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Health-state utilities in long-term advanced melanoma survivors comparable with the general population

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Abstract

Background Checkpoint inhibitors have been shown to substantially improve the survival of patients with advanced melanoma. With this growing group of survivors treated with immunotherapies, assessing their health-state utilities is essential and can be used for the calculation of quality-adjusted life years and for cost-effectiveness analyses. Therefore, we evaluated the health-state utilities in long-term advanced melanoma survivors.

Methods Health-state utilities were evaluated in a cohort of advanced melanoma survivors 24–36 months ($N=37$) and 36-plus months ($N=47$) post-ipilimumab monotherapy. In addition, the health-state utilities of the 24–36 months survivor group were assessed longitudinally, and utilities of the combined survival groups ($N=84$) were compared with a matched control population ($N=168$). The EQ-5D was used to generate health-state utility values, and quality-of-life questionnaires were used to establish correlations and influencing factors of utility scores.

Results Health-state utility scores were similar between the 24–36 months'- and the 36-plus months' survival group (0.81 vs 0.86; $p=.22$). In survivors, lower utility scores were associated with symptoms of depression ($\beta=-.82$, $p=.022$) and fatigue burden ($\beta=-.29$, $p=.007$). Utility scores did not significantly change after 24–36 months of survival, and the utilities of survivors were comparable to the matched control population (0.84 vs 0.87; $p=.07$).

Discussion Our results show that long-term advanced melanoma survivors treated with ipilimumab monotherapy experience relatively stable and high health-state utility scores.

Keywords Health-state utilities · EQ-5D · Quality-of-life · Advanced melanoma survivors

Background

The survival of patients with advanced melanoma (unresectable stage III and stage IV disease) was traditionally limited. However, with the introduction of immunotherapy (anti-CTLA-4 and anti-PD-1 monoclonal antibodies), survival rates have substantially increased and instigated a momentous shift in the treatment paradigm [1–3]. With the widespread use of immunotherapy in daily clinical practice, a substantial number of patients with advanced melanoma are currently experiencing long-term survival [4, 5].

While the impact of immunotherapy on health-related quality of life (HRQoL) outcomes during the induction phase has been evaluated in many trials, only a few studies have evaluated HRQoL outcomes after initial treatment [6, 7]. In comparison to the general population, long-term survivors (> 24 months post-treatment) reported lower physical, emotional, and cognitive functioning, along with more financial difficulties than the general population [7–10]. These impairments and symptoms will likely affect the health-state utilities of long-term advanced melanoma survivors treated with immunotherapy.

Health-state utilities (HSUs) present survivors' level of physical, psychological, and social functioning after cancer treatment and enable comparisons of the burden of disease across conditions [11]. Investigating HSUs is important as patient-level utility data are used to determine the HRQoL

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benefits provided by immunotherapy, which are subsequently used in cost-effectiveness analyses when evaluating the cost of immunotherapy per quality-adjusted life year [12]. Previous studies investigating HSUs during immunotherapy in advanced melanoma patients showed that utility scores ranged from 0.70 to 0.80 [13–16]. However, no data on health-state utilities are available for long-term advanced melanoma survivors after treatment, despite the likelihood that treatment-induced impairments (decreased physical functioning) and symptoms (fatigue, mental ill health) will continue to affect their HSUs [7, 17]. Moreover, whether and to what degree survivors' health might improve or stabilize long-term after treatment remains unknown. Currently, 26–30% of advanced melanoma patients treated with ipilimumab monotherapy will experience survival beyond 5-years, and 52–60% of patients treated with ipilimumab plus nivolumab will experience survival beyond 5-years. With this group of long-term advanced melanoma survivors rapidly increasing, investigating their health-state utility is vital to identify long-term challenges that can be addressed in survivorship care and inform reimbursement decisions for immunotherapy [18].

