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ORIGINAL RESEARCH

First-line avelumab treatment in patients with metastatic Merkel cell carcinoma: 4-year follow-up from part B of the JAVELIN Merkel 200 study

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Background: Results from the JAVELIN Merkel 200 study led to the approval of avelumab [an anti—programmed death-ligand 1 (PD-L1) antibody] for the treatment of metastatic Merkel cell carcinoma (mMCC) in multiple countries and its inclusion in the treatment guidelines as a preferred or recommended therapy in this setting. Here, we report 4-year follow-up results from the cohort of patients with mMCC who received avelumab as first-line treatment.

Patients and methods: In part B of JAVELIN Merkel 200, a single-arm, open-label, phase II study, patients with mMCC who had not received prior systemic therapy for metastatic disease received avelumab 10 mg/kg via intravenous infusion every 2 weeks until confirmed disease progression, unacceptable toxicity, or withdrawal. In this analysis, long-term overall survival (OS), patient disposition, and subsequent treatment were analyzed.

Results: In total, 116 patients received first-line avelumab. At the data cutoff (2 February 2022), the median follow-up was 54.3 months (range 48.0-69.7 months). Seven patients (6.0%) remained on treatment and an additional 21 patients remained in follow-up (18.1%); 72 patients (62.1%) had died. The median OS was 20.3 months [95% confidence interval (CI) 12.4-42.0 months], with a 4-year OS rate of 38% (95% CI 29% to 47%). In patients with PD-L1+ or PD-L1− tumors, the 4-year OS rate was 48% (95% CI 26% to 67%) and 35% (95% CI 25% to 45%), respectively. In total, 48 patients (41.4%) received poststudy anticancer drug therapy, most commonly etoposide (20.7%), carboplatin (19.0%), and avelumab (12.1%).

Conclusions: Avelumab first-line monotherapy in patients with mMCC resulted in meaningful long-term OS, which compared favorably with historical studies of first-line chemotherapy. These results further support the role of avelumab as a standard of care for patients with mMCC.

Key words: Merkel cell carcinoma, avelumab, immunotherapy, overall survival

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer associated with Merkel cell polyomavirus infection, ultraviolet exposure, increasing age, and immunosuppression.[1,2] Before the approval of immune checkpoint inhibitors, patients with metastatic MCC (mMCC) had a poor prognosis, with a historical 5-year overall survival (OS) rate of ∼17%.[1,2] MCC is considered chemosensitive; however, responses to chemotherapy are not often durable.[1,3]

Avelumab [an anti—programmed death-ligand 1 (PD-L1) antibody] is an approved treatment for patients with mMCC in multiple countries and is included in treatment guidelines as a preferred or recommended therapy for patients with disseminated or unresectable disease.[4-7] The approval of avelumab in this setting was based on findings from JAVELIN Merkel 200, a phase II study. In part A of this study, avelumab treatment resulted in meaningful long-term OS in patients with mMCC that had progressed after prior chemotherapy. After 5 years of follow-up, the median OS was 12.6 months and the 5-year OS rate was 26%.[8] Part B of

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JAVELIN Merkel 200 investigated avelumab as a first-line treatment for mMCC. In the primary analysis, reported after ≥15 months of follow-up, the durable response rate was 30.2%, median progression-free survival was 4.1 months, and median OS was 20.3 months; the 6-month and 1-year OS rates were 75% and 60%, respectively.[9]

Here, we report findings after 4 years of follow-up from part B of JAVELIN Merkel 200, including updated data for OS, patient disposition, and subsequent treatment.

