Confirming the Psychometric Performance of the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) Questionnaire in Patients with Merkel Cell Carcinoma

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BACKGROUND

- Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma of the skin with a 5-year mortality of approximately 40%[1]
  - Approximately one-third of patients will experience recurrence, including metastatic disease in a substantial proportion,[2,3] which historically has had a poor prognosis[4]
- Assessment of the disease and its treatment impact on patients' lives is frequently required by regulatory authorities and may be obtained by collecting patient-reported outcomes (PROs) data
- In the context of rare diseases such as MCC, validated disease-specific instruments are often not available, and PROs from related diseases are used
- To ensure valid and reliable data for meaningful interpretation of PRO data, it is crucial to explore the psychometric properties of these instruments
- The Functional Assessment of Cancer Therapy-Melanoma (FACT-M) is a well-established PRO instrument originally developed for use in melanoma
- Preliminary evidence regarding the psychometrics of the melanoma-specific FACT-M in patients with MCC exists and has been reported for Part A (patients who had previously received chemotherapy) of the Javelin Merkel 200 trial[5]

OBJECTIVES

- **To substantiate the psychometric performance of FACT-M in a broader sample of patients with MCC who either had previously received chemotherapy (Part A) or were naive to systemic therapy (Part B)**

METHODS

Study design

- The JAVELIN Merkel 200 trial (EMR 100070-003; NCT02155647) is a single-arm, open-label, multicenter, international phase 2 study conducted in the United States, Europe, Australia, and Japan
- Adult patients with histologically confirmed stage IV MCC were included in the study and received avelumab at a dose of 10 mg/kg as a 1-hour intravenous infusion once every 2 weeks[6]

PRO assessments

- The FACT-M assessed PRO data over the previous 7 days using 51 items grouped into 6 subscales and 3 summary scores; in addition, 3 MCC-specific scores were derived
- The generic EQ-5D questionnaire assessed health status for the current day through 5 single-item dimensions and a vertical visual analogue scale (VAS); these data were used to assess FACT-M responsiveness
- FACT-M and EQ-5D data were collected electronically at baseline, week 7, and then every 6 weeks until disease progression and/or treatment discontinuation
- Most psychometric properties were assessed using baseline data, while 7-week data were used to assess FACT-M responsiveness

Statistical analysis

- Data from Part A (previously treated patients) and Part B (treatment-naive patients) were pooled for the following reasons:
  - Qualitative interviews showed that patients from both Part A and Part B reported similar experiences related to their MCC[7]
  - To increase the accuracy and robustness of the psychometric properties by using a larger sample size
  - To justify that the FACT-M is suitable for application in all patients with MCC, whether or not they had been previously treated
- **Table 1** shows the psychometric properties evaluated

Table 1. Analyses to assess the psychometric properties of the FACT-M in the MCC population

Psychometric property	Analyses conducted	Assumptions
Construct validity: convergent and divergent	Multitrait, correlation	Individual items are expected to correlate highly with their own domain (r≥0.4) and higher with their own domain compared with other domains
Construct validity: clinical/known group	Testing difference in score distribution between groups with varying performance (ECOG PS 0 [fully active] vs ECOG PS 1 [restricted physically strenuous activity])	Differences in FACT-M scores are expected between groups of varying clinical severity (p<0.05)
Internal consistency reliability	Cronbach α coefficients	Cronbach α coefficients are expected to be at least the recommended threshold of 0.7
Responsiveness	FACT-M change from baseline scores by change in tumor size and EQ VAS scores categorized into 3 groups (improved, stable, worsened)	Differences in FACT-M scores from baseline through week 7 are expected between groups (p<0.05)

ECOG PS, Eastern Cooperative Oncology Group performance status

RESULTS

Patients

- The intention-to-treat (ITT) population in the EMR 100070-003 trial (Parts A and B) consisted of 204 patients
- Among these, 172 patients provided PRO data and were included in the analyses of the psychometric properties of the FACT-M (**Table 2**)
- The mean age of patients was 71 years, 70% were male, and the ECOG PS of 1 indicated that 40% were restricted in physically strenuous activity

Table 2. Baseline sociodemographic and clinical characteristics by treatment status

