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Avelumab use in Merkel cell carcinoma treatment

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Avelumab is a programmed death-ligand 1 (PD-L1) blocking human IgG1 lambda monoclonal antibody. It was the first immunotherapy to be approved for the treatment of MCC. In March 2017, the FDA granted accelerated approval to avelumab for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC) –irrespective of prior therapy. In July 2017, the European Medicines Agency (EMA) recommended the approval of avelumab as a monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (mMCC). Approvals were based on the efficacy and safety demonstrated in JAVELIN Merkel 200 (NCT02155647), a multi-center, open-label, single-arm, phase II clinical trial [1]. Part A of the study consisted of patients treated in the second line with metastatic, chemotherapy-refractory MCC. Part B consisted of systemic treatment-naive patients who received avelumab as a first-line treatment for metastatic or distally recurrent MCC. In the first line the ORR is 39.7%. Durable responses lasting at least 6 months were observed and the majority of responses are observed early with the median time to response of 6.1 week. PFS rate at 6 and 12 months are 41% and 31%, respectively. Median OS is 20.3 months. The OS rate at 1 year is 60%.

Key words: Merkel cell carcinoma, avelumab, immunotherapy, skin

Introduction

The development of immune checkpoint inhibitors (ICIs) represents a revolutionary innovation in the field of oncology. It is rapidly evolving and offers an attractive therapeutic option for many cancers, including Merkel cell carcinoma (MCC). MCC is a rare, neuroendocrine, clinically aggressive, cutaneous malignancy with a high mortality rate and a dramatically increasing incidence rate, rising from 0.5 to 0.7 per 100,000 persons between 2000 and 2013 [2, 3]. In both Europe and the United States, approximately 2500 new cases of MCC are diagnosed each year and metastatic disease is diagnosed in 5–12% of patients [4, 5]. Population ageing in the 21st century is predicted to have a major impact on MCC incidence, which is estimated to reach 3,284 cases in 2025 [3, 6, 7].

Merkel cell carcinoma has a significantly higher prevalence in elderly people and tends to affect individuals later in life compared with melanoma. The median age at diagnosis is 75–79 years for both genders *versus* 65–69 years and 60–64 years for male and female melanoma patients, respectively [3]. Of note, the rate of most cancers tends to decline among individuals over the age of 85, however, the rate of MCC continues to rise. Important risk factors associated with this cancer type include light skin colour, male sex, immunosuppression, exposure to ultraviolet radiation, and Merkel cell polyomavirus (MCPyV) infection, which is present in approximately 80% of MCC tumors [8]. Its most significant characteristics are summarized in an acronym: AEIOU – asymptomatic/lack of tenderness, expanding rapidly, immunosuppression, older than age 50, and UV-exposed site on a person with fair skin [7, 9].

Historically, MCC was associated with very poor outcomes, especially for patients with metastatic disease. Traditional treatment options for MCC included surgery, radiation,

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chemotherapy, and treatment for metastatic or stage IV MCC was most often palliative. Before the dawn of immunotherapy in the treatment of MCC in 2016, there was no effective therapeutic option that offered a confirmed survival benefit for MCC patients with metastatic disease not amenable to surgery and/or radiotherapy. Despite its low incidence compared with melanoma, research on immune-checkpoint inhibitors in MCC continues to gain attention. Patients with this tumor type have been shown to be good candidates for immunotherapy due to high immunogenicity [6, 7, 10]. A study of 5823 prospectively enrolled MCC cases from the National Cancer Data Base (NCDB) reported that the relative survival at five years post diagnosis was:

- ~64% for patients presenting with local disease,
- ~39% for patients with regional nodal disease,
- ~18% for patients presenting with distant metastatic MCC [11, 12].

It has been estimated that mortality rates increased from 0.03 to 0.43 per 100,000 persons, from 1986 to 2011 in the US, based on data from the Surveillance, Epidemiology and End Results program [5]. Moreover, MCC is generally associated with less favourable prognoses, higher recurrence and mortality rates compared with melanoma [13].

