Research Article

Nonprogression with avelumab treatment associated with gains in quality of life in metastatic Merkel cell carcinoma

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Aim: To assess the association between tumor response and health-related quality of life (HRQoL) in patients with metastatic Merkel cell carcinoma treated with the anti-PD-L1 avelumab. **Materials & methods:** Phase II single-arm trial (NCT02155647) data of 88 patients were analyzed. Correlations between percentage reduction in tumor size and change from baseline in Functional Assessment of Cancer Therapy – General (FACT-G), FACT – Melanoma (FACT-M) and EuroQol-5 Dimension scores were calculated. HRQoL and utility by tumor response (per the Response Evaluation Criteria In Solid Tumors version 1.1) was estimated. **Results:** Tumor shrinkage correlated positively with patients' change from baseline in the FACT-M total (0.364 [95% CI: 0.050; 0.607]) and subscale scores. Differences in HRQoL and utility between nonprogressive disease and progressive disease were clinically relevant. **Conclusion:** In patients with metastatic Merkel cell carcinoma, nonprogression during treatment with avelumab correlated with gains in HRQoL.

Merkel cell carcinoma (MCC) is a rare, very aggressive primary cutaneous carcinoma of the skin [1]. In Europe, a crude incidence rate of 0.19 per 100,000 between 2000 and 2007 was reported [2]. In the USA, the incidence rate reported in the most recent analysis of Surveillance, Epidemiology, and End Results data was 0.79 per 100,000 in 2011 [3]. The disease-associated mortality of MCC is estimated to be between 33 and 46%, reflecting the aggressiveness of the tumor [4,5].

Standard of care across all treatment guidelines is surgery in stages I–III of the disease. MCC is considered to be a chemotherapy-sensitive tumor, and chemotherapy is indicated for the treatment of stage IV MCC [6]. However, the effectiveness of chemotherapy in terms of survival benefit is difficult to assess from the literature [7]. Although chemotherapy may result in initial tumor regression, retrospective studies have shown overall survival to be less than 10 months and patients experience significant toxic effects [8–14]. No current consensus exists on the most effective treatment strategy, particularly in advanced tumor stages; however, there is now evidence indicating immunotherapy to be a promising approach in the treatment of MCC [15]. In that respect, PD-L1 has been shown to play a key role in the reactivation of the immune response against multiple cancers [16] and may provide a feasible target for intervention.

Avelumab is a fully human IgG1 monoclonal antibody targeting and blocking PD-L1 interaction with its receptor PD-1 [15]. In the primary analysis of a single-arm, Phase II study, JAVELIN Merkel 200 (Part A, 2L+ metastatic MCC [mMCC] patients), avelumab therapy resulted in an objective response rate of 33% [17]. The proportion of

patients who were progression-free at 6 months was 40%, which is higher than observed with chemotherapy as reported in a retrospective review of stage IV MCC patients [9]. Avelumab has recently been approved by the US FDA and the European Commission for the treatment of mMCC and is the first drug with an approved indication in this tumor type [18].

To date, there is little knowledge about quality of life (QoL) and the impact of disease progression in patients with mMCC. A recent qualitative analysis of patient interviews, conducted alongside the avelumab Phase II trial, showed that for most patients, MCC was symptomless and painless prior to, as well as following diagnosis [19]. Although patients were for the most part able to conduct activities of everyday life, they reported a significant psychological impact. Patients reported a clear benefit with avelumab treatment, as reflected by improved tumor status as well as improved physical and mental health. Patients reported high satisfaction with avelumab, which they described as less debilitating and/or better tolerated than chemotherapy or radiotherapy.

The importance of patient-reported outcomes (PROs) as measured using existing validated instruments has been acknowledged by regulatory bodies [20,21]. Generic instruments can facilitate comparisons across populations, yet may lack sensitivity to detect changes in specific conditions [22,23]. Conversely, disease-specific instruments have an increased sensitivity to detect changes within a certain condition, but lack the potential to compare results across populations [24,25]. Thus, it is recommended to use a combination of both generic and disease-specific instruments [26].

