Avelumab for advanced Merkel cell carcinoma in the Netherlands: a real-world cohort

Sonja Levy, Maureen J B Aarts, Ferry A L M Eskens, Kristien B M I Keymeulen, Lukas B Been, Dirk Grünhagen, Alexander van Akkooi, Mathilde Jalving, Margot E T Tesselaar

ABSTRACT

Background Merkel cell carcinoma (MCC) is associated with high recurrence rates and poor survival when metastatic disease is present. The immune checkpoint inhibitor avelumab has shown high response rates (RRs) and durable responses in patients with advanced MCC (aMCC) in clinical trials. To date, only results from clinical trials, patients treated in an expanded access program and very small numbers of patients have been reported. In this study, detailed real-world efficacy and toxicity data of avelumab in patients with aMCC are reported.

Methods Patients with aMCC treated in four dedicated referral centers in the Netherlands were analyzed from February 2017 until December 2019. Patients were included if they had received at least one administration of avelumab, regardless of previous lines of therapy. Patient data were collected retrospectively from patient records. Primary endpoints were response rate (RR) and duration of response (DOR). Secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity.

Results Fifty-four patients received avelumab. Eight (15%) patients had locally advanced disease (laMCC). In 40 (74%) patients, avelumab was first-line treatment, these included all patients with laMCC. The median follow-up was 8.9 (range 0.5–35.9) months. RR was 57% (n=31) with 24% (n=13) of patients achieving a complete response. The median DOR was 8.4 (range 1.3–22.1) months and 23 (43%) patients had an ongoing response at the end of the study. The median PFS was 8.6 (95% CI 1.6–15.5) months, and the median OS was 25.8 (95% CI 9.1–42.4) months. Six (11%) patients experienced grade 3 toxicity. No grade 4–5 toxicity was seen.

Conclusions In this real-world cohort, clinical efficacy and toxicity outcomes in clinical practice were in line with results from clinical trials and showed relatively high RRs and durable responses in patients with aMCC.

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and potentially aggressive neuroendocrine carcinoma of the skin with an incidence of around 0.5–0.8/100 000.1–4 Incidence has been rising over the last few decades.2 3 This is thought to be due to not only improved diagnostics and better awareness of this illness, but also increasing sun exposure and an aging population. The median age of presentation is 75 years and in approximately 7%–27% of patients regional or distant metastases are present at diagnosis.1 2 Prior to the introduction of immunotherapy for this disease, patients who no longer had curative, surgical treatment options due to metastatic MCC (mMCC) or locally advanced MCC (laMCC), had 5-year overall survival (OS) rates of only 7%–12%.5 6 Treatment strategies for advanced MCC (aMCC), including both laMCC and mMCC, were historically based on those for other small cell malignancies, such as small cell lung cancer, and mostly consisted of polychemotherapy. Although initial response rates (RRs) of aMCC to platinum-based chemotherapy were high, patients rapidly relapsed and no durable responses or survival benefit have been reported.1 7

MCC is associated with two different pathways of pathogenesis. The first route involves the Merkel cell polyomavirus (MCV). MCV is present in up to 80% of patients with MCC in the Northern hemisphere and integrates into the genome of cells driving oncogenic processes such as expression of T-antigen oncoproteins.8–11 In MCV-negative MCC, exposure to ultraviolet (UV) radiation appears important in the pathogenesis. MCV-negative tumors mostly arise from sun-exposed areas of the skin and show a high mutational burden and adaptive immune responses that are associated with chronic exposure to UV radiation.12 13 These alternative pathways of pathogenesis both provide a good rationale for treatment with immune checkpoint inhibitors (ICI).14 15

Several clinical trials showed beneficial results of ICI, such as programmed cell death-1 (PD-1) inhibitors, in the treatment of aMCC.8 16 17 Pembrolizumab was shown to have an objective RR (ORR) of 56%, with
progression-free survival (PFS) at 6 months of 67% in 26
patients with aMCC.\textsuperscript{17}