PATIENTS AND METHODS

Study design and patients

JAVELIN Merkel 200 (NCT02155647) was an international, single-arm, open-label, multicenter, phase II study, and its design has been reported previously.[9] In brief, in part B, eligible patients were aged ≥18 years and had histologically confirmed, measurable, stage IV mMCC and had not received prior systemic therapy for metastatic disease. Patients who had received adjuvant chemotherapy were eligible if treatment had ended ≥6 months before study enrollment. Previous immune checkpoint inhibitor therapy was not permitted. Other inclusion criteria were Eastern Cooperative Oncology Group performance status of 0 or 1; estimated life expectancy of ≥3 months; and adequate hematologic, hepatic, and renal function. Patients were unselected for tumor PD-L1 expression and Merkel cell polyomavirus status. Patients received avelumab 10 mg/kg via a 1-hour intravenous infusion every 2 weeks as monotherapy until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. Patients received premedication with an antihistamine and acetaminophen before the first four avelumab infusions.

Outcomes and statistical analysis

In the analysis reported here, long-term OS was assessed. Updated data for other endpoints, such as durable response, progression-free survival, and safety, were not collected. OS was analyzed using the Kaplan–Meier method, and 95% confidence intervals (CIs) for the median were calculated using the Brookmeyer–Crowley method. The median follow-up was calculated using the reverse Kaplan–Meier method. PD-L1+ status was defined as PD-L1 expression on ≥1% of tumor cells using the investigational PD-L1 73-10 immunohistochemistry assay (Agilent Technologies, Carpinteria, CA). Subsequent treatment received after discontinuation of the study treatment and the best response to subsequent treatment per the treating investigator were also collected.

RESULTS

Patient disposition

In total, 116 patients were enrolled and received one or more doses of avelumab (Table 1). Patient baseline characteristics have been reported previously[9] and are summarized in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103461. At the data cutoff (2 February 2022), the median follow-up, defined as the time from the start of the study treatment to the data cutoff, was 54.3 months (range 48.0-69.7 months). Of the seven patients (6.0%) who remained on avelumab treatment, five had a partial response (PR), one had stable disease (SD), and one had progressive disease (PD), which occurred shortly before the data cutoff. Overall, 109 patients (94.0%) had discontinued avelumab: 54 (46.6%) as a result of PD, 27 (23.3%) as a result of adverse events (AEs), 6 (5.2%) as a result of withdrawal of consent, 5 (4.3%) because of death, 1 (0.9%) as a result of loss to follow-up, and 16 (13.8%) because of other reasons.

Table 1. Patient disposition

Patients	Values ($N = 116$), n (%)
Received one or more doses of study treatment	116 (100.0)
Study treatment ongoing	7 (6.0)
Discontinued study treatment	109 (94.0)
Reason for discontinuation of study treatment	
Disease progression	54 (46.6)
Adverse event	27 (23.3)
Withdrawal of consent	6 (5.2)
Death	5 (4.3)
Loss to follow-up	1 (0.9)
Other	16 (13.8)
Discontinued treatment but still in follow-up	21 (18.1)
Discontinued from the study	88 (75.9)
Reasons for discontinuation from the study	
Death	71 (61.2)
Loss to follow-up	4 (3.4)
Withdrawal of consent	4 (3.4)
Other[a]	9 (7.8)
Reinitiated study treatment with avelumab	2 (1.7)

[a]Including patient decision ($n = 2$), initiation of other anticancer therapy ($n = 2$), completion of the 5-year follow-up period ($n = 1$), patient relocation ($n = 1$), investigator decision ($n = 1$), partial response ($n = 1$), and progressive disease ($n = 1$).

Twenty-one patients (18.1%) had discontinued avelumab but remained in study follow-up, and 88 patients (75.9%) had discontinued from the study. The reasons for study discontinuation were death in 71 patients (61.2%), withdrawal of consent in 4 (3.4%), loss to follow-up in 4 (3.4%), and other reasons in 9 [7.8%; patient decision ($n = 2$), initiation of other treatment ($n = 2$), follow-up complete ($n = 1$), patient relocation ($n = 1$), investigator decision ($n = 1$), PR ($n = 1$), and PD ($n = 1$)]. Two patients (1.7%) reinitiated study treatment with avelumab after previously discontinuing treatment.

