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Evaluation of Health-Related Quality of Life (HRQoL) Among Patients Treated with Lifileucel After Progression on Immune Checkpoint Inhibitors (ICIs) and Targeted Therapies: Analyses from the C-144-01 Trial

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BACKGROUND & OBJECTIVE

- Treatment options for patients with advanced (unresectable or metastatic) melanoma are limited after progression on immune checkpoint inhibitors (ICI) and targeted therapies.[1]
- In addition to poor survival outcomes in post-ICI and targeted therapy settings[1], substantial symptom burden of advanced melanoma can have widespread impacts on patients' quality of life (QoL), which is often worsened by sleep problems, anxiety, stress pain and discomfort related to their disease condition.[2] A recent systematic review conducted by Bagge et al. (2022) assessing health-related QoL (HRQoL) from 16 published studies using the Functional Assessment of Cancer Therapy-Melanoma questionnaires showed decreasing assessment scores (i.e. decreased QoL) with increasing stages of disease.[2]
- Lifileucel is a one-time autologous tumor-infiltrating lymphocyte cell therapy[1,3], distinct from ICIs and targeted therapies which have recently transformed the treatment landscape for advanced melanoma.[4]
- Efficacy and safety of lifileucel for patients with advanced melanoma who are relapsed or refractory to ICIs was investigated in C-144-01 (NCT02360579) study, which is a global, multicenter, single-arm, Phase II trial.[5] Results from C-144-01 study demonstrated durable response benefits for lifileucel [5], and led to its approval by FDA[6] and Health Canada[7] for the treatment of adults with advanced melanoma who had progressed on ICIs and, if BRAF V600-positive, also on BRAF ± MEK inhibitors.
- In the C-144-01 study, the Full Analysis Set (FAS) which consisted of 153 patients pooled across Cohort 2 (n=66) and Cohort 4 (n=87) represented a heavily pre-treated patient population.[7] In the FAS, patients received a median of 3 prior lines of therapy (LoT) (mean: 3.29, range: 1-9).[8] In a subset of FAS where patients received lifileucel infusion within proposed dosing range specified in summary of product characteristics and manufactured at commercially-approved facilities (n=106), median number of prior LoT was also 3 (mean: 3.41, range: 1-9).[9]
- HRQoL data in advanced melanoma after progression on ICIs and targeted therapies remain scarce, as most published EQ-5D studies reflect relatively earlier-line settings or mixed populations compared to C-144-01 study population. Limited evidence on the HRQoL data of heavily pretreated advanced melanoma patients from clinical trial or real-world settings underscores the need to characterize HRQoL outcomes for this population and inform economic evaluations for potential health technology assessments.
- The primary objective of this study was to perform a descriptive analysis of HRQoL data collected in the C-144-01 trial and to derive EQ-5D utility values targeted for the UK population from EORTC questionnaires using a published algorithm. The secondary objective of this study was to explore differences in HRQoL data across key clinical subgroups.