		Part A (treated) (n=70)	Part B (naive) (n=102)	Total (N=172)	p-value*
Sex, n (%)	Male	52 (74.3)	69 (67.6)	121 (70.3)	0.349
	Female	18 (25.7)	33 (32.4)	51 (29.7)	
Age, years	Mean (SD)	70.2 (11.2)	72.5 (9.8)	71.6 (10.4)	0.151
Pooled geographic region, n (%)	N. America	40 (57.1)	27 (26.5)	67 (39.0)	**<0.0001**
	Europe	22 (31.4)	63 (61.8)	85 (49.4)	
	Rest of world	8 (11.4)	12 (11.8)	20 (11.6)	
ECOG PS at baseline, n (%)	0	38 (54.3)	66 (64.7)	104 (60.5)	0.170
	1	32 (45.7)	36 (35.3)	68 (39.5)	
Site of primary tumor, n (%)	Nonskin	9 (12.9)	7 (6.9)	16 (9.3)	0.110
	Skin	55 (78.6)	91 (89.2)	146 (84.9)	
	N/A	0	4 (3.9)	4 (2.3)	
	Missing	6 (8.6)	0	6 (3.5)	
Tumor size at baseline	Evaluable (NR)	61 (9)	100 (2)	161 (11)	**0.028**
	Mean (SD), mm	103.7 (79.7)	79.5 (58.5)	88.6 (68.1)	
Time since first metastatic disease, months	Mean (SD)	16.9 (23.4)	5.5 (7.7)	10.1 (17.0)	**<0.0001**

NA, not applicable; **NR**, not reported
* p-value for between-group comparisons: *t*-test for continuous variables, χ^2 or Fisher exact for categorical variables

Construct validity of FACT-M in patients with MCC

Convergent validity

- Convergent validity was generally good, with criteria met by 100% of items for physical, social, and functional well-being in all MCC-specific scales and by 83% of items for emotional well-being (**Table 3**)

Divergent validity

- Divergent validity was highest for social well-being and lowest in the melanoma subscale, with 100% and 38% of items meeting the divergent validity criterion, respectively (**Table 3**)
- Lower results seen for the melanoma subscale may be due to the fact that it contains a range of aspects related to concerns in the context of melanoma in addition to physical, emotional, or functional well-being, explaining the higher correlations with these subscales

Clinical/known group validity

- Clinical validity was demonstrated, as patients who were fully active (ECOG PS 0) showed higher FACT-M mean scores, reflecting better functioning compared with those who were restricted in physically strenuous activity (ECOG PS 1; **Figure 1**)
- Differences between the 2 ECOG PS groups led to p-values below 0.05 for all scores except social/family well-being and MCC-specific psychological impact

Internal consistency reliability

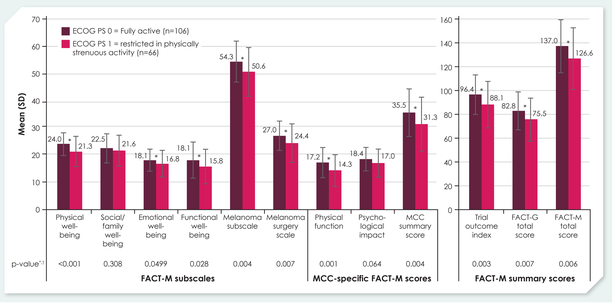
- Cronbach α coefficients were all superior to the recommended threshold of 0.7, supporting the internal consistency of all FACT-M–generated scores, including the proposed MCC-specific scores (**Table 3**)

Table 3. Internal consistency reliability and construct (convergent/divergent, clinical) validity of FACT-M in the MCC population (N=172)*

			Scale structure	
FACT-M subscale, summary, and MCC-specific scales	**No. of items**	**Cronbach α†**	**Range of item-subscale correlations‡**	**Convergent#/ divergent‖ validity, % of items**
FACT-G subscales				
Physical well-being	7	0.84	0.53-0.71	100/57
Social/family well-being¶	6	0.83	0.55-0.70	100/100
Emotional well-being	6	0.80	0.36-0.70	83/67
Functional well-being	7	0.89	0.52-0.77	100/71
Melanoma-specific subscales				
Melanoma	16	0.84	0.19-0.76	50/38
Melanoma surgery	8	0.82	0.20-0.77	75/75
Summary scales				
FACT-M TOI**	30	0.94	–	–
FACT-G total score	27	0.93	–	–
FACT-M total score	43	0.95	–	–
MCC-specific scores				
Physical function	6	0.89	0.61-0.76	100/100
Psychological impact	6	0.84	0.55-0.72	100/100
MCC summary	12	0.90	–	–