Among generic instruments, the EuroQol – 5 Dimensions (EQ-5D) questionnaire has been widely used in oncology [27] and has been shown to be reliable and responsive and to have content as well as construct validity. No disease-specific instruments exist to specifically capture health-related quality of life (HRQoL) in patients with MCC. However, the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) has shown promising characteristics for patients with malignant melanomas and was reported to have significant correlations with other instruments measuring similar constructs, such as the European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire (EORTC–QLQ) Melanoma Module and the Profile of Mood States. Furthermore, the FACT-M has been shown to distinguish between disease stages, showing significant decreases in scores of patients with advanced disease compared with patients in early stages of the disease [28]. Using data from the JAVELIN Merkel 200 Phase II trial, a psychometric validation of the FACT-M in MCC has been carried out, demonstrating acceptable psychometric properties in this patient population [29].

The purpose of this study was to assess the association between HRQoL and disease progression in patients with mMCC treated with avelumab.

Materials & methods
Study design
This study used data collected in Part A of trial EMR 100070–003/NCT02155647/ JAVELIN Merkel 200, a single-arm, open-label, multicenter, international Phase II study in patients with distant mMCC. Patients enrolled in the trial were required to have histologically confirmed stage IV MCC, must have received at least one line of chemotherapy for the treatment of mMCC and must have progressed after the most recent line of chemotherapy. Eligible patients were adults aged at least 18 years who had an Eastern Cooperative Oncology Group performance score of 0 or 1 at trial entry, an estimated life expectancy of more than 12 weeks, at least one unidimensional measurable lesion by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 and adequate hematological, hepatic and renal function. Details on the definitions of these inclusion criteria as well as additional patient eligibility criteria are reported elsewhere [15].

Patients received avelumab at a dose of 10 mg/kg as a 1-h intravenous infusion every 2 weeks until significant clinical deterioration, unacceptable toxicity or any protocol-specified criterion for withdrawal from the trial or trial drug was fulfilled.

Data reported in this study are based on the protocol specified analysis with a cut-off date on 3 September 2016, 12 months after start of study treatment of the last patient.

Patient reported outcome study assessments
PRO data were collected electronically at sites throughout the treatment period (at baseline, week 7 and then every 6 weeks) and at the end-of-treatment visit.

HRQoL was assessed with the melanoma-specific FACT-M questionnaire and the generic 5-level EQ-5D (EQ-5D-5L) questionnaire.

FACT-M

The FACT-M comprises 51 items grouped into nine multi-item scores, including six subscale scores and three summary scores [24,30]. The six subscales consist of four subscales from the FACT – General (FACT-G; physical well-being, social well-being, emotional well-being, functional well-being), one Melanoma scale and one Melanoma surgery scale. The three summary scores include the FACT-M trial outcome index (TOI), the FACT-G total score and the FACT-M total score.

EQ-5D

The EQ-5D is a self-administered, generic, preference-based HRQoL instrument developed by the EuroQol group [31,32]. The five level version (EQ-5D-5L) that was used in this study includes five single-item dimensions with five response levels each and a vertical visual analog scale (VAS) for the patients to rate their current health state. The VAS ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). Health states defined by responses to the five items can be transformed into a single utility value (EQ-5D index) using a scoring algorithm that is based on valuations of representative general population samples. In this study, utility values were calculated using the country-specific value set for the USA, which is based on the cross-walk methodology developed by the EuroQol group [33].

Tumor response

Tumor response was determined by radiological assessment by an independent review committee per RECIST version 1.1 [34]. Response status was categorized as nonprogressed health states (stable disease [SD], partial response or complete response) versus progressive disease (PD). For each HRQoL assessment, tumor response status was determined as the result of the tumor response evaluation (based on radiological evaluation and physical examination of skin lesions, if appropriate) that took place within a time window of ±7 days around the date of the HRQoL assessment. HRQoL data that were collected outside of these time windows around tumor response evaluations were excluded from the analysis, as were observations when a patient's tumor response was 'not evaluable'.