We hypothesize that long-term advanced melanoma survivors can still experience improvement in their state of health beyond 24 months post-treatment. Therefore, we evaluated health-state utility scores among advanced melanoma survivors. Further, potential determinants and changes over time of HSUs were assessed, along with a comparison of HSUs scores of long-term advanced melanoma survivors with matched controls without cancer.

Methods

Patients

In total, 14 melanoma centers in the Netherlands and one academic center in Belgium participated in this cohort study. Survivors eligible for the study were: (1) treated with at least one cycle of ipilimumab for advanced melanoma (unresectable stage III/IV); (2) not diagnosed with recurrent or progressive systemic disease at enrollment; (3) survived at least 24-months after the last administration of ipilimumab and; (4) aged at least 18 years at the start of ipilimumab treatment. The medical specialist informed potentially eligible survivors about the study. Survivors interested in participating in the study provided signed informed consent. Questionnaires were mailed to the survivors between February 2017 and June 2018. The participating survivors were divided into the following two groups based on their time since completing ipilimumab treatment: 24–36 months' survival group and the 36-plus months' survival group. Based on survival curves of previous melanoma studies, a threshold of 36 months was used to compare a population at risk of recurrence with a population that likely will experience long-term remission [19]. In addition, a control population of 2671 persons without cancer from the general population was recruited from the 'Patient-Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship' (PROFILES) registry to individually match with survivors based on gender, age, and education [20]. All participants provided verbal and written consent, and the institutional review board approved this study (METC16.0634). According to Dutch law, this study did not require approval from an Ethics Committee, and the primary study results have already been published [7].

Materials

Outcome measurements

The *EuroQol five-dimensions—5-level* (EQ-5D) questionnaire and the complementary *EuroQoL Visual Analogue Scale* (EQ-VAS) were used to assess HSUs in long-term advanced melanoma survivors [21]. The EQ-5D is a standardized 5-dimensional multi-attribute utility questionnaire that measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each item is scored on a 5-point Likert scale, ranging from 0 (no problems) to 5 (extreme problems). The answers to the EQ-5D are subsequently converted into EQ5D-index scores, with index scores ranging from 0 (deceased) to 1 (perfect health). The supplementary EQ-VAS is used to measure survivors' self-rated health on a scale between 0 ("The worst health you can imagine") and 100 ("The best health you can imagine"). The EQ-5D has shown to be a psychometrically robust and straightforward way to measure the generic health-related quality of life [22].

As previous studies have shown that mental ill health and fatigue likely affect HSUs [7, 17], we also asked patients to fill out the three items of the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) fatigue subscale [23], the Hospital Anxiety and Depression Scale (HADS) [24] and the Cancer Worry Scale (CWS) [25], in addition to the EQ-5D items. These questionnaires are widely used and validated instruments to measure quality of life, anxiety, depression, and fear of recurrence in oncological hospital contexts [23–25]. The scores of each questionnaire were calculated according to their respective scoring manuals.

Demographic and clinical characteristics.

Sociodemographic data (age, education, and marital status) were obtained by five self-reported questions. Comorbidities

were assessed with the Self-administered Comorbidity Questionnaire (SCQ), a generic questionnaire with 14 common medical conditions [26]. Clinical data (diagnosis, stage of disease, and treatment modalities received) were obtained from the medical records.

Procedure

All participants received the survey (containing the previously mentioned questionnaires) at least 24-months after ipilimumab treatment. Survivors without evidence of disease in the 24–36 months' survival group received two follow-up surveys (one after 12-months and one after 24-months post-completion of the first survey), to assess in a longitudinal analysis the 24-months' trajectory of HSU scores in the 24–36 months' survival group. Survivors in the 36-plus months' survival group received one survey. In addition, we matched members of the non-cancer control population with survivors on a 1:2 ratio (1 patient paired with 2 controls) based on the following demographic characteristics: year of birth, gender, and education (low = no or primary school, medium = lower general secondary education or vocational training, high = pre-university education or high vocational training or university). The control population completed the same questionnaires as the survivor population.