In 2016, the JAVELIN study, a phase II clinical trial that
investigated avelumab treatment in patients with aMCC,
showed significant and durable responses.\textsuperscript{8} In this study,
88 patients who had progressed after chemotherapy were
treated with avelumab and an ORR of 31.8% was seen,
with 8 patients achieving a complete response (CR) and
20 patients a partial response (PR). The median follow-up
was 10.4 months. Based on this study, patients in the Neth-
erlands were able to receive avelumab within an expanded
access program (EAP). Avelumab was granted accelerated
approval for aMCC by the Food and Drug Administration
in North America in March 2017, which was followed by
the European Medicines Agency in September of 2017.
In November of 2017, reimbursement in the Netherlands
followed and avelumab was integrated into the routine
management of patients with aMCC.\textsuperscript{18}

The population of patients with aMCC is frequently
elderly and frail, making it essential to determine whether
the results described in a clinical trial population can be
replicated in a real-world setting. In 2019, Knepper \textit{et al}
performed a large genomic analysis of patients with MCC,
and investigated the response to various ICI in 36 patients
with aMCC, of which 10 were treated with avelumab.
There, a RR of 44% was seen in all 36 patients.\textsuperscript{13} More
recently, a large study was performed in an elegant
attempt to evaluate the clinical efficacy and safety of
avelumab in the real-world population. There, the authors
included patients with aMCC who had received avelumab
in the EAP. They found that ORR was 47%, with 23% of
patients achieving a CR. Unfortunately, although a large
number of patients were evaluable for response (n=240,
46% of total), data were limited because the evaluation of
progression and toxicity were not documented according
to a study or clinical protocol, but was at the discretion
of the treating physician to document in the EAP system.
Also, the duration of response (DOR) was merely based
on the resupply of avelumab and data on the medical
history of patients included were sparse.\textsuperscript{19}

Both the clinical trials and the results from the EAP
indicate an auspicious effect of avelumab in treatment
with aMCC, but detailed data on patients with aMCC
treated with avelumab in routine clinical practice are still
lacking.

In the Netherlands, patients with aMCC are treated in
four dedicated tertiary referral centers across the country.
In this nationwide study, we aimed to evaluate the efficacy
and toxicity of avelumab in a large real-world cohort of
patients with aMCC treated in routine clinical practice in
the Netherlands.

\textbf{METHODS}

\textbf{Patients}

Patients with aMCC treated with avelumab since the intro-
duction of the EAP in the Netherlands were included
from all four MCC referral centers from February 2017
until December 2019. Data were collected retrospec-
tively and patients were followed-up until death or end
of follow-up. Patients were excluded if they had received
other types of ICI prior to avelumab. Histopathological
analyses were performed during the diagnostic workup
according to the standard of care for these tumors. MCV
positivity was determined immunohistochemically using a
CM2B4 monoclonal antibody as described previously.\textsuperscript{20,21}

Avelumab was administered in a 2 weekly interval as per
institutional protocol. Premedication consisting of 2 mg
elemastine and 1000 mg paracetamol was administered
intravenously during the first three cycles and continued
thereafter only if infusion reactions occurred.

Patient characteristics, response to avelumab, adverse
effects, and toxicity were gathered from electronic patient
records. All patients gave consent to use their medical
data according to institutional protocols.

\textbf{Outcomes}

Primary endpoints were RR and DOR. Response evalua-
tion by CT or positron emission tomography (PET-CT)
was performed at approximately 12-week intervals. As
this study was not conducted within a trial setting, the
response was reported in radiological records according
to routine diagnostic practice. When the radiological
evaluation was not possible, clinical parameters such as
changes in visible skin lesions that were measured with a
caliper or other evaluable parameters such as perform-
ance status were used. For biochemical response
measurements, all centers used lactate dehydrogenase
(LDH) with an upper limit of normal (ULN) 248 U/L,
and additionally, neuron-specific enolase (NSE) with a
ULN 18.2 μg/L was used in the largest referral center.\textsuperscript{22}
Responses were extracted retrospectively from patient
records and radiology reports. The measurements in the
reports initially described by a radiologist were reassessed
according to RECIST criteria. PR was defined as radi-
ographic shrinkage of tumors ≥30%. In the absence of
radiological response evaluation, visible and/or palpable
shrinkage ≥30% of skin tumors and/or lymph nodes were
evaluated. CR was defined as a complete metabolic and
radiological response on PET-CT. When mixed response
(MR) was present at ≥2 consecutive response evalua-
tions, defined as ≥30% tumor shrinkage, with simulta-
neous growth ≥20% of other lesions and/or occurrence
of new lesions, a consensus on continuation or cessation
of avelumab was reached in a multidisciplinary team
(MDT). The decision to perform salvage treatment
including surgery or radiotherapy was also reached in
an MDT. Progressive disease (PD) was defined as radi-
ographic tumor growth ≥20% and/or growth of visible
skin tumors, and/or increase of biochemical markers such as
LDH and/or NSE above the ULN, and/or deterioration of a
patients’ performance status due to aMCC. DOR was
defined as the time from first documented PR or CR until
documented PD, death, or end of follow-up.