Statistical analyses

Several different approaches were applied to analyze the association between clinical response and patients' health status.

Tumor size & change from baseline in HRQoL & utility scores

First, the association between percentage reduction of tumor size and changes from baseline in EQ-5D and FACT-M scores was evaluated by calculating correlation coefficients and simple linear regressions at week 7. This time point was chosen for sample size reasons, and because it enabled the most balanced mix of patients with versus without disease progression, providing sufficient variation in tumor size reduction across patients.

Tumor response & change from baseline in HRQoL & utility scores

Second, the association between tumor response and change in FACT-M and EQ-5D scores from baseline was estimated by using linear mixed models (LMMs). LMMs take into account that patients have repeated measurements over time by introducing a random effect for each patient. One LMM was fitted for change from baseline in each of the six FACT-M subscales and each of the three FACT-M summary scores, as well as for change from baseline in EQ-VAS and EQ-5D utility scores. These analyses were based on data from visits between baseline and week 49. Each LMM included the following covariates: baseline value of the considered score, number of visit and a time-dependent variable on response status (nonprogressed vs progressed). Analyses included patients who had an evaluable score at baseline and at least one postbaseline assessment.

Tumor response & mean utility scores

Third, further LMMs were fitted to estimate adjusted mean EQ-5D utilities (rather than mean change from baseline) by treatment response at the corresponding visit (nonprogressed vs progressed). Since utilities based on general population preferences from the UK are most frequently used in literature and are typically also used by most countries without their own value set, these analyses were also conducted for the UK value set developed by Devlin *et al.* [35]. These LMMs were fitted to EQ-5D utility scores from all available time points, including baseline. The model included response status as the only fixed effects covariate. From this regression model, adjusted mean

utilities were derived for nonprogressed and progressed observations, respectively. Response status at baseline was set to SD.

Adjustments for the impact of adverse events on mean utility scores

To assess the impact of adverse events (AEs) on EQ-5D utilities and to provide estimates of mean EQ-5D utilities adjusted for the effect of AEs, a further binary, time-dependent covariate was added to the LMM, reflecting whether a patient had at least one AE ongoing at the time of EQ-5D assessment. Presence of AEs was determined based on reported start and end dates of each individual AE. From this additional regression model, mean utilities for nonprogressed versus progressed health states adjusted for AEs were obtained by predicting utilities for an average patient in this health state assumed to have no AEs. In addition, the average loss in EQ-5D utilities associated with experiencing an AE ('disutility') was obtained as the regression coefficient of the AE variable in the LMM. A number of different types of AEs were considered including AEs of grade 3 or 4, treatment-related AEs of any grade or serious AEs.

Statistical analyses were performed using SAS software for Windows version 9.4 (SAS Institute, Inc., NC, USA).

Results

Patient population

Among the 88 patients who received at least one dose of trial treatment, 72 (81.8%) patients completed at least one item of the EQ-5D and 70 patients completed at least one item of the FACT-M questionnaires, respectively, at baseline. The number of patients who completed the EQ-5D (FACT-M) questionnaire was 54 (53) at week 7, 43 (42) at week 13 and 32 (31) at week 25.

Median time since diagnosis of metastatic disease was 10.4 months (range: 1.5–159.0) – see Table 1. The primary tumor site was skin in most patients. Patients had a median follow-up time of 16.4 months (range: 12.1–25.4) from first trial treatment to data analysis cut-off date. The proportion of patients who were progression-free at 6 months was 40.0% (95% CI: 29; 50).

Mean FACT-G total score at baseline was 78.2 (SD: 19.28); mean FACT-M total score was 128.7 (SD: 25.24). EQ-5D VAS at baseline was 65.2. Mean EQ-5D utility in the trial at baseline was 0.799 (SD: 0.155) for the US tariff and 0.823 (SD: 0.196) for the UK tariff, respectively.