Analysis

We performed statistical analyses based on data suitability, appropriate assumption checks (such as the Shapiro–Wilk test, Q–Q plot, and the residuals vs predicted plot to check the normality assumption [27, 28]), and corrective measurements in case of assumption violations. Interpretation of endpoint values was based on statistical significance ($p = < 0.05$), and interpretation on clinical relevance was based on questionnaire-guideline based *Minimal important differences* (MIDs) of the EQ-5D (0.08 for the EQ5D-index, and 7-points for the EQ-VAS) [21].

Welch's *t*-tests (or Wilcoxon rank sum tests in case the data violated the normality assumption) were used to compare EQ5D-index and EQ-VAS scores between both survivor groups, and between all survivors and the control population [29]. Furthermore, a multivariable regression model was constructed to investigate the association of age, gender, education, fear of recurrence, anxiety, depression, and fatigue with HSUs in survivors. The backward method for this model was used to minimize suppressor effects [30]. We used EQ-VAS scores as the outcome measurement for HSUs in the multiple regression, since the EQ-VAS provides a direct valuation of survivors' state of health, whereas EQ5D-index scores are converted and weighted based on general population samples [31]. In addition, a mixed-effects model was created to examine potential changes over time in advanced melanoma survivors' state of health 24–36 months post-ipilimumab treatment. The EQ5D-index and EQ-VAS scores were measured at two additional time points (12-months and 24-months post-initial HSU assessment). A single random intercept was considered in the mixed effect model with a grouping variable, the patients' id, to account for repeated measurement of the same patient. No other covariates except time were used in the model. All analyses were performed using R studio version 1.4.1103, and the mixed-effects model was computed with the lme4 package [32, 33]. Lastly, for matching survivors with controls, propensity score matching using the R package Matching (4.10–8) was used [34].

Results

Description of survivor and control population characteristics

Of 106 invited long-term survivors of advanced melanoma, 84 (79%) survivors returned the EQ-5D questionnaire. All survivors were diagnosed with unresectable stage III/IV melanoma, of whom 13 survivors (15%) had brain metastasis at the start of ipilimumab treatment. The majority of survivors had at least one comorbidity (58%). Most survivors received previous systemic therapy before ipilimumab treatment (64%), but this was mainly in the 36-plus months' survivor group (81%) compared to the 24–36 months' survivor group (35%). This difference between both groups was due to adjustments in the European Medicines Agencies (EMA) guidelines [35]. The mean time from the last dose to survey completion for survivors was 49 months (IQR: 29–69 months). Baseline demographics and treatment characteristics are summarized in Table 1.

Health-state utilities in long-term advanced melanoma survivors

Both the EQ5D-index and the EQ-VAS data violated the normality assumption. Therefore, Wilcoxon rank sum tests were used.

Of the 84 survivors included in the analysis, 37 survivors were included in the 24–36 months' survival group and 47 survivors were included in the 36-plus months' survival group). The difference of EQ5D-index scores between 24–36 months survivors ($\mu = 0.81$ $SD = 0.17$) and 36-plus months' survivors ($\mu = 0.86$ $SD = 0.12$) were not clinically relevant (μ diff = − 0.05) nor statistically significant ($p = 0.22$). As for the EQ-VAS scores, the mean difference between both groups ($\mu = 78$ $SD = 15$ vs $\mu = 80$ $SD = 14$) also showed to not be clinically relevant (μ diff = − 1.7) nor significantly significant ($p = 0.61$) (see Table 2).