Overall survival

The median OS was 20.3 months (95% CI 12.4-42.0 months; Figure 1A), unchanged from the primary analysis.[9] The OS rates (95% CI) at 2, 3, and 4 years were 49% (40% to 58%), 44% (34% to 53%), and 38% (29% to 47%), respectively. For illustrative purposes, OS data from this study are plotted alongside OS data from previous real-world studies in patients with mMCC treated with first-line chemotherapy in Figure 1A. In patients assessable for PD-L1 status ($n = 108$), the median OS was 38.7 months (95% CI 11.3 months-not estimable) in patients with PD-L1+ tumors ($n = 21$) and 16.1 months (95% CI 9.6-42.0 months) in patients with

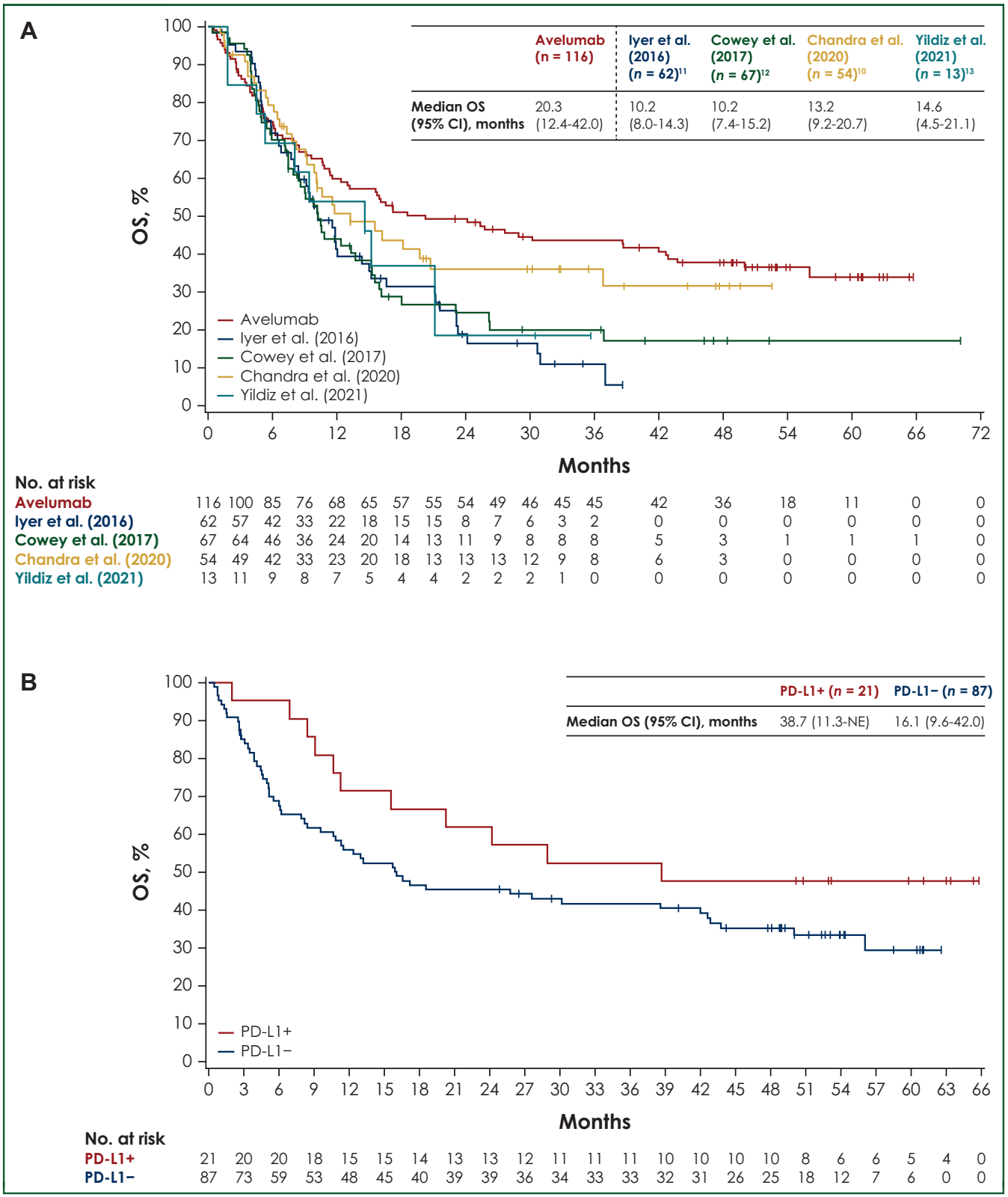

Figure 1. Analysis of OS. (A) OS with first-line avelumab in the overall population. For illustrative purposes, OS from retrospective studies of first-line chemotherapy in patients with mMCC (including reanalysis of individual participant data by the current study sponsor) are also shown[10-13]; however, this is not a head-to-head comparison. In the study by Yildiz et al.,[13] 2 of 13 patients had received second-line avelumab treatment. In the study by Cowey et al.,[12] first-line chemotherapy regimens received were carboplatin + etoposide ($n = 44$), cisplatin + etoposide ($n = 11$), topotecan ($n = 6$), and other regimens ($n = 6$); chemotherapy regimens were not reported in the other studies shown. (B) OS in subgroups defined by PD-L1 status.

CI, confidence interval; mMCC, metastatic Merkel cell carcinoma; NE, not estimable; OS, overall survival; PD-L1, programmed death-ligand 1.

PD-L1− tumors ($n = 87$; Figure 1B). The OS rates in patients with PD-L1+ or PD-L1− tumors were 52% (95% CI 30% to 71%) and 42% (95% CI 31% to 52%) at 3 years and 48% (95% CI 26% to 67%) and 35% (95% CI 25% to 45%) at 4 years, respectively.