In 2017, the U.S. Food and Drug Administration (FDA) granted accelerated approval to avelumab (BAVENCIO, EMD Serono, Inc.), an anti-PD-L1 blocking human IgG1 lambda monoclonal antibody, for first-line treatment of patients 12 years and older with metastatic MCC. Approval was based on data from an open-label, single-arm, multi-center clinical trial (JAVELIN Merkel 200) demonstrating a clinically meaningful and durable overall response rate (ORR). In 2018, the FDA granted accelerated approval to pembrolizumab (KEYTRUDA®, Merck & Co. Inc.) for adult and pediatric patients with recurrent locally advanced or metastatic MCC. Approval was based on data from a multi-center, non-randomized, open-label clinical trial (KEYNOTE-017). The major efficacy outcome measures were overall response rate (ORR) and response duration assessed by blinded independent central review per RECIST 1.1. [14].

Avelumab – second-line treatment

Avelumab was first studied in second line treatment. The eligibility criteria for part A of the JAVELIN Merkel 200 study required that all enrolled patients were at least 18 years of age, had a good performance status (Eastern Cooperative Oncology Group 0–1 [ECOG 0–1]), life expectancy of >3 months, histologically confirmed mMCC with disease progression following at least one previous systemic therapy used in the metastatic setting, at least one unidimensional measurable lesion by RECIST v. 1.1 criteria (response evaluation criteria in solid tumors), and adequate hematological, renal, and hepatic function. Patients with autoimmune conditions were ineligible for enrollment. The participants received avelumab at a dose of 10 mg/kg of body weight intravenously once every 2 weeks until experiencing disease progression or unacceptable toxicity. 59% of patients were reported to have had one prior anti-cancer therapy for mMCC and 41% had two or more prior therapies. The median age was 72.5 years (range, 64.5–77.0). Tumors were assessed every 6 weeks and the primary end-point was confirmed objective response (OR; CR or PR) based on independent assessment and RECIST v. 1.1 criteria. Efficacy and safety populations included patients who received at least one dose of the study drug.

The study cohort included 88 patients with a median follow-up time of 10.4 months from the first received dose of avelumab treatment to the first analysis cut-off date in 2016 [1]. The ORR was found to be 31.8% (95% CI: 21.9–43.1%; n = 28), with CR in eight patients and PR in 20 patients. Stable disease (SD) was observed in nine patients. The responses were long-lasting and, at the time of analysis, were maintained in 23 patients. The duration of response (DOR) was at least 6 months in 92% of cases. In comparison, an observational study published in the same year, reported that the proportion of patients with chemotherapy-refractory mMCC who responded to chemotherapy in the second-line setting was 23%, with a 6-month DOR in 6–7% of cases [15].

In this study the mPFS was 2.7 months (95% CI: 1.4–6.9), and the rate of PFS at 6 months was 40%. The PFS curve reached a plateau. The mOS was 11.3 months (95% CI: 7.5–14.0) and the OS rate at 6 months was 69%. In this analysis, five grade 3 treatment-related adverse events were reported in four (5%) patients: lymphopenia in two patients, aminotransferase increase in one patient, creatine phosphokinase increase in one patient, and blood cholesterol increase in one patient. There were no treatment-related grade 4 AEs or treatment-related deaths reported. PD-L1 expression (≥1% positive cells) was assessable in 74 patients and it was found to be present in 58 cases (78%). MCPyV status was assessed in 77 cases and 60% (n = 46) were positive. Better outcomes were reported in patients who received fewer prior lines of systemic therapy [1].