Table 1 Sociodemographic data and treatment characteristics

	24–36 months' survival group $N=37$	36-plus months' survival group $N=47$
Gender		
Male	22 (59%)	27 (57%)
Female	15 (41%)	20 (43%)
Age		
Mean, SD	63, 15	65, 13
Range	23, 87	29, 86
Education		
Low	2 (6%)	1 (2%)
Middle	26 (70%)	31 (66%)
High	9 (24%)	15 (32%)
Cumulative dose IPI (mg)		
Median	946	1040
range	(488–13,000)	(366–176,000)
Line of treatment		
First	24 (65%)	9 (19%)
Second	9 (24%)	24 (51%)
Third	4 (11%)	13 (28%)
Fourth	0 (%)	1 (2%)
Dose per kilogram		
3 mg/kg dose	33 (89%)	38 (81%)
10 mg/kg dose	3 (8%)	8 (17%)
Unknown	1 (3%)	1 (2%)
Comorbidities		
0	14 (38%)	21 (44%)
1	13 (35%)	14 (30%)
>2	10 (27%)	12 (26%)

IPI ipilimumab, *N* number of individuals, *SD* standard deviation

Factors associated with utility scores in long-term advanced melanoma survivors

While the normality assumption was violated for the EQ-VAS, the Q-Q plot of the model showed no deviations, and the residuals vs predicted plot showed no trend. It was therefore assessed that the model was fairly robust against the violation of the normality assumption (both plots can be found in the supplementary material) [36].

The multivariate regression analyses showed that a two-factor model gave the best fit, explaining approximately 25% of the variance of HSUs in long-term advanced melanoma survivors ($p<0.001$). The results showed that two factors were significantly associated with HSU scores, which were fatigue ($\beta=-0.29$, $p=0.007$) and depression ($\beta=-0.82$, $p=0.022$). Thus, survivors who reported higher levels of fatigue or more depression-related issues scored lower on the EQ-VAS (a full overview of the results is provided in the supplementary material).

Utility scores in advanced melanoma survivors over time

Although the normality assumption was violated for both the EQ5D-index and EQ-VAS data, mixed-effects model estimates are generally robust to these violations [37, 38]. Consequently, we continued with the analysis.

Of the 40 survivors 24–36 months post-treatment, 30 completed the first follow-up questionnaire (75%), and 20 (50%) completed the second follow-up questionnaire after 12 and 24-months of initial assessment, respectively (reasons for drop-out can be found in the supplementary information).

The scores on the EQ5D-index and EQ-VAS demonstrated that survivors' state of health 24–36 months post-treatment did not change over time on a statistically significant or clinically relevant scale (see Table 3). As for the random effect of the model, the high intraclass correlation coefficient values (0.75 and 0.74) showed that interpersonal

Table 2 Health-state utilities of long-term advanced melanoma survivors

Characteristics	24–36 months' survival group	36-plus months' survival group	Difference	*95% CI*	*P* -value
EQ5D-index					
N	37	47			
Mean, SD	0.81, 0.17	0.86, 0.12	− 0.05	− 0.12, 0,01	0.22
Range	0.43, 1.00	0.47, 1.00			
Missing	3	2			
EQ-VAS					
N	37	47			
Mean, SD	78, 15	80, 14	− 1.7	− 8.2, 4.8	0.61
Range	40, 100	30, 100			
Missing	3	2			

CI confidence interval, *N* number of individuals, *SD* standard deviation, *VAS* EuroQoL Visual Analogue Scale

Table 3 Linear Mixed Model on EQ5D-index and VAS scores

EQ5D-index *assessment time points*	Estimates	*95% CI*	*P* -value
24–36 months (*N* = 40)	0.83	0.78–0.89	< 0.001
36–48 months (*N* = 30)	− 0.00	− 0.08–0.05	0.826
48–60 months (*N* = 20)	+ 0.04	− 0.09–0.05	0.076
Anova test			0.12
Random effect			
σ2	0.02		
ICC	0.75		
General			
N	30		
EQ-VAS *assessment time points*	Estimates	95% CI	*P* -value
24–36 months (*N* = 40)	78.89	73.29–84.50	< 0.001
36–48 months (*N* = 28)	− 0.39	− 4.42–3.63	0.848
48–60 months (*N* = 17)	+ 1.39	− 3.26–6.04	0.549
Anova test			0.29
Random effect			
σ2	169.88		
ICC	0.74		
General			
N	28		
Observations	75		

CI confidence interval, *ICC* intraclass correlation coefficient, *N* number of individuals, *SD* standard deviation, *σ2* variance, *EQ-VAS* EuroQoL Visual Analogue Scale

differences between the long-term advanced melanoma survivors explained most of the variance in the model.