Secondary endpoints were PFS, OS and toxicity. PFS and
OS were defined as the time from the first administration
of avelumab until documented progression or death, respectively. Patients were censored at the end of the study. Toxicity was evaluated according to CTCAE V.5.0, grades 1–5 were included.

Statistical analysis

Descriptive statistics with median and ranges were used for continuous variables and frequency and percentages for categorical variables. Pearson’s $\chi^2$ test was used to compare responses between groups and for the forest plot, univariable Clopper-Pearson calculations were performed to establish confidence intervals for proportions of patients that responded to avelumab. The Kaplan-Meier method was used to evaluate OS and PFS and the log-rank test was performed for comparison between first-line and second-line treatment. IBM SPSS V.25 was used to perform all statistical analyses.

RESULTS

Baseline characteristics

We identified 55 patients with aMCC who had received at least one dose of avelumab, 54 of these patients fulfilled the inclusion criteria. One patient was excluded due to prior treatment with ICI (nivolumab). Two patients received avelumab in the EAP. The first administration of avelumab was in February 2017, the last patient started treatment in September 2019.

Patients were first diagnosed with MCC at a median age of 71 (range 50–86) and had a median age of 73 (range 53–88) years at the start of avelumab. Thirty-four (63%) patients were male individuals. Primary tumor localizations were head and neck, trunk, extremities, or unknown primary tumor (UPMCC) in 13 (24%), 8 (15%), 25 (46%), and 8 (15%) patients, respectively. Eight (15%) patients had locally advanced (stage IIIB/laMCC) disease and 46 (85%) had the distant disease (stage IV/mMCC) at the start of avelumab administration. Of the latter, 35 (65%) patients had distant nodal and/or (sub)cutaneous disease, and in 19 (30%), visceral and/or peritoneal/mesenterial metastasis were present. In 12 (22%) patients, one organ site was involved, and in 4 (7%) patients, disease was present in two organs. Seven (13%) patients had a history of immunosuppression, including chronic lymphatic leukemia, Waldenström’s macroglobulinemia, human deficiency virus, idiopathic pulmonary fibrosis, and a kidney transplant. MCV status was determined in 21 patients. Of these, 15 (71%) was positive. PD-(L)1 expression was not determined in routine clinical practice, hence no data on PD-(L)1 expression were available. LDH levels were available for 50 patients at the start of avelumab. Of these, 29 (58%) had elevated LDH levels above ULN. Baseline characteristics are shown in table 1. Avelumab was first-line treatment for all patients with laMCC (n=8, 15%) and in 32 (59%) patients with mMCC; the remaining 14 (26%) patients with mMCC received avelumab as second-line treatment. Prior therapy in all patients consisted of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics for all included patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>All patients (N=54)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (63)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (37)</td>
</tr>
<tr>
<td>Immunosuppression history, n (%)</td>
<td></td>
</tr>
<tr>
<td>CLL</td>
<td>3 (6)</td>
</tr>
<tr>
<td>WM</td>
<td>1 (2)</td>
</tr>
<tr>
<td>HIV</td>
<td>1 (2)</td>
</tr>
<tr>
<td>IPF</td>
<td>1 (2)</td>
</tr>
<tr>
<td>KT recipient</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>71.1 (50.2–86.3)</td>
</tr>
<tr>
<td>At start IT</td>
<td>73.0 (53.0–88.0)</td>
</tr>
<tr>
<td>Primary tumor site, n (%)</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>13 (24)</td>
</tr>
<tr>
<td>Trunk</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Extremity</td>
<td>25 (46)</td>
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<tr>
<td>Unknown primary</td>
<td>8 (15)</td>
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<tr>
<td>WHO performance status, n (%)</td>
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<tr>
<td>0</td>
<td>17 (32)</td>
</tr>
<tr>
<td>1</td>
<td>32 (59)</td>
</tr>
<tr>
<td>2</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Disease status, n (%)</td>
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<tr>
<td>Locally advanced</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Distant disease</td>
<td>46 (85)</td>
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<tr>
<td>Metastasis, n (%)</td>
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<tr>
<td>Visceral metastases*</td>
<td>19 (35)</td>
</tr>
<tr>
<td>Nodal or (sub)cutaneous metastases</td>
<td>35 (65)</td>
</tr>
<tr>
<td>No. of organ sites involved,† n (%)</td>
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</tr>
<tr>
<td>1</td>
<td>12 (22)</td>
</tr>
<tr>
<td>2</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Line of therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>40 (74)</td>
</tr>
<tr>
<td>Second</td>
<td>14 (26)</td>
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<tr>
<td>Radiotherapy</td>
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<tr>
<td>Yes</td>
<td>31 (57)</td>
</tr>
<tr>
<td>No</td>
<td>23 (43)</td>
</tr>
<tr>
<td>MCV, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15/21 (71)</td>
</tr>
<tr>
<td>No</td>
<td>6/21 (29)</td>
</tr>
<tr>
<td>LDH, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21/50 (39)</td>
</tr>
<tr>
<td>No</td>
<td>29/50 (54)</td>
</tr>
<tr>
<td>Missing</td>
<td>4/50 (7)</td>
</tr>
</tbody>
</table>