Correlation between reduction in tumor size & health status

A positive association between percentage reduction in tumor size and patients' HRQoL (change from baseline) was generally observed at week 7. The largest correlation coefficients were observed among the functional well-being (correlation coefficient $[\rho]$ = -0.468 [95% CI: -0.679; -0.173]), FACT-M TOI (ρ = -0.364 [95% CI: -0.607; -0.050]), FACT-M total (ρ = -0.364 [95% CI: -0.607; -0.050]), FACT-G total (ρ = -0.338 [95% CI: -0.588; -0.021]) and EQ-5D index score (ρ = -0.318 [95% CI: -0.570; -0.004]). Derived from this association, based on a univariate linear regression model, a 30% decrease in tumor size (which would qualify for partial response for target lesions according to RECIST) corresponds to a predicted mean 5.5-point improvement on the FACT-M total score (extrapolated from the regression coefficient of 0.184 [95% CI: -0.340; -0.027] per percentage point). This is considered a clinically meaningful improvement on this QoL score, assuming that the minimally important difference (MID) of the FACT-M obtained from melanoma patients is also valid for the MCC population [29,36]. Correlation coefficients calculated between tumor size change and change in EQ-5D VAS score were small (ρ = -0.188), indicating no clear association.

Association between tumor response & change in HRQoL scores from baseline

Mean change from baseline in FACT-M and EQ-5D scores by tumor response status (nonprogressed vs progressed) are shown in Table 2. Mean differences in change from baseline scores between non-PD and PD were in the range of published MIDs for melanoma subscale (difference = 2.79, p = 0.005), melanoma surgery scale (difference = 1.48, p = 0.089), TOI (difference = 5.68, p = 0.004), FACT-G total score (difference = 4.37, p = 0.022), FACT-M total score (difference = 7.03, p = 0.006), EQ-5D VAS (difference = 7.04, p = 0.024) and EQ-5D utility score (difference = 0.07, p = 0.003).

Table 1. Patient characteristics.	
Baseline characteristics	Patients (n = 88)
Age (years), median (range):	72.5 (33–88)
– <65, n (%)	22 (25)
– ≥65, n (%)	66 (75)
Sex, n (%):	
– Male	65 (74)
– Female	23 (26)
Site of primary tumor, n (%):	
– Skin	67 (76)
– Lymph node	12 (14)
– Other	2 (2)
– Missing	7 (8)
Visceral disease at study entry, n (%):	
– Present	47 (53)
– Absent	41 (47)
ECOG performance status score, n (%):	
– 0	49 (56)
– 1	39 (44)
Time since first diagnosis (months), median (range)	19.8 (2.9–159.0)
Time since first diagnosis of metastatic disease (months), median (range)	10.4 (1.5–159.0)
Number of previous systematic anticancer treatments, n (%):	
– 1	52 (59)
– 2	26 (30)
– 3	7 (8)
– ≥4	3 (3)
Follow-up/efficacy outcomes	
Follow-up (months), median (range)	16.4 (12.1–25.4)
Progression-free survival rate at 12 months	30% (95% CI: 21; 41)
Overall survival rate at 12 months	52% (95% CI: 41; 62)
Confirmed best overall response, n (%):	
– Complete response (CR)	10 (11)
– Partial response (PR)	19 (22)
– Stable disease	9 (10)
– Progressive disease	32 (36)
– Nonevaluable	18 (20)
Objective response rate (CR + PR), % (95.9% CI)[†]	33.0% (95% CI: 23.3; 43.8)

Data are median (range) or n (%) if not stated otherwise.
[†] Exact confidence interval using the Clopper–method.
ECOG: Eastern Cooperative Oncology Group.

Mean EQ-5D utility by tumor response

The LMMs that were fitted to estimate mean EQ-5D utility by tumor response (progressed vs nonprogressed) included a total of 322 observations from 70 patients. Of those, 267 observations were collected before documented disease progression and 55 observations were collected at or after disease progression. Mean utilities predicted from the LMM for progression and nonprogression health states are shown in Table 3. Estimates adjusted for the impact of AEs are also presented.