Comparison of long-term advanced melanoma survivors with matched controls

Wilcoxon rank sum tests were used in this analysis, as EQ5D-index and EQ-VAS data showed non-normal distributions.

Of the 2671 eligible participants of the control population, 168 participants were individually matched with a total of 84 long-term advanced melanoma survivors. Differences of EQ5D-index scores between controls ($\mu = 0.87$ $SD = 0.15$) and long-term advanced melanoma survivors ($\mu = 0.84$ $SD = 0.15$) were neither statistically significant ($p = 0.07$) nor clinically relevant (μ diff = 0.03). As for the EQ-VAS, scores of the controls ($\mu = 76$ $SD = 18$) were significantly higher than those of the survivors ($\mu = 69$ $SD = 24$) on a statistically significant scale ($p = 0.02$) and close to a clinically relevant scale (μ diff = 6.9) (see Table 4).

Discussion

The present study provides new information on the health-state utilities of a new group of long-term cancer survivors after the first-generation immunotherapy. Due to this rapidly increasing survivor population, examining their health status is paramount to identify challenges that can be addressed in survivorship care and inform decisions on immunotherapy reimbursement. The EQ-5D utility scores found in this cohort were surprisingly high, as their mean

Table 4 Health-state utilities of controls vs survivors

Characteristic	Controls *N* = 168	Survivors *N* = 84	Difference	*95% CI*	*P* -value
VAS					
Mean, SD	76.4, 18	69.5, 24	6.9	1.0, 13	0.022
EQ-5D-INDEX					
Mean, SD	0.87, 0.15	0.84, 0.15	0.03	0.00, 0.07	0.074

CI confidence interval, *N* number of individuals, *SD* standard deviation, *VAS* EuroQoL Visual Analogue Scale

utility scores (0.84) are relatively similar to utility scores of stage 0-IA melanoma patients (0.81) [16], and comparable to the matched control population (0.87). The absence of statistically and clinically relevant differences in the health-state utilities between survivors and controls may reflect the adaptation of their new health situation, known as 'response shift', since survivors have a poorer health-related quality of life than the control population [7] [39]. Of note, the comparison between survivors' EQ-VAS scores and controls did show a statistically significant difference. An alternative explanation can be that this survivor population initially had a better health condition before and after treatment than the average advanced melanoma survivor. For example, the percentage of survivors in this population with brain metastases at diagnosis (15%) was lower than the average rate of brain metastases at diagnosis for this patient population based on clinical literature (approximately 20%) [40] [41]. Furthermore, the first study regarding this survivor population showed that the number of survivors with at least one comorbidity was lower than the control population [7, 40, 41]. Interestingly, symptoms of depression and fatigue were important correlated factors with lower self-reported utilities on the EQ-VAS scores. Although fatigue is one of the most commonly reported symptoms in cancer survivors, this study highlights the need for continued survivorship care to enhance the quality of life after treatment.

In this study, contrary to our hypothesis, the results show that long-term advanced melanoma survivors are unlikely to experience appreciable improvement or deterioration of their state of health 24 months after treatment. This observation is in line with the results of the study by Dixon et al., in which melanoma patients treated with interferon-alpha showed increased EQ-5D scores from baseline (0.76) to 24 months post-therapy (0.83) [12, 42]. Even though no comparable data is available that measures health-state scores beyond 24 months, our results indicate that 24 months after treatment, the health state of advanced melanoma patients stabilizes.