At the data cutoff, 72 patients (62.1%) had died. The most common cause of death was disease progression in 57 patients (49.1%); other causes were AE not related to the study treatment in 3 (2.6%), other reasons in 5 (4.3%), and unknown in 7 (6.0%). No deaths as a result of treatment-related AEs were reported.

Subsequent treatment

Overall, 48 patients (41.4%) received one or more subsequent systemic anticancer drug treatments after discontinuing avelumab. The most commonly administered subsequent drugs were etoposide ($n = 24$, 20.7%), carboplatin ($n = 22$, 19.0%), and avelumab ($n = 14$, 12.1%; Table 2), and the most commonly administered subsequent chemotherapy regimen was carboplatin + etoposide ($n = 14$, 12.1%). The best response to the first poststudy treatment was complete response (CR) in 6 patients (12.5%), PR in 10 (20.8%), SD in 3 (6.3%), PD in 13 (27.1%), and not reported/not evaluable in 16 (33.3%; Table 3). Of the 32 patients who discontinued avelumab as a result of PD, the best response to the first poststudy treatment was CR in 1 (3.1%), PR in 8 (25.0%), SD in 2 (6.3%), PD in 12 (37.5%), and not reported/not evaluable in 9 (28.1%), and the median duration of the first subsequent treatment was 2.14 months (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103461). Of the 12 patients who received subsequent radiotherapy before or during their first poststudy drug treatment, the best response to the first poststudy drug treatment was CR in 1 (8.3%), PR in 3 (25.0%), PD in 6 (50.0%), and not reported in 2 (16.7%). Of these patients, objective responses were reported in two patients (50%) who received chemotherapy and two patients (25.0%) who received immunotherapy. In patients who received chemotherapy ($n = 26$; Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.103461) or immunotherapy ($n = 20$) as their first poststudy treatment, an objective response (CR or PR) was reported in 10 (38.5%) and 6 (30.0%), respectively.