Updated analyses were published in 2018 and provided confirmation of continued durable responses and meaningful survival outcomes. The patient cohort had a median follow up for 29.2 months (24.8–38.1) [16]. The mOS was 12.6 months (95% CI: 7.5–17.1), and the OS rate at 2 years was 36%. The median treatment duration was 3.9 months (0.5–36.3). The confirmed ORR was 33.0% (95% CI: 23.3–43.8) and remained unchanged from analyses conducted at 12 and 18 months [17]. The median DOR was not reached (2.8–31.8). The PFS values were 29% after 12, 29% after 18, and 26% after 24 months of follow-up. Clinical activity was observed irrespectively of PD-L1 expression status and MCPyV status [16, 18]. The results of the next updated analysis were published in 2020, and provided further confirmation of avelumab efficacy in the group of previously pretreated patients [19]. Again, the ORR was

33.0% (95% CI: 23.3–43.8%). CR was observed in 10 patients (11.4%). In 17 of 29 patients who achieved a response to treatment (58.6%), the response was maintained. Four patients had a continuous response lasting at least 3 years. DOR was 40.5 months (median; 95% CI: 18.0 months – not estimable). PFS rate at 2 years and 3 years was 26% (95% CI: 17–36%) and 21% (95% CI: 12–32%), respectively. After ≥44 months of follow-up, OS was 12.6 months (median; 95% CI: 7.5–17.1 months). OS rates at 3 years and 3.5 years were 32% (95% CI: 23–42%), and 31% (95% CI: 22–41%) respectively.

In avelumab therapy, high tumor mutational burden and high expression of MHC I (major histocompatibility complex class I) were associated with trends in the improvement of OS and ORR. Long-term responses, i.e., responses for at least 3 years, were observed regardless of PD-L1 expression. Any grade AEs and grade ≥3 AEs were reported in 97.7% and 73.9%, respectively. Any grade TRAEs and TRAES G ≥3 occurred in 77.3% and 11.4% of participants, respectively. The most frequently reported TRAEs were fatigue, diarrhea, and nausea. Immune-related adverse events (irAE) were reported in 19 patients (21.6%). Four irAE were grade ≥3: increased transaminases, increased alanine aminotransferase, autoimmune disorder, and hypothyroidism. Eight patients (9.1%) discontinued therapy due to TRAEs. There were no deaths related to the study treatment [19].

The most recent analysis of this patient group was performed after >5 years of follow-up (median 65.1 months, range 60.8–74.1 months) and published in December 2021 [20]. The median OS remained unchaged at 12.6 months (95% confidence interval [CI] 7.5–17.1 months). The 5-year OS rate was reduced to 26% (95% CI: 17–36%). Only one patient (1.1%) continued to receive avelumab, and another patient (1.1%) had reinitiated treatment following previous discontinuation. Despite the fact that resposes to avelumab occurred regardless of PD-L1 status, interestingly, it was observed that patients with PD-L1+ tumors had longer OS and higher 5-year OS rate compared with patients with PD-L1 negative tumors. Consistent with the trends observed in previous analyses, the median OS was 12.9 months (95% CI: 8.7–29.6 months) *versus* 7.3 months (95% CI: 3.4–14.0 months) and the 5-year OS rate was 28% (95% CI: 17–40%) *versus* 19% (95% CI: 5–40%), respectively (HR 0.67; 95% CI: 0.36–1.25) [19]. Nonetheless, the OS of both subgroups greatly exceeded that recorded in retrospective analyses of second-line or subsequent chemotherapy in patients with mMCC, whose 1-year OS rate was 0%. This further supports the evidence that avelumab can offer a significant OS benefit irrespective of tumor PD-L1 status. During the course of the >5 year follow-up, death occurred in 71.6% of patients, however, there were no cases attributed to treatment-related adverse events. In conclusion, avelumab showed durable responses in the long-term OS study and manageable safety profile in patients who received prior systemic chemotherapy.