*Also including distant mesenterial or peritoneal metastasis. †Organ sites included liver, bone, adrenal cortex, pancreas, intestine, pleura.

CLL, chronic lymphatic leukemia; IPF, idiopathic pulmonary fibrosis; IT, immunotherapy; KT, kidney transplant; LDH, lactate dehydrogenase; MCV, Merkel cell polyomavirus; WM, Waldenström’s macroglobulinemia.
platinum-based chemotherapy. Additionally, 31 (57%) patients had received radiotherapy on either primary tumor area or metastasis prior to avelumab initiation. All patients had a performance score (PS) ≤ 2. Patients with a PS of 2 (n=5, 9%) were all in the mMCC group. In patients with laMCC, 3 (38%) had PS 0 and 5 (63%) had PS 1, compared with 14 (30%) and 27 (58%) patients with mMCC, respectively. Patients received a median of 10 (range 1–39) doses of avelumab and the median follow-up time was 8.9 (range 0.5–35.9) months.

Response to avelumab

Three patients (6%) were not evaluable for response: two died due to comorbidities before response evaluation. Comorbidities included rapidly progressive dementia and a superinfection due to pre-existent idiopathic pulmonary fibrosis shortly after avelumab administration. One patient discontinued avelumab after one infusion due to an allergic reaction and was referred to the general practitioner for palliative care.

Out of all 54 patients, objective response to avelumab was seen in 57% (n=31). In 24% (n=13) of patients, best overall response (BOR) was a CR, PR was seen in 33% (n=18), stable disease in 6% (n=3), MR in 4% (n=2), and PD in 28% (n=15) of patients with mMCC, respectively. Patients received a median of 10 (range 1–39) doses of avelumab and the median follow-up time was 8.9 (range 0.5–35.9) months.

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In patients with UPMCC, 63% (n=5) had an objective response, whereas in patients with known primary locations 56% (n=26) had a response (p=0.752). CRs occurred in 25% (n=2) of patients with UPMCC, and in 24% (n=11) of patients with known primary tumors (p=0.947).

Out of the 19 patients with visceral metastases (including peritoneal or mesenteric metastases), 63% (n=12) had a response compared with 54% (n=19) out of the remaining 35 patients who had nodal or subcutaneous metastases only (p=0.529). CRs were achieved in 37% (n=7) of patients with visceral metastases and in 17% (n=6) of patients without visceral metastases (p=0.106).

