

| | 2019 | | | 2021 | | 2022 | | 2023 | |
|---|---|---|---|---|---|---|---|---|---|
| | Tisagenlecleucel (DLBCL) | Tisagenlecleucel (ALL) | Axicabtagene ciloleucel (DLBCL) | Brexucabtagene autoleucel | Idecabtagene vicleucel | Ciltacabtagene autoleucel | Tisagenlecleucel | Axicabtagene ciloleucel | Lisocabtagene maraleucel |
| **Source of QoL data** | JULIET clinical trial | ELIANA clinical trial | ZUMA-1 clinical trial | ZUMA-2 clinical trial/ use of utility decrement estimated from NICE assessment of ibrutinib | KarMMa clinical trial | CARTITUDE-1 clinical trial/ LocoMMotion study | ELARA clinical trial | ZUMA-7 clinical trial/ ZUMA-1 clinical trial | TRANSFORM clinical trial/ TRANSCEND NHL 001 clinical trial |
| **Questionnaire used** | SF-36 | EQ-5D-Y for patients aged 8 to 12 years, EQ-5D-3L for older patients | EQ-5D-5L | EQ-5D-5L collected, EQ-5D-3L used | EQ-5D-5L | EQ-5D-5L | EQ-5D-3L | EQ-5D-5L | EQ-5D-5L |
| **Number of questionnaires** | Not mentioned | Not mentioned | N=34 | N=68 (n=65 in PFS and n=3 in PPS) | Not mentioned | Not mentioned | N=255 (PFS: n=210, PPS: n=28, after initiation of a subsequent treatment: n=17) | Not mentioned for EFS, n=34 for PES | Not mentioned |
| **Mapping method/ assumptions made** | Algorithm-based mapping from SF-36 to EQ-5D-3L using the UK tariffs.<br>Utility scores for PFS and PPS were documented from JULIET trial.<br>Utility decrements related to AEs were documented from Tolley 2013.<br>Utility decrements associated to stem-cell transplant and to graft-versus-host disease were also considered.<br>➔ Recurrence of mapping algorithm was accepted, in the absence of EQ-5D data collected in the trial. Use of UK tariffs increased the uncertainty | Mapping of utility scores from ELIANA clinical trial using French tariffs<br>Utility decrements related to AEs were documented from Tolley 2013.<br>Utility decrements related to transplants were considered and documented from literature.<br>➔ Utility scores and sources were accepted | Algorithm-based mapping from EQ-5D-5L to EQ-5D-3L using the French tariffs<br>Utility scores were estimated based on the cohort 3 of the ZUMA-1 trial (N=34 patients treated with axi-cel). For the BS arm, it was assumed utility score was equal to the one in the axi-cel arm.<br>Utility score of general French population was applied for patients considered cured.<br>Utility decrements related to AEs were applied only to axi-cel arm.<br>➔The sample on which data were collected was assumed very small. Transferability of data was discussed, and absence of considering hypogammaglobulinaemia utility decrement was criticised | **Pre-progression state:** Mapping of EQ-5D-5L data from ZUMA-2 trial to EQ-5D-3L using the van Hout el al algorithm and applying French tariffs.<br>EQ-5D-5L utility scores were estimated using a mixed effect linear model<br>**Post-progression state:** Given the low number of observations in ZUMA-2 trial, a ratio calculated from ibrutinib NICE assessment was used.<br>Utility decrements related to AEs were considered only in the intervention arm based on NICE assessment of axi-cel and assumptions.<br>➔ Use of a ratio from studies that were not transferable to ZUMA-2 was criticised<br>➔ Low number of observations in PPS was criticised | Utility scores estimated based on French tariffs of EQ-5D-5L and using a MMRM, deriving from the KarMMa trial.<br>It is assumed that utility scores were health-state dependent.<br>Utility decrements related to AEs were considered and derived from the literature, including those related to CAR-T cell specific AEs.<br>➔ Data sources, methods used, and assumptions made were acceptable | **Pre-progression state:** Mapping method based on the French tariffs of EQ-5D-5L from the CARTITUDE-1 trial.<br>Utility scores estimated based on MMRM<br>**Post-progression state:** Utility decrement calculated in LocoMMotion study applied to utility score of pre-progression state.<br>Utility decrements related to AEs were considered and derived from the literature<br>➔The application of a utility decrement to derive a post-progression utility score given the low number of questionnaires was criticised<br>➔ The lack of transferability between CARTITUDE-1 and LocoMMotion was also highlighted | Mapping of EQ-5D-3L using the French tariffs from the ELARA trial.<br>Utility scores were estimated based on a calibrated generalised linear model.<br>Utility scores were dependent on the line of treatment.<br>Utility decrement related to AEs was considered and documented from the literature<br>➔ The number of questionnaires available post initiation of subsequent line of treatment was criticised | Utility scores estimated from ZUMA-7 based on French tariffs of EQ-5D-5L and derived from an MMRM.<br>Utility scores were dependent on health states.<br>Utility decrements related to AEs were considered and estimated from ZUMA-7 trial.<br>➔ The low number of questionnaires available in the post-event state was criticised<br>➔ The non-significant difference between pre-event and post-event utility scores was also highlighted | Utility scores estimated based on French tariffs of EQ-5D-5L.<br>**Event-free survival (EFS) state:** Mean utility score of patients at randomisation in the TRANSFORM trial, bounded by utility score of the general French population adjusted for age and sex (0.894).<br>Beyond 5 years, age- and sex-adjusted utility score of the general population patients were considered cured.<br>**Post-event survival:** Utility decrement estimated from TRANSCEND applied to EFS utility score, considered for first 5 years. Utility score of general population applied beyond.<br>➔The low number of questionnaires available in the was criticised<br>➔ Further statistical justification was required to justify the use of the general population utility score |
| **Utility scores used** | Health state / KYMRIAH arm: Utility score (SD)<br>PFS: 0.83 (0.14)<br>PPS: 0.71 (0.20) | Health state / KYMRIAH arm: Utility score (SD)<br>PFS: 0.76 (0.04)<br>PPS: 0.58 (0.07) | Health state (number of questionnaires) / Axi-cel arm: Utility score / Model input<br>PFS CR (N=25): 0.663 / 0.673<br>PR (N=11): 0.731<br>SD (N=13): 0.604<br>PPS N=5: 0.602 / 0.602 | Health state / Utility score<br>PFS: 0.803<br>PPS: 0.700 | Health state / Utility score<br>Pre-treatment utility decrement: -0.06<br>PFS: 0.803<br>PPS: 0.700 | Health state / Utility score<br>Pre-CAR-T injection: 0.8647<br>Progression free survival: 0.8891<br>Post-progression survival: 0.8194 | Health state / Utility score<br>Current line of treatment: 0.814<br>Subsequent line of treatment: 0.769 | Health state / Utility score<br>Pre-event: 0.892<br>Post-event: 0.874<br>AE: -0.026 | Health state / Utility score<br>Event-free survival (First 5 years): 0.894 (±0.003)<br>Event-free survival (Beyond 5 years): 0.894 (±0.003)<br>Post-event survival (First 5 years): 0.815 (NA)<br>Post-event survival (Beyond 5 years): 0.894 (±0.003) |
| **Level of reservation raised (if any)** | Minor | None | Minor/Important | Minor/Important | None | Minor | Minor | Important | Major |