Avelumab – first-line treatment

Subsequently avelumab was studied in first line. The enrollment criteria for patients who participated in part B of the JAVELIN Merkel 200 trial were the same as those in part A, however, the efficacy of avelumab was explored in a cohort of eligible patients with metastatic MCC who had not received prior systemic therapy for metastatic disease [21]. As previously mentioned, the therapy was approved in 2017 by the US FDA and the EMA as a first-line treatment for patients who were at least 12 years of age with metastatic MCC. The preliminary results of part B of the study using avelumab in chemotherapy-naive mMCC patients were published in 2017 [22]. At the analysis cut-off point, 29 of the 112 planned patients had been enrolled in the trial. The median age was 75.0 years (range 47–87). The drug was administered at a dose of 10 (mg/kg) as a 1-hour intravenous infusion once every 2 weeks until the patient experienced unacceptable toxicity, therapeutic failure or significant clinical decline [22].

After a follow-up period of at least 3 months, 16 of 29 patients were found to have an unconfirmed ORR of 68.8% (95% CI: 41.3–89.0) with CR in 18.8% and confirmed ORR 56.3% (95% CI: 29.9–80.2; 1 unconfirmed PR with discontinuation) [22]. All recorded responses were ongoing at the time of this analysis. The safety assessment revealed that 20 of 29 patients (69.0%) experienced a TRAE, including grade ≥3 TRAE in 5 patients (17.2%), which led to treatment discontinuation in all cases. They included two cases of infusion-related reactions, one case of aspartate aminotransferase increase, one case of alanine aminotransferase increase, one case of cholangitis, and one case of paraneoplastic syndrome [22]. There were no treatment related deaths at this time [21].

Subsequent analyses were published in 2018 and used novel statistical methods to extrapolate long-term patient survival data. For patients treated with avelumab in the first-line setting, the expected mean survival rate was calculated to be 49.9 months (6.3; 179.4), and 1 year and 5 year survival rates were 66% and 23%, respectively [23]. For patients treated with avelumab in the second-line or later setting, the expected mean survival rate was calculated to be 42.3 months (28.4; 77.4), and 1 year and 5 year survival rates were 51% and 19%, respectively. Based on this extrapolation, it was expected that the hazard of death was greater for chemotherapy-refractory patients than for treatment-naive patients.

At the next analysis cut-off point, 39 of 112 planned patients had been enrolled in the trial, with a median follow-up of 5.1 months (range, 0.3–11.3 months) [21]. Efficacy was assessed in 29 of 39 patients who had at least 3 months of follow-up. They were found to have a confirmed ORR of 62% (95% CI: 42.3–79.3%), which consisted of 4 patients (13.8%) having CR and 14 patients (48.3%) having PR. At the time of analysis 14 of 18 responses (77.8%) were continuing. Additionally, 3 patients (10.3%) had stable disease. The majority of responses to treatment (89%) were recorded during the first assessment since treatment initiation, approximately at 6 weeks [21].

All enrolled participants were evaluable for safety and 28 of 39 (71.8%) experienced a TRAE, while TRAEs of grade 3 occurred in 8 patients (20.5%). There were no grade 4 TRAEs or treatment-related deaths reported. In patients who responded to aveumab treatment, the proportion of responses with a duration ≥3 months was 93% (95% CI: 61–99%), while the proportion of responses with a duration ≥6 months was 83% (95% CI: 49–96%), based on the Kaplan-Meier estimates [21].

For all the 116 patients in longer follow-up, the ORR was 39.7% (95% CI: 30.7–49.2%), of which 19 patients (16.4%) showed CR and 27 patients (23.3%) showed PR. Durable responses lasting at least 6 months were observed in 35 patients, resulting in a DRR of 30.2% (95% CI: 22.0–39.4%). Importantly, the majority of responses were observed early; 43 (93.5%) of 46 patients responded to treatment by 3 months and the median time to response was 6.1 weeks (range: 5–36). In PD-L1+ patients (n = 21) ORR was 61.9% (95% CI: 38.4–81.9%), and in the PD-L1--participants (n = 87) the ORR was 33.3% (95% CI: 23.6–44.3%). Median DOR was 18.2 months (95% CI: 11.3 months – not estimable). The PFS rate at 6 months and at 12 months was 41% (95% CI: 32–50%) and 31% (95% CI: 23–40%), respectively. Median OS was 20.3 months (95% CI: 12.4 months – not evaluable). The OS rate at 1 year was 60% (95% CI: 50–68%), and in PD-L1+ and PD-L1 groups 1 year OS rates were 71% (95% CI: 47–86%) and 56% (95% CI: 45–66%), respectively [19].