Limitations of this study are the sole inclusion of long-term advanced melanoma survivors with sufficient understanding of the Dutch language and the absence of data about why invited survivors did not want to participate in the study, creating a potential selection bias. Furthermore, results should be interpreted with caution due to the relatively small sample size and the substantial disparity between survivors regarding prior lines of treatment received. The strengths of this study include the near-complete national coverage of all melanoma centers in the Netherlands (14 of the 15), the high response rate of participants, and the age-, gender and education-matched control population.

In conclusion, the main findings of this study reflect that long-term advanced melanoma survivors experience relatively high and stable HSUs 24-months post-ipilimumab. Furthermore, symptoms of depression and fatigue show to be important targets to address in survivorship care for this group, as both factors were associated with lower HSUs. While the present study is based on the first group of long-term advanced melanoma survivors after immunotherapy, our results should be corroborated in a larger international study, including more long-term survivors who received standard of care immunotherapy. Nevertheless, the present study provides a novel set of utility scores in a new group of survivors that can be used for further cost-effectiveness analyses in subsequent melanoma research.

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Author contributions MDE, LVP, RT and AHB designed the study and wrote the study protocol. AR, MJB, AJE, GAH, JWBG, MJBA, EK, DP, GV, AAV, KMPS, EAR, BN and CUB recruited patients and collected data. AHB and LVP coordinated the study. MDE, AHB and RT did the statistical analyses. MDE, LVP, VR and AHB wrote the first draft of the manuscript. All authors interpreted the data, reviewed the manuscript, and approved the final version.

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Data availability The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests A.H. Boekhout received a research grant from Bristol-Myers Squibb for this study. A. Rogiers: Bristol-Myers Squibb and Merck Sharp & Dome (consulting and advisory board). M. Boers-Sonderen: Bristol-Myers Squibb, Pierre Fabre, and Roch (advisory board). A.J.M. van den Eertwegh: Sanofi, Bristol-Myers Squibb and Roche (study grant); MSD Oncology, Roche, Pfizer, and Sanofi (travel expenses); Bristol-Myers Squibb (honoraria); Bristol-Myers Squibb, MSD Oncology, Amgen, Roche, Novartis, Sanofi, Pfizer, Ipsen, and Merck (advisory board). G.A. Hospers: Bristol-Myers Squibb, Amgen, Roche, Pfizer, Novartis, MSD (consulting and advisory board) and received research grants from Bristol-Myers Squibb and Seerave. J.W.B. de Groot: Bristol-Myers Squibb, MSD Oncology, Novartis, Pierre Fabre and Servier (consulting and advisory board). M.J.B. Aarts: Bristol-Myers Squibb, Merck Sharp & Dome, Pfizer, Pierre Fabre, Astellas, Ipsen and Novartis (consulting). K.P.M. Suijkerbuijk reports personal fees as a consult advisor (paid to institution) advisory role: Roche, Novartis, MSD, BMS, Pierre Fabre (all paid to institution). H.W. Kapiteijn: Amgen, Bristol-Myers Squibb, Novartis, Roche, Merck, Pierre-Fabre, EISAI, Bayer and Genzyme-Sanofi (consulting and advisory board); and received a research grant from Bristol-Myers Squibb. A.A.M. van der Veldt: Bayer (travel expenses) and Bristol-Myers Squibb, Merck Sharp & Dome, Roche, Novartis, Pierre Fabre, Pfizer, Sanofi, Eisai and Ipsen (consulting and advisory board). K.J. Jansen is working at Bristol-Myers Squibb. B. Neyns: Bristol-Myers Squibb, Merck Sharp & Dome, Novartis, and Roche (honoraria), and

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Ethical approval The study was approved by the institutional review board of the NKI (METC16.0634) and meets the institutional review board standards.

Consent to participate This study was performed in accordance with the Declaration of Helsinki.

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