Utility based on US and UK value sets were 0.8024 and 0.8269 in the nonprogression health state, respectively. Utility values based on US and UK value sets were 0.7352 and 0.7415 in the progression health state, respectively. Differences between health states (0.067 for US value set [p = 0.0002]; 0.085 for UK value set [p < 0.0001]) were statistically significant and clinically relevant, based on published estimates of MID of 0.06 for the US tariff and

Table 2. Difference in the evolution of HRQoL scores over the course of the trial between disease progressed and nonprogressed patients.

FACT-M subscales and summary scores	n	LS means (overall response status by IERC per RECIST)				Difference in estimate	p-value	Published MIDs in melanoma population
		Nonprogressed (CR/PR/SD)		Progressed (PD)				
		Estimate	p-value	Estimate	p-value			
FACT-G subscales								
Physical well-being (PWB)	172	-0.39	0.544	-1.57	0.023*	1.18	0.080	2.00–3.00†
Social/family well-being (SWB)	172	-1.83	0.005*	-1.89	0.009*	0.06	0.941	–
Emotional well-being (EWB)	172	1.70	0.001*	0.18	0.743	1.52	0.008*	2.00†
Functional well-being (FWB)	172	0.67	0.279	-1.12	0.101	1.79	0.015*	2.00–3.00†
Melanoma-specific subscales								
Melanoma subscale (MS)	172	1.49	0.081	-1.30	0.162	2.79	0.005*	2.00–4.00‡
Melanoma surgery scale (MSS)	172	-0.05	0.953	-1.52	0.070	1.48	0.089	1.00–2.00‡
Summary scales								
FACT-M TOI	172	1.66	0.360	-4.01	0.039*	5.68	0.004*	5.00–9.00‡
FACT-G total score	172	-0.07	0.970	-4.44	0.020*	4.37	0.022*	3.00–7.00†
FACT-M total score	174	1.39	0.558	-5.64	0.027*	7.03	0.006*	–
EQ-5D								
Visual analog Scale (VAS)	174	4.39	0.024*	-2.64	0.325*	7.04	0.024*	7.00§
Utility (US value set)	172	-0.01	0.780	-0.08	0.002*	0.07	0.003*	0.06§

Results from linear mixed models with the lowest Akaike's Information Criteria adjusting for time of questionnaire completion, baseline score and overall response status. Overall response status is based on IERC assessment according to RECIST 1.1 and include the following categories: complete responder or partial responder or stable disease and progressive disease.

*Denotes p-values which were statistically significant (p < 0.05). p-values were calculated from Student's *t*-test.
†Cella *et al.*
‡Askew *et al.*
§Pickard *et al.*
CR: Complete responder; EQ-5D: EuroQol – 5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy – General; FACT-M: Functional Assessment of Cancer Therapy – Melanoma; IERC: Independent Endpoint Review Committee; LS: Least square; MID: Minimal important difference; PD: Progressive disease; PR: Partial responder; RECIST: Response Evaluation Criteria In Solid Tumors; SD: Stable disease; TOI: Trial outcome index.

0.07 or 0.09 for the UK tariff [37,38]. The MID is the smallest change in outcome that a patient would identify as important.

Impact of AEs on mean EQ-5D utility

Patients with an ongoing AE of grade 3 or 4 at the time of the EQ-5D assessment had on average only slightly lower EQ-5D utility scores than patients without AEs (-0.033 [95% CI: -0.075; 0.008] for the US value set, and -0.033 [95% CI: -0.080; 0.015] for the UK value set, respectively) – see Table 4. These differences were neither clinically meaningful nor statistically significant (p = 0.1113 and p = 0.1779, respectively). Disutilities for treatment-related AEs of any grade were even smaller (-0.004 and -0.005 for US and UK value set, respectively). Only serious treatment-emergent AEs (13 observations) were associated with a clinically meaningful loss in utility (-0.061 for US value set; -0.098 for UK value set).