The most recent efficacy and safety data analysis of this study was published in July 2021. A cohort of 116 patients treated with avelumab in the first-line setting had a median follow-up of 21.2 months (range: 14.9–36.6) [24]. The median duration of treatment was 24 weeks (range: 2.0–154.0). At this cut-off point, 26 patients (22.4%) continued to receive treatment. The most numerous reasons for treatment cessation were PD (n = 48; 41.4%) and AE (n = 23; 19.8%). Any grade TRAEs occurred in 94 patients (81.0%), which included grade ≥3 reported in 21 patients (18.1%). Any grade irAEs occurred in 35 patients (30.2%), which included grade ≥3 reported in 7 patients (6%), namely pruritus, increased ALT, autoimmune nephritis, autoimmune neuropathy, dermatitis psoriasiform, diabetes mellitus, and increased liver function tests. There were no treatment-related deaths reported in this cohort (tab. I).

For avelumab, first line treatment patients whose response rates were numerically higher had tumors that were

Table I. Major avelumab toxicities reported in JAVELIN Merkel 200 study

Study	Grade 1 or 2 toxicity	Grade 3 or 4 toxicity
JAVELIN Merkel 200 treatment line 1 [24]	ALT increased* (n = 4; 3.5%) AST increase (n = 1; 0.9%) asthenia (n = 16; 13.8%) chills (n = 12; 10.3%) decreased appetite (n = 5; 4.3%) fatigue (n = 23; 19.8%) infusion-related reaction (n = 12; 10.4%) lipase increase (n = 2; 1.7%) maculopapular rash* (n = 6; 5.2%) pruritus* (n = 14; 12%)	ALT increased* (n = 1; 0.9%) amylase increase (n = 3; 2.6%) AST increase (n = 1; 0.9%) autoimmune nephritis* (n = 1; 0.9%) autoimmune neuropathy* (n = 1; 0.9%) cholangitis (n = 1; 0.9%) colitis (n = 1; 0.9%) decreased appetite (n = 1; 0.9%) dehydration (n = 1; 0.9%) dermatitis psoriasiform* (n = 1; 0.9%) diabates mellitus* (n = 1; 0.9%) fatigue (n = 1; 0.9%) gait disturbance (n = 1; 0.9%) infusion-related reaction (n = 1; 0.9%) lipase increase (n = 4; 3.4%) liver function test increase* (n = 1; 0.9%) paraneoplastic encephalomyelitis (n = 1; 0.9%) paraneoplastic syndrome (n = 1; 0.9%) polyneuropathy in malignant disease (n = 1; 0.9%) pruritus* (n = 1; 0.9%) troponin increase (n = 1; 0.9%) tumor lysis syndrome (n = 1; 0.9%)
JAVELIN Merkel 200 treatment line >1 [20]	asthenia (n = 7; 8%) blood creatine phosphokinase increase (n = 1; 1%) decreased appetite (n = 5; 6%) diarrhoea (n = 8; 9%) fatigue (n = 21; 24%) hyperthyroidism* (n = 2; 2%) hypothyroidism* (n = 3; 3%) infusion-related reaction (n = 15; 17%) maculopapular rash (n = 5; 6%) nausea (n = 8; 9%) pneumonitis* (n = 1; 1%) rash (n = 6; 7%) type I diabetes mellitus* (n = 1; 1%)	aminotransferase increase (n = 1) blood cholesterol increase (n = 1; 1%) blood creatine phosphokinase increase (n = 1; 1%) lymphopenia (n = 2; 2%)