In 14 patients who received further avelumab outside of the study (i.e. commercially supplied treatment), reasons for discontinuation of the study treatment were PD in 6, AE in 3, and other reasons in 5 [patient decision ($n = 2$), investigator decision ($n = 1$), complete metabolic remission ($n = 1$), and not specified ($n = 1$)]. Investigator-assessed responses at the time when avelumab was discontinued in these 14 patients were CR in 1, PR in 6, PD in 6, and not evaluable in 1 (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103461 and Figure 2). The best response to subsequent avelumab was CR in five patients, SD in one, PD in two, and not reported in six. In seven patients who had CR or PR when avelumab was discontinued, the best response to subsequent avelumab was CR in three, SD in one, and not reported in three (none of these seven patients received any other systemic therapy before poststudy avelumab). In six patients who had PD when avelumab was discontinued, the best response to subsequent avelumab was CR in one, PD in two, and not reported in three (5/6 patients received ≥1 different drug therapy and/or radiotherapy before subsequent avelumab). In one patient whose response was not evaluable when avelumab was discontinued, the best response to subsequent avelumab was CR (the patient did not receive any other therapy before poststudy avelumab).

Table 2. Subsequent systemic anticancer treatments received in any line

Anticancer treatments	Values ($N = 116$), *n* (%)
Any subsequent anticancer drug therapy	48 (41.4)
Chemotherapy[a]	31 (26.7)
Avelumab	14 (12.1)
Pembrolizumab	9 (7.8)
Ipilimumab	6 (5.2)
Nivolumab	4 (3.4)
ADU-S100	1 (0.9)
ALRN-6924	1 (0.9)
AMG 232	1 (0.9)
Atezolizumab	1 (0.9)
Cavrotolimod	1 (0.9)
Cetuximab	1 (0.9)
Olaparib	1 (0.9)
RO7198457	1 (0.9)
Sabatolimab	1 (0.9)

Patients who received one or more subsequent treatments are included in ≥1 row of the table.
[a]Chemotherapy drugs administered (as single agents or in combination) were etoposide ($n = 24$), carboplatin ($n = 22$), paclitaxel ($n = 6$), cisplatin ($n = 5$), temozolomide ($n = 3$), fluorouracil ($n = 2$), folinic acid ($n = 2$), capecitabine ($n = 2$), cyclophosphamide ($n = 2$), doxorubicin ($n = 2$), dacarbazine ($n = 1$), epirubicin ($n = 1$), irinotecan ($n = 1$), oxaliplatin ($n = 1$), pegylated liposomal doxorubicin hydrochloride ($n = 1$), and vincristine ($n = 1$). Some patients received more than one drug.

DISCUSSION

Updated data from part B of the JAVELIN Merkel 200 study show that first-line avelumab monotherapy resulted in meaningful long-term OS in patients with mMCC, with a 4-year OS rate of 38%. The median OS was 20.3 months, which is numerically higher than the OS observed in historical studies of first-line chemotherapy (range, 10.2-14.6 months).[10-13] After >4 years of follow-up, 62.1% of patients had died and 6.0% remained on treatment. The most common cause of death was disease progression, and no deaths as a result of treatment-related AEs were reported. This study population included an unusually high proportion of patients with PD-L1− tumors (75.0% versus 18.1% with PD-L1+ tumors). Consistent with part A of this study and the primary analysis in part B, OS appeared to be longer in patients with PD-L1+ versus PD-L1− tumors.[8,9] However, responses to avelumab occurred irrespective of PD-L1 status, and long-term OS rates were favorable in subgroups with PD-L1+ or PD-L1− tumors compared with historical studies of chemotherapy; thus, the data do not support patient selection based on PD-L1 status.

Among the 48 patients who received subsequent therapy after discontinuing from the study, responses occurred in

Table 3. The first subsequent systemic anticancer regimen after the study and the best response to subsequent treatment