Discussion

Using data from the Phase II trial JAVELIN Merkel 200, these analyses explored the association between tumor response and HRQoL in patients with mMCC treated with avelumab after treatment with at least one line of chemotherapy. Results show that reduction in tumor size correlates with improvements in patients' health status, as measured by both generic and skin cancer specific HRQoL instruments. Results also demonstrated significantly higher HRQoL and utility for patients with non-PD compared with PD, measured as per RECIST criteria. Clinically meaningful differences, of similar magnitude to previously published MIDs, [36,39] were observed for most FACT-M changes from baseline scores.

Over the last decades, PROs have become an important end point in metastatic oncology and/or melanoma trials and are frequently used in evaluations by regulatory and reimbursement authorities [20,21]. PROs provide important patient perspectives on the disease and the treatment received that are not captured by traditional efficacy data or AE reporting. Currently, no validated tools exist to capture HRQoL in patients with MCC. The FACT-M had

Table 3. Mean EuroQol – 5 Dimensions utility between disease progressed and nonprogressed patients.

EQ-5D utility	Statistics	Response status (based on RECIST 1.1)		Difference[†]	p-value
		Nonprogressed (CR/PR/SD)	Progressed (PD)		
US value set					
Observed values	n[‡]	267	55	–	–
	Min; max[§]	0.204; 1.000	0.126; 1.000	–	–
Adjusted means from LMM (main analysis)	Mean (95% CI)	0.8024 (0.7668; 0.8380)	0.7352 (0.6922; 0.7781)	0.0672 (0.0317; 0.1028)	0.0002
	SE	0.01787	0.02172	0.01808	
Adjusted means from LMM (controlled for grade 3/4 AEs)	Mean (95% CI)	0.8057 (0.7704; 0.8410)	0.7490 (0.7033; 0.7946)	0.0567 (0.0189; 0.0946)	0.0034
	SE	0.01769	0.02312	0.01922	
Adjusted means from LMM (controlled for treatment-related AEs)	Mean (95% CI)	0.8034 (0.7667; 0.8401)	0.7375 (0.6901; 0.7848)	0.0659 (0.0286; 0.1033)	0.0006
	SE	0.01843	0.02398	0.01898	
UK value set					
Observed values	n[‡]	267	55	–	–
	Min; max[§]	-0.165; 1.000	0.007; 1.000	–	–
Adjusted means from LMM (main analysis)	Mean (95% CI)	0.8269 (0.7842; 0.8696)	0.7415 (0.6907; 0.7923)	0.0854 (0.0445; 0.1263)	<0.0001
	SE	0.02140	0.02567	0.02079	
Adjusted means from LMM (controlled for grade 3/4 AEs)	Mean (95% CI)	0.8302 (0.7879; 0.8725)	0.7550 (0.7012; 0.8088)	0.0752 (0.0316; 0.1187)	0.0008
	SE	0.02117	0.02722	0.02212	
Adjusted means from LMM (controlled for treatment-related AEs)	Mean (95% CI)	0.8283 (0.7844; 0.8722)	0.7447 (0.6890; 0.8005)	0.0836 (0.0406; 0.1266)	0.0002
	SE	0.02202	0.02823	0.02185	

p-values were calculated form Student's t-tests.
[†]MID = 0.06 for US tariff (Pickard et al.) and 0.07–0.09 for UK tariff (Pickard et al.; Walters et al.).
[‡]Unit of analysis is EQ-5D measurement not patient, so n > number of patients.
[§]Observed data, not based on linear mixed model. Overall response status is based on IERC assessment according to RECIST 1.1 and includes the following categories: complete responder or partial responder or stable disease (CR/PR/SD) and PD.
AE: Adverse event; CR: Complete responder; EQ-5D: EuroQol – 5 Dimensions; IERC: Independent Endpoint Review Committee; LMM: Linear mixed model; MID: Minimally important difference; PD: Progressive disease; PR: Partial responder; RECIST: Response Evaluation Criteria In Solid Tumors; SD: Stable disease; SE: Standard error.

Table 4. Disutilities for different types of adverse events – adjusted for the effect of disease progression.