In the 50 patients for whom LDH levels were known, no differences in response to avelumab between elevated LDH levels and normal LDH levels were seen. In patients with elevated LDH levels, response was seen in 62% (n=13) of patients compared with 55% (n=16) of patients who had normal LDH levels (p=0.634). Interestingly, in patients who had received avelumab as second-line treatment, 11 of 14 (79%) had a response compared with patients who received avelumab as first-line treatment, of which 20 of 40 (50%) patients had a response (p=0.063). In contrast, CRs were present in 28% (n=11) of patients receiving the first-line avelumab, compared with 14% (n=2) of patients treated with second-line avelumab (p=0.302). We saw no difference in response to avelumab for patients who had received radiotherapy prior to avelumab initiation: of the 31 patients who underwent radiotherapy, 52% (n=16) had a response compared with 65% (n=15) out of 23 patients who did not (p=0.317).

In patients with a history of immunosuppression, 29% (n=2) had a PR, and no CRs occurred in this group.
The median DOR was 8.4 (range 1.3–22.1) months, and median PFS was 8.6 (95% CI 1.6–15.5) months. The estimated median OS was 25.8 (95% CI 9.1–42.4) months. We saw no significant differences in PFS and OS between patients treated with avelumab in first-line or second-line setting, \( p=0.337 \) and \( p=0.548 \), respectively. PFS and OS are shown in figure 3A,B. Responses were ongoing in 23 (43%) patients at the end of follow-up. PD occurred in 7 of 19 patients for whom BOR was PR. All seven patients were on active therapy at the time of progression. For patients who achieved CR: at the end of the study, 12 of 13 patients remained free of disease, with a median DOR of 12.8 (range 3.6–22.1) months. The remaining patient had achieved a CR after 2.6 months and had discontinued avelumab treatment after 19 cycles (8.8 months). Recurrence occurred 17.2 months after the start of therapy. During follow-up, no relapses were observed with avelumab were initiated for patients who had initially responded but then progressed. Clinical activity of avelumab in all patients evaluable for response are shown in figure 4.

Out of all 54 patients, 6 (11%) experienced grade 1 toxicity, which was mostly fatigue. Four (7%) patients experienced grade 2 toxicity, which constituted of allergic reactions requiring oral intervention, hypothyroidism, and hepatitis. Grade 3 toxicity including allergic reactions and renal insufficiency resulting in clinical admission were seen in five (9%) patients. No grade 4 or 5 toxicities were seen. Toxicities are shown in table 2.

**DISCUSSION**

In this real-world cohort of patients with aMCC, avelumab treatment resulted in high RRs, durable responses, and manageable toxicities. This study describes a detailed and relatively large cohort of patients with aMCC outside the setting of a clinical trial or an EAP, showing a true representation of the real-world clinical practice for patients with aMCC. We demonstrate that avelumab now has a prominent role in both first-line and second-line treatment for aMCC.

In the 40 patients in our study who received avelumab in the first-line setting, we found a RR of 50% with 28% achieving a CR. The EAP study found similar results in 15 patients who were treated with the first-line avelumab, where 47% of patients had a response. This is also in concordance with results seen in clinical trials involving

**Table 2  Avelumab-associated toxicities**

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Allergic/infusion reaction</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
</tr>
<tr>
<td>Allergic</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>15 (28)</td>
</tr>
</tbody>
</table>
pembrolizumab or avelumab as first-line treatment for aMCC.17 23 24

Regarding previous lines of therapy, in the cohort of 36 patients treated with various ICIs that were investigated by Knepper et al, a dramatic decrease in response was seen in patients treated with higher therapy lines. There, a RR of 75% was found for patient treated with ICI as first-line therapy, 39% as second-line therapy, and 18% in third-line or higher-line therapy.15 Similarly, in our cohort, patients treated with first-line avelumab also had a more favorable outcome. We found that nearly all CRs arose in patients treated with the first-line avelumab, and responses were similar in both laMCC and mMCC, indicating that tumors in patients without prior lines of chemotherapy might be more sensitive to PD-(L)1 blockade. This supports the clinical practice that we see evolving in the Netherlands in which avelumab is increasingly being used as first-line therapy for mMCC.