METHODS

- Patients' HRQoL was assessed in the C-144-01 study using the EORTC questionnaire as an exploratory endpoint.[8] Because the EQ-5D instrument was not collected directly in the study, a validated mapping approach was needed to estimate EQ-5D-3L utilities from the existing data.
- Per trial protocol, data were not collected for patients who 1) Progressed or started a new anticancer therapy 2) Did not receive full lifileucel regimen.
- In line with NICE Technical Support Document 10[9] which provides guidance on the mapping of HRQoL data from clinical trials when direct utility values are unavailable, a literature review was conducted to identify validated methods for mapping data to EQ-5D-3L or EQ-5D-5L scores. Selection criteria included:
  - Availability of published coefficients for direct application
  - Use of validated regression techniques with a preference for ordinary least square regression models
  - Inclusion of cancer or severe disease populations.
  - Applicability to the available dataset where models requiring age, sex, additional demographics or biomarker data were excluded.
- Based on the availability of model coefficients, strength of validation and overlap with the target UK population, three published algorithms were evaluated for the mapping between the data and EQ-5D scores: 1) Kim et al. (2012): Calibrated using a Korean cancer patient cohort[10], 2) Versteegh et al. (2012); Calibrated using a Dutch cohort with multiple myeloma and non-Hodgkin lymphoma[11], 3) Wojciechowski et al. (2023): Calibrated using a French cohort with a rare hematological disease.[12]
- The analysis included 417 observations in total from 152 patients from the FAS representing nearly the entire FAS.[8] Each patient included in the analysis of HRQoL data had at least one completed assessment. Among all observations, 405 belonged to 146 patients with a baseline assessment.
- A significant proportion (57.9%) of patients had only one or two assessments available and the average time between visits with assessments was 131 days [8] limiting the ability to reliably characterize changes in HRQoL over time. Despite the sparsity of data causing an inability to fully analyze a time trend of the scores, no imputation was performed for missing data.
- The mapping algorithms used by Versteegh et al. (2012), and Wojciechowski et al. (2023) were developed using cohorts with hematological diseases with limited compatibility for the UK tariffs and prone to generating clinically implausible (i.e. negative) EQ-5D scores on a broader spectrum that were less consistent with the published benchmarks in advanced melanoma than the algorithm used by Kim et al. (2012). Therefore, Kim et al. (2012) algorithm was selected for the mapping of data from the trial. The output from this algorithm was EQ-5D-3L scores.
- Descriptive statistics (mean, median, standard deviation, range) were calculated for all mapped utilities. Subgroup analyses compared utilities by response status (responder vs non-responder) and by number of prior LoT (≤ 2 vs > 2; ≤ 3 vs > 3; ≤ 4 vs > 4; ≤ 5 vs > 5). Box-and-whisker plots were generated to display distributions and 95% confidence intervals (CIs), while histograms were used to illustrate the whole spectrum of the mapped utility distributions.

RESULTS

- The mean and median utility for the entire population used in this analysis were 0.870 (95% CI 0.862–0.878) and 0.884, respectively; with a corresponding range 0.468–0.994. The distribution of the mapped EQ-5D scores was left-skewed, with approximately 75% of the values >0.80.
- Stratified by clinical response, mean EQ-5D utilities were 0.873 (95% CI: 0.858-0.889) and 0.867 (95% CI: 0.851-0.882) for responders and non-responders, respectively.
- Cumulative prior therapy exposure was associated with slightly lower HRQoL. Mean EQ-5D scores among patients with ≤ (2, 3, 4, 5) prior LoT were 0.902 (95% CI: 0.886-0.919), 0.884 (95% CI: 0.871-0.897), 0.878 (95% CI: 0.866-0.889) and 0.874 (95% CI: 0.862-0.885), respectively.

Table 1: Number of Observations in Subgroup Analyses

Subgroup	Number of Observations (n)
Responder	194
Non-Responder	223
≤ 2 Prior LoT	141
> 2 Prior LoT	276
≤ 3 Prior LoT	278

Subgroup	Number of Observations (n)
> 3 Prior LoT	139
≤ 4 Prior LoT	328
> 4 Prior LoT	89
≤ 5 Prior LoT	364
> 5 Prior LoT	53