Type of adverse event		US value set				UK value set			
Name	n (with AE)[†]	Mean disutility[‡]	SE	95% CI	p-value	Mean disutility[‡]	SE	95% CI	p-value
Grade 3 or 4 AE	40	-0.03341	0.02092	-0.07458; 0.007762	0.1113	-0.03250	0.02407	-0.07988; 0.01487	0.1779
Treatment-related AE of any grade	154	-0.00360	0.01559	-0.03427; 0.02708	0.8177	-0.00502	0.01794	-0.04032; 0.03029	0.7799
Treatment-emergent AE of any grade	237	-0.02292	0.01494	-0.05232; 0.006489	0.1262	-0.02823	0.01713	-0.06196; 0.00549	0.1005
Serious treatment-emergent AE	13	-0.06073	0.03664	-0.1328; 0.01137	0.0985	-0.09847	0.04207	-0.1812; -0.01570	0.0199
Treatment-emergent grade 3 or 4 AE	37	-0.02405	0.02127	-0.06591; 0.01781	0.2591	-0.01668	0.02444	-0.06479; 0.03143	0.4955

Disutilities were estimated from a linear mixed model including response status (progressed vs nonprogressed) and the AE variable as covariates.
[†]Unit of analysis is HRQoL measurement not the patient, so n > number of patients.
[‡]Negative number indicates a disutility.
AE: Adverse events; HRQoL: Health-related quality of life; SE: Standard error.

been developed to address disease-specific QoL concerns among patients with melanoma, and it has subsequently been validated for use in patients with all stages of the disease [24,30]. MCC and melanoma are both aggressive skin malignancies; despite some differences between MCC and melanoma, including worse prognosis for MCC, the content of the FACT-M seems appropriate to assess QoL in patients with MCC. This was further confirmed by a thorough psychometric validation of the FACT-M in the JAVELIN Merkel 200 trial population [29].

Avelumab has been shown to achieve meaningful clinical benefit in mMCC with an ORR of 33.0% (95% CI: 23.3; 43.8), and Kaplan–Meier estimated proportion of responses with at least 6 months' duration was 93% (95% CI: 74; 98). The 6-month progression-free survival rate was 40% (95% CI: 29; 50). The analyses reported here add further evidence to support the value of avelumab from the patient perspective, indicating that delaying disease progression translates into prolonging maintenance of HRQoL. Whereas PD was associated with significant and clinically meaningful reductions in HRQoL and utility, patients in nonprogressed health states (including SD and partial or complete response) had stable HRQoL scores or experienced small – although not clinically meaningful – improvements in HRQoL. In contrast, studies have shown that treatment with chemotherapy often comes at the cost of decrements in HRQoL caused by side effects of therapy [40,41].

The analyses of EQ-5D scores adjusted for the impact of AEs showed that the majority of side effects of avelumab do not have a detrimental impact on HRQoL. This is in line with the fact that most AEs related to avelumab were low grade, consisting mostly of fatigue and infusion-related reaction. Taken together, this indicates that avelumab is well tolerated and that its safety profile was manageable, whereas previous studies in patients with mMCC treated with chemotherapy have shown high rates of significant toxicities [8–11].

Baseline HRQoL scores in this trial of mMCC patients were lower than average HRQoL scores reported for an adult US general population, reflecting the burden that mMCC has on patient health status [42], but they were similar to reference values reported for an adult metastatic cancer population [37,42,43]. Mean FACT-M scores were lower than reported in a previous study of patients with stage IV melanoma [24,44]. This could be due to the fact that MCC is in general a more aggressive tumor than melanoma [6]. However, differences between the two studies at baseline could also be impacted by other characteristics of the underlying populations; such as type of treatment or patient age. Mean age of melanoma patients by disease stage was not reported, however, it is likely that patients with stage IV melanoma were younger than those with mMCC, as median age in the overall melanoma study population (including stage I–IV) was only 52 years, as compared with 72.5 in the JAVELIN Merkel 200 trial [24].