	Patients, *n*	Median duration of subsequent treatment (months)	Best response to subsequent treatment, *n* (%)				
			CR	PR	SD	PD	NR/NE
Discontinued avelumab and received any systemic anticancer regimen	48	5.60	6 (12.5)	10 (20.8)	3 (6.3)	13 (27.1)	16 (33.3)
Carboplatin + etoposide	14	6.19	—	6 (42.9)	1 (7.1)	3 (21.4)	4 (28.6)
Avelumab	10	19.47	4 (40.0)	—	1 (10.0)	—	5 (50.0)
Pembrolizumab	6	6.97	1 (16.7)	—	—	4 (66.7)	1 (16.7)
Cisplatin + etoposide	4	3.10	1 (25.0)	2 (50.0)	—	1 (25.0)	—
Carboplatin	2	21.54	—	—	—	—	2 (100)
Etoposide	2	1.05	—	—	—	1 (50.0)	1 (50.0)
Ipilimumab	2	1.41	—	—	—	2 (100)	—
Nivolumab + ipilimumab	2	3.96	—	1 (50.0)	1 (50.0)	—	—
ALRN-6924	1	0.72	—	—	—	1 (100)	—
Carboplatin + paclitaxel	1	0.03	—	1 (100)	—	—	—
FOLFOX	1	49.77	—	—	—	—	1 (100)
Pegylated liposomal doxorubicin hydrochloride	1	0.03	—	—	—	—	1 (100)
Paclitaxel	1	1.54	—	—	—	—	1 (100)
Sabatolimab	1	0.39	—	—	—	1 (100)	—

CR, complete response; NE, not evaluable; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease.