Although only 14 patients in our cohort were treated with avelumab as second-line therapy for aMCC, still interesting results were seen. When comparing our patients receiving avelumab as a second-line treatment for aMCC with those from clinical trials, we saw similar rates of CRs: 14% in our cohort compared with 9% in the JAVELIN trial.8 In contrast, the overall ORRs were quite different, with 79% in our second-line patients compared with 32% in the trial. There, over half of the patients were treated with more than one prior line of chemotherapy, and the authors suggest that this could have led to more immunologically depleted patients, resulting in worse RRs. This is substantiated by the updated results of the JAVELIN trial after a median follow-up of 41 months, where a trend towards a higher ORR in patients with fewer prior lines of therapy was seen.24 This could explain the higher RR in our cohort as we had no patients with more than one prior line of therapy.

In earlier years, when polychemotherapy was the treatment of choice for aMCC, a more advanced disease stage was associated with a worse prognosis. Several epidemiological studies have found that a more advanced disease stage is an independent predictor for survival.1 25–30 Interestingly, in studies where patients with aMCC were treated with ICI, no significant difference in response to treatment were seen between stage IIIb or IV disease, but a trend towards lower RRs remained.8 17 In our cohort, 35% of patients had visceral metastases at treatment initiation. This is a smaller percentage than was shown in the clinical trials, were visceral metastases have been reported to be present in 53%–67% of patients.8 16 However, older studies that focused on chemotherapy for aMCC, found similar or even lower percentages of visceral metastases than in our cohort, suggesting that the percentage of visceral metastases varies greatly between different study populations.7 31 Besides this, although we saw no statistically different responses, we saw a trend towards higher RRs in patients with visceral metastases. This seems contradictory to the results from clinical trials.8 32 Finding these differences may be attributable to the small number of patients with visceral metastases (n=19). Another explanation might be that because of the retrospective nature of this study, we did not perform other measurements of disease burden, such as sum of lesion diameter parameters. This might underestimate the disease burden in patients with nodal and/or subcutaneous disease only, subsequently overestimating disease burden in patients with visceral metastases. Nevertheless, our cohort represents an accurate representation of radiological documentation and response to avelumab in patients with aMCC in routine clinical practices. Therefore, these results remain generalizable to clinical practices elsewhere.

Patients with UPMCC have been shown to have a longer OS and a higher tumor mutational load than patients with known primary tumor locations.33 34 It has, therefore, been implied that patients with UPMCC are more likely to respond to immunotherapy.33 However, both clinical trials involving ICI and this real-world cohort did not show different RRs in patients with a UPMCC.8 Potential differences may have been missed due to the fact that we had only eight (15%) patients with UPMCC.8 Yet our findings are in concordance with results shown in a Dutch cohort of 351 patients, where UPMCC was not associated with a survival benefit in multivariable analysis.35

As we did not perform additional genomic sequencing, data on mutational burden were not available. To determine whether the mutational burden indeed plays a role in the response, larger studies are needed. Recently, several potential strategies to involve and study larger numbers of patients with aMCC have been described.36 Future studies should aim to elucidate which patients would benefit from ICI by investigating which possible biomarkers or genomic characteristics of the tumor are associated with response to PD-(L)1 blockade.

CONCLUSION

In the Netherlands, avelumab is increasingly being used as first-line and second-line systemic treatment for aMCC. In this real-world cohort, RRs, DOR, PFS, and toxicity results are promising and essentially in line with results found in clinical trials. Although higher RRs were seen in patients treated in the second line, more complete and durable responses were seen in patients who received avelumab as first-line treatment.

Author affiliations
1Department of Medical Oncology, Antoni van Leeuwenhoek Netherlands Cancer Institute, Amsterdam, The Netherlands
2Department of Medical Oncology, Maastricht University Medical Center+, Maastricht, Limburg, The Netherlands
3Department of Medical Oncology, Erasmus Medical Center, Rotterdam, Zuid-Holland, The Netherlands
4Department of Surgery, Maastricht University Medical Center+, Maastricht, Limburg, The Netherlands
5Department of Surgical Oncology, University Medical Center Groningen, Groningen, The Netherlands
6Department of General Surgery, Erasmus Medical Center, Rotterdam, Zuid-Holland, The Netherlands

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