The observed decline in utility associated with disease progression in this study is consistent with (and even more pronounced than) the results from similar studies in other indications. For example, Griebsch et al. examined whether disease progression is associated with HRQoL using empirical data from two randomized controlled trials in non-small-cell lung cancer [45]. It was found that disease progression was associated with a decline in utility of 0.06 points (derived with the EQ-5D using the UK general population value set). Singh and colleagues examined the association between disease progression and EQ-5D utilities obtained by mapping from the FACT-G questionnaire in patients with neuroendocrine tumors of gastrointestinal or lung origin [46]; they reported preprogression utilities of 0.826 (for a US value set) and 0.779 (for a UK value set), respectively, versus postprogression utilities of 0.795 (US value set) and 0.725 (UK value set), respectively. Although statistically significant, this difference was not clinically relevant based on published MIDs of 0.06 for the US tariff and 0.07–0.09 for the UK tariff, respectively [37,38].

The differences between mean utilities estimated by the UK and US tariff are consistent with previous studies that have shown that EQ-5D index scores are slightly higher when using US weights as compared with UK weights [47].

The association between disease progression and decline in HRQoL demonstrated in this analysis, has important healthcare policy and clinical implications. In the era of patient-centered medicine, end points such as HRQoL are increasingly important and should be part of the larger context of clinical benefit. Our results show that disease progression is associated with HRQoL and utility, supporting the use of progression-free survival as a patient relevant outcome in clinical trials in patients with MCC. The HRQoL and utility values reported in this study may be used in health technology appraisals. In particular, empirical estimates of mean utility by tumor response are an important input parameter in health economic models that are built to simulate the effectiveness of treatments over a lifetime horizon [48]. Health economic models are required by many national regulatory bodies as part of their Health Technology Assessment.

In the JAVELIN Merkel 200 trial, collection of HRQoL data was only required until disease progression. This resulted in scarcity of data post disease progression; however, there was at least one assessment at or after disease progression for each patient with PD. The collected data appears adequate for the derivation of robust estimates for HRQoL and utility postprogression. If HRQoL further worsens after disease progression, then the difference

between pre- and postprogression may even have been underestimated in this study. Another limitation is that patients may have rescheduled their visits if they were bothered by severe AEs, which may lead to an underestimation of disutilities related to AEs.

In conclusion, this study showed that patients on avelumab who are progression-free have significantly better HRQoL and health status than patients after disease progression. This indicates that durable response rates observed with avelumab would also be expected to translate into prolonging maintenance of HRQoL. The impact of AEs on HRQoL and utility during treatment with avelumab was minimal, suggesting an acceptable safety profile from a patient perspective.

Summary points

- This study is one of the first to describe health-related quality of life (HRQoL) in patients with metastatic Merkel cell carcinoma (MCC), a rare and aggressive cutaneous malignancy.
- In the JAVELIN Merkel 200 trial, 88 patients with metastatic MCC were treated with avelumab, a fully human IgG1 monoclonal antibody targeting and blocking PD-L1 interaction with its receptor PD-1.
- Reduction of tumor size experienced under treatment with avelumab correlates with improvements in patients' health status, as measured by both generic and skin cancer specific HRQoL instruments.
- A 30% decrease in tumor size (which would qualify for partial response for target lesions according to the Response Evaluation Criteria In Solid Tumors [RECIST]) corresponds to a clinically meaningful improvement of 5.5 points on the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) total score.
- Progressive disease (as per RECIST) is associated with statistically significant and clinically meaningful reductions in HRQoL and utility, while patients in nonprogressed health states had stable HRQoL or experienced small improvements in HRQoL.
- The majority of adverse events experienced under treatment with avelumab (including grade 3 or 4 adverse events) do not have a detrimental impact on HRQoL.
- Study results indicate that delaying disease progression under treatment with avelumab translates into prolonging maintenance of HRQoL.
- The association between disease progression (as per RECIST) and decline in HRQoL supports the use of progression-free survival as a patient-relevant outcome in clinical trials in MCC patients.

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