TOI, trial outcome index
* FACT-M includes FACT-G plus melanoma subscales; † Recommended threshold, α>0.7; ‡ Pearson correlation coefficients; § Correlation of items with its own dimension ≥0.4; ‖ Correlation with its own dimension higher than the correlation with any other dimension; ¶ Convergent and divergent validity were calculated without the "satisfaction with sex life" item due to high absence in item response; ** TOI includes physical and functional well-being, and melanoma subscale

Figure 1. Clinical validity at baseline: FACT-M scores by ECOG PS at baseline (N=172)

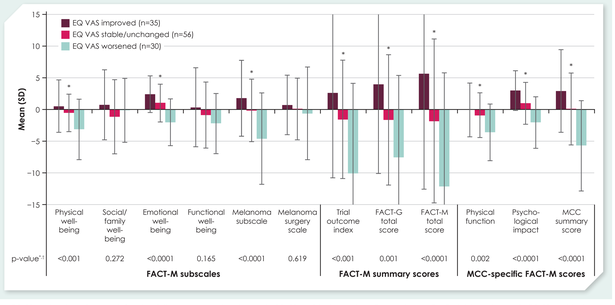


* p<0.05; † Parametric p-value for between-group comparisons: *t*-test for continuous variables

FACT-M: ability to detect change over time

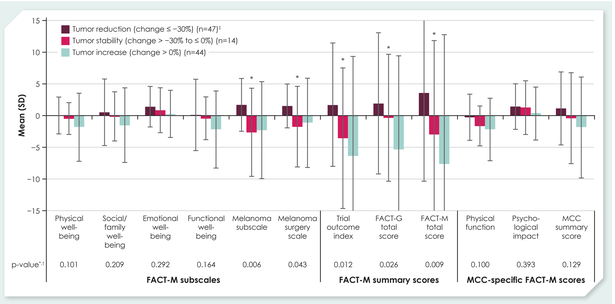
- When using "change in EQ VAS" as an anchor to differentiate between groups of change (**Figure 2**), a logical pattern in FACT-M scores was observed:
  - Improvement in FACT-M scores for the EQ VAS–improved group (except for MCC-specific physical function, which was negative but close to 0)
  - Worsening in FACT-M scores for the EQ VAS–worsened group (except for social/family well-being, which was close to 0)
  - Slight decrease in FACT-M scores, with changes generally negative for the EQ VAS–stable group (except for emotional well-being and MCC-specific psychological impact)
- Similar logical patterns were observed when using "change in tumor size" as an anchor to differentiate between groups of change (**Figure 3**)

Figure 2. FACT-M responsiveness across change groups defined by the EQ-5D VAS



The EQ-5D VAS categories are defined as follows: Improved = change in EQ-5D VAS between baseline and week 7 > 7; stable = change in EQ-5D VAS between baseline and week 7 between −7 and 7; worsened = change in EQ-5D VAS between baseline and week 7 < 7
* p<0.05; † Parametric p-value for between-group comparisons: *t*-test for continuous variables

Figure 3. FACT-M responsiveness across change groups defined by change in tumor size (N=172)



* p<0.05; † Parametric p-value for between-group comparisons: *t*-test for continuous variables; ‡ n=1 missing data for melanoma surgery scale

LIMITATIONS

- The sample size was small for advanced psychometric tests such as confirmatory factor analysis to test the FACT-M factor structure for use in MCC
- However, given the context of a rare disease such as MCC, the current sample size is still very respectable and enabled us to carry out robust psychometric analyses to confirm the use of FACT-M in MCC patients

CONCLUSIONS

- **Results from the psychometric analyses of the present study confirmed the construct validity of the FACT-M in patients with MCC (good internal consistency, strong clinical validity, ability to detect changes over time)**
- **The proposed MCC-specific subscales showed perfect fit, suggesting that these abbreviated subscales may be particularly suitable for this population**
- **In the context of rare diseases, this analysis substantiates the previously reported psychometric performance of the FACT-M in patients with metastatic MCC regardless of prior treatment status, reaffirming its suitability in this patient population**

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DISCLOSURES

MB is an employee of EMD Serono (a business of Merck KGaA), MS is an employee of Merck KGaA, MH was an employee of EMD Serono when this analysis was performed, and SN and MH are employees of ICON, plc, and provide consulting services to EMD Serono.

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