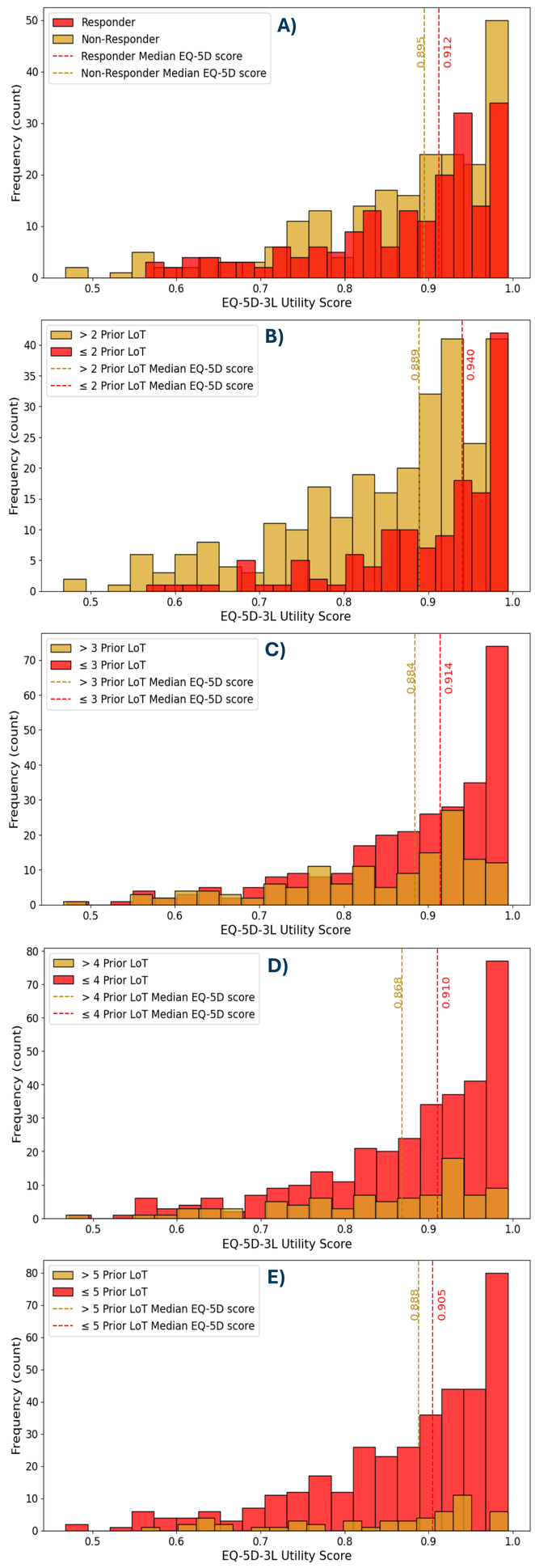
- When patients were classified with respect to prior LoT, distributions of observations between the contrasts displayed a higher imbalance as cumulative number of prior LoT increased. For example, while there were 276 assessments for patients with >2 prior LoT, there were only 53 assessments for patients with >5 prior LoT. This shrinkage in the sample size of observations led to wider 95% CIs around the mapped EQ-5D scores (**Figure 1 and 2**).
- In the absence of published utility scores for heavily pretreated advanced melanoma patients in the post-ICI and targeted therapy settings, the mapped EQ-5D scores were compared to the utility values obtained from previous NICE appraisals assessing the long-term economic value of ICIs and targeted therapies in advanced melanoma published between 2011 and 2019. Across 10 appraisals (TA268, TA269, TA319, TA321, TA357, TA366, TA384, TA396, TA400 and TA562)[14-23] the average utility score for patients in second line advanced melanoma was estimated as 0.77 (95%CI: 0.409 – 0.983) with a range 0.68-0.84. Similarly, across 6 appraisals (TA268, TA269, TA321, TA357, TA396 and TA562) the average utility score for patients in third or later line advanced melanoma was estimated as 0.67 (95%CI: 0.385 – 0.895). Across the published appraisals used to generate benchmark utility scores, in the trials supporting TA268 and TA319, HRQoL data were collected using non-EQ-5D instruments.
- Across all treated patients and subgroups with clinical relevance, regardless of the prior LoT and response status, average mapped EQ-5D scores for lifileucel patients were consistent or higher than the average utility scores in previously treated advanced melanoma obtained from previous NICE appraisals.