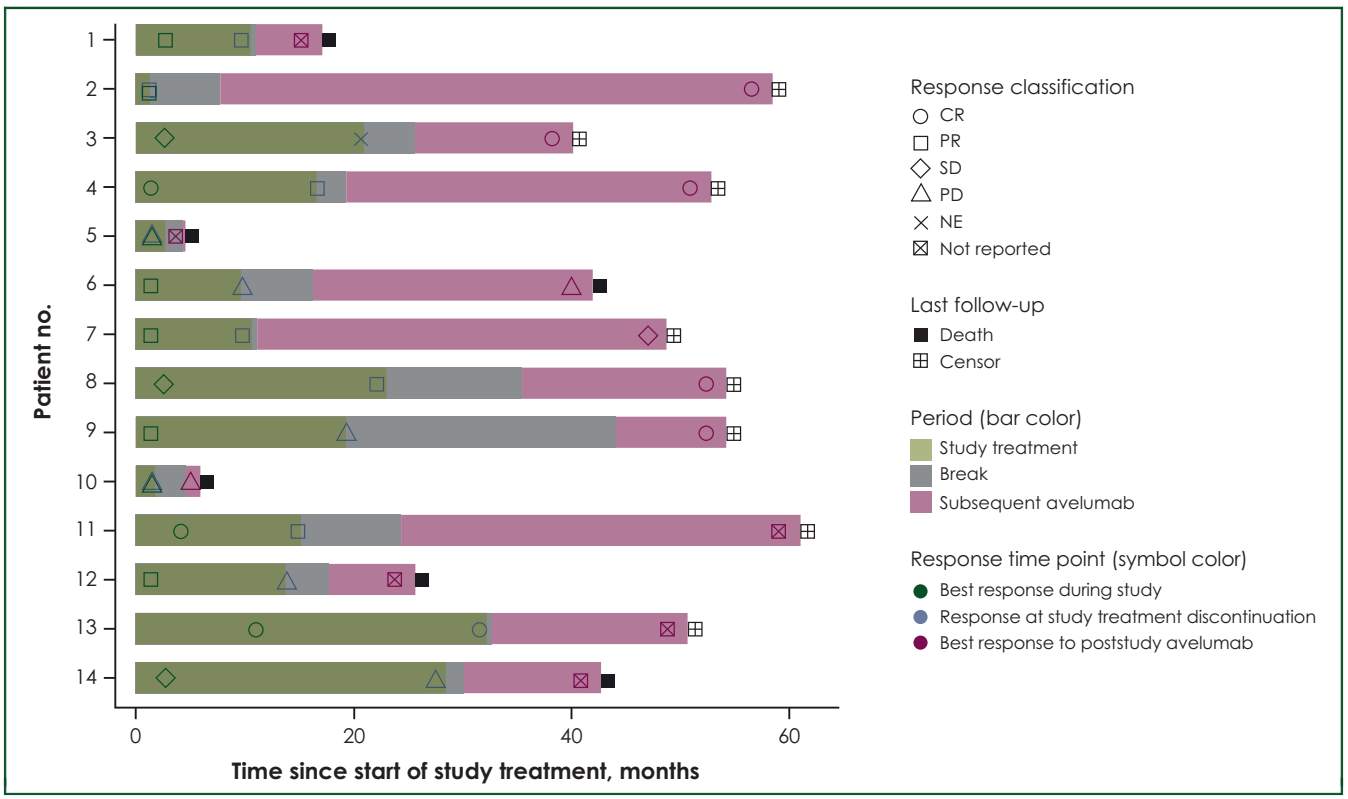

Figure 2. Swimmer plot of patients who received poststudy avelumab. The best response during study treatment was confirmed best overall response determined by the independent endpoint review committee; the response at treatment discontinuation and during subsequent treatment was determined by the treating investigator. 'Break' indicates treatment break or intervening treatment(s).
CR, complete response; NE, not evaluable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

patients who received chemotherapy (particularly platinum doublets) or immunotherapy. Responses to alternative immunotherapies in patients with mMCC who had disease progression during avelumab or pembrolizumab treatment have been reported previously.[14,15] In a phase II study of pembrolizumab in patients with locally advanced or metastatic MCC, responses with subsequent chemotherapy, immunotherapy, or other therapies were reported.[9] In addition, in a phase II study of nivolumab plus ipilimumab administered with or without stereotactic body radiotherapy in 26 patients with advanced MCC and previous PD-L1 treatment, the ORR was 31%.[16] In other reports of patients with mMCC who have had disease progression with immunotherapy, it has been suggested that radiotherapy may sensitize tumors to subsequent immunotherapy[15,17]; however, in the phase II study of nivolumab plus

ipilimumab, no increase in efficacy was observed with the addition of stereotactic body radiotherapy.[16] In our study, responses to subsequent immunotherapy also appeared similar in patients with or without radiotherapy, although patient numbers were small. Further studies are needed to investigate optimal treatment sequencing after first-line avelumab in patients with mMCC.

In the 14 patients who received commercial avelumab after discontinuing from the study, 5 had a poststudy CR; response at study discontinuation in these 5 patients was PR in 3, PD in 1, and not evaluable in 1, suggesting that most of these patients had an ongoing clinical benefit when they switched to commercial avelumab. Furthermore, 10 of 14 patients did not receive any other systemic anticancer therapy before restarting avelumab treatment, including 4 of the 5 who had a CR.

Limitations of this study are its single-arm design and the restriction of the long-term analysis to OS, patient disposition, and subsequent treatment. Safety data were not collected for this analysis; however, the safety of avelumab in this study population was analyzed in detail in an earlier report.[9] Cross-trial comparisons of OS with historical studies, which are included for illustrative purposes, may be associated with selection bias and other confounding factors; thus, comparisons should be interpreted with caution. Although the size of the study population is relatively small compared with studies in other tumor types, the rarity of MCC makes it difficult to conduct larger clinical studies. In fact, JAVELIN Merkel 200 is the largest clinical study ever reported in patients with MCC, and part B is the largest study to be reported in patients receiving first-line treatment for mMCC. Thus, the long-term data reported here provide a substantial contribution to clinical evidence in MCC.

In conclusion, this 4-year follow-up analysis from part B of JAVELIN Merkel 200 shows the long-term OS benefits of first-line avelumab treatment in patients with mMCC and further supports its use as a standard of care for patients with mMCC and its recommendation for use in international treatment guidelines.

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DISCLOSURE

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DATA SHARING

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck's (CrossRef Funder ID: 10.13039/100009945) Data Sharing Policy. All requests should be submitted in writing to Merck's data sharing portal (https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html). When Merck has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck will endeavor to gain agreement to share data in response to requests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines. The protocol was approved by the independent ethics committee or institutional review board at each participating center, and all patients provided written informed consent before enrollment.

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