**Figure 1. Evolution over time of reservations raised in efficiency opinions retained in the analysis**




- From 2019 to 2023, the choices made when documenting QoL in cost-effectiveness analyses evolved as well as their assessment method. It seems that low number of questionnaires remain a common limitation, and that applying QoL observed in the pivotal clinical trials seems to be the option with the safest outcomes in terms of reservations
- The use of the utility scores of the French general population raised several critiques. On that matter, Perthus et al. conducted a real-world study among French patients with lymphoma treated with CAR-T cell therapy aiming to assess their QoL. Despite its limitations, it showed that patients who experienced remission witnessed a significant QoL improvement from baseline at 6 months and that the QoL raw score reached the general population's normal values by 3 months (10)

## Conclusions

Documenting QoL in CEAs in France evolved over time in parallel with the guidelines' evolution showing willingness of manufacturers to meet the HAS expectations while using more robust methods.

Use of QoL data estimated in clinical trials seems to be the most accepted approach. QoL data collection should be a focus point since the elaboration of the clinical trial protocol. Further guidelines specific to innovative therapies could also leverage QoL data related uncertainty.

**Abbreviations:** AEs, adverse events; ALL, acute lymphoblastic leukaemia; BSC, best supportive care; BTK, Bruton tyrosine kinase; CAR-T, chimeric antigen receptor T-cell; CEA, cost-effectiveness analysis; CEESP, Commission on Environmental, Economic and Social Policy; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; EQ-5D-3L, EuroQol 5 dimensions 3 levels; EQ-5D-5L, EuroQol 5 dimensions 5 levels; EQ-5D-Y, EuroQol 5 dimensions Young; FL3B:, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; HTA, health technology assessment; MCL, mantle cell lymphoma; MM, multiple myeloma; MMRM, mixed model repeated measures; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PES, post-event survival; PMBCL, primary mediastinal B-cell lymphoma; PPS, post-progression survival; QoL, quality of life; R/R, relapsing or refractory; UK, United Kingdom

**References:** 1. KYMRIAH CEESP opinion (DLBCL indication). Saint Denis, France: HAS, 15 January 2019; 2. KYMRIAH CEESP opinion (ALL indication). Saint Denis, France: HAS, 15 January 2019; 3. YESCARTA CEESP opinion (DLBCL indication). Saint Denis, France: HAS, 15 January 2019; 4. TECARTUS CEESP opinion. Saint Denis, France: HAS, 8 June 2021; 5. ABECMA CEESP opinion. Saint Denis, France: HAS, 23 November 2021; 6. CARVYKTI CEESP opinion. Saint Denis, France: HAS, 13 December 2022; 7. KYMRIAH (FL) CEESP opinion. Saint Denis, France: HAS, 13 December 2022; 8. YESCARTA CEESP opinion. Saint Denis, France: HAS, 29 August 2023; 9. BREYANZI CEESP opinion. Saint Denis, France: HAS, 19 December 2023; 10. Perthus A et al. Hemasphere. 2024 May 27; doi:10.1002/hem3.72

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