DISCUSSION & LIMITATIONS

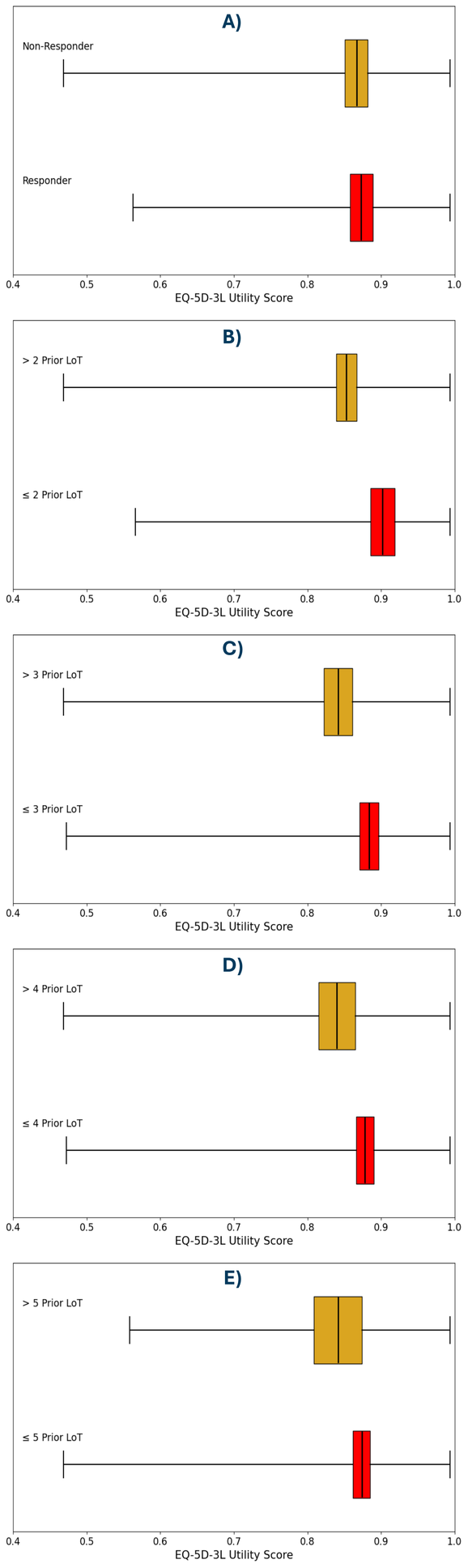
- This descriptive analysis provides one of the first detailed assessments of HRQoL outcomes in patients with heavily pretreated advanced melanoma refractory to both ICIs and targeted therapies and contributes to the basis for understanding HRQoL trends in advanced melanoma.
- Sources of inconsistencies contributing to the sparsity of the HRQoL data in the trial included not always collecting surveys at baseline due to protocol misunderstandings, allowing patients to refuse participation in the questionnaires, not ensuring patients answered all questions when given the assessment. Therefore, missingness of HRQoL data was not random in the study which could affect the statistical reliability of mapped utility estimates.
- The HRQoL data was only an exploratory outcome of the study, but its collection was not designed with the same rigor as primary endpoint or efficacy outcomes from the study. Therefore, collected data were not completely suitable to dress economic evaluation.
- The candidate and selected models mapping the data to EQ-5D scores were based on populations with differing demographics and disease characteristics (e.g. Korea, France) than the UK. Therefore, robustness of the mapped scores and their appropriateness as a direct input in economic modelling should be approached with caution due to potential confounding effects from the study populations used to derive the mapping algorithms.
- Mapped EQ-5D scores reflect patients' HRQoL only for a limited duration after infusion as per trial protocol HRQoL data were collected only until progression/subsequent anti-cancer therapy. For a more thorough and longitudinal assessment of lifileucel's impact on patients' QoL, HRQoL data after progression/subsequent anti-cancer therapy would be needed.

RESULTS (continued)

Figure 1. Distribution of mapped EQ-5D-3L scores with respect to response outcomes (Panel A) and prior LoT (Panels B-E).



Figures 2. Summary (95% CI and range) of mapped EQ-5D-3L scores with respect to response outcomes (Panel A) and prior LoT (Panels B-E).



LoT: Line of Therapy

CONCLUSIONS

- For previously treated advanced melanoma patients receiving lifileucel, pre-progression EQ-5D utilities were successfully derived from the collected data using a validated mapping algorithm. The selected model generated a range of clinically plausible, stable estimates that were consistent with published utility scores for second or later line advanced melanoma, reassuring external validity.[14,18,19,20]
- Subgroup analyses revealed clinically expected differences, with slightly higher utilities in responders and in patients with fewer prior LoT, reflecting the relationship between disease control and improved QoL.
- Results indicate that lifileucel treatment does not only provide durable clinical benefit but may also help maintain or improve QoL in patients with advanced melanoma who have progressed on multiple prior therapies.
- Sparsity of data and single-arm nature of C-144-01 study may limit the generalizability of the findings to broader heavily pretreated advanced melanoma populations, emphasizing the value of additional data from confirmatory studies to verify appropriateness of mapped EQ-5D scores in economic evaluations.

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