* – TRAEs including immune-related adverse events (irAEs)

PD-L1 positive, Merkel cell polyomavirus (MCPyV) negative, and with increased intratumoral CD8+ T-cell density. The study cohort was largely dominated by patients with PD-L1– tumors (75.0% *vs.* 18.1% with PD-L1+ tumors). Conversely, part A of the JAVELIN Merkel 200 trial, which examined the efficacy of avelumab in mMCC patients in the second-line setting, had a majority of participants with PD-L1+ tumors, specifically 78% of assessable patients had PD-L1+ tumors [1]. This was also true for the Keynote-027 trial, which examined the efficacy of pembrolizumab in mMCC patients in the first--line setting, including patients having PD-L1+ tumors [25]. Consistent with results from part A of this trial, patients with both PD- L1+ and PD-L1– tumors in the systemic treatment--naive cohort experienced responses to treatment, however, higher response rates were observed in those with PD- L1+ tumors. MHC class I expression did not correlate with response to treatment or patient OS [1].

Based on the findings reported from part A and B of the trial, it appears that response rates of mMCC patients treated with avelumab (anti-PD-L1) in the first-line setting may be higher than those with chemotherapy-refractory tumors treated in the second-line or later setting. The ORR of participants in part A (n = 88) of the JAVELIN Merkel 200 trial was 33.0% *versus* 39.7% in part B (n = 116) and the median OS was 12.6 months *versus* 20.3 months, respectively [20, 24]. This finding is also supported by results from the phase II Keynote-017 trial (n = 50) of first-line treatment with pembrolizumab (anti-PD-1) of patients with stage IIIB (n = 7) or stage IV (n = 43) MCC, where the ORR was 56% and median OS was not reached after a median follow-up of 14.9 months [25].

Avelumab – expanded access program

The efficacy of avelumab in the real world was assessed in the expanded access program, which included mMCC patients with disease progression during or after chemotherapy and patients ineligible for chemotherapy or clinical trial participation. The efficacy and safety results were consistent with these from the JAVELIN Merkel 200 clinical trial. The enrolled population also included patients who had an ECOG PS 2 or 3, who had brain metastases stable after therapy, or were potentially immunocompromised. The median duration of avelumab treatment was 7.9 months (range, 1.0–41.7). 240 of 494 enrolled patients were evaluable for efficacy. The ORR was 46.7% in the evaluable patients, 22.9%, and 23.8% of participants achieved CR and PR. The safety data are limited. The most frequently reported AEs were an infusion-related reaction, fever, fatigue, rash, asthenia, abdominal pain, chills, and dyspnea. The relatively high number of infusion-related reactions resulted in the recommendation to use a premedication (paracetamol with antihistaminic) for at least the first four cycles of avelumab therapy [26]. In a European EAP 150 patients were treated and the objective response rate was 48.0%. In the responding patients, the median duration of treatment (DoT) was 7.4 months, with the longest duration of 41.7 months. Again the most common AEs were infusion-related reaction reported in 2.4% of cases and pyrexia in next 2.1% of patients. No new toxicities were observed in this study [27]. Moreover, in our real world study we enrolled 161 MCC patients who were treated with curative intent. Lymph node metastases at diagnosis were found in 26.9% of patients. Sentinel lymph node biopsy (SLNB) was performed in 36.5% of patients and was positive in 10.5%; 51.9% of our patients received perioperative treatment. After treatment, the relapse rate was 38.3%. With a median follow-up of 2.3 years, the median DFS was not reached, and the 1-year rate was 65%. The negative risk factors for shorter DFS were male gender, metastases in LN at diagnosis, no SLNB performed in patients without clinical nodal metastases, and no perioperative radiotherapy treatment. The estimated OS was 6.9 years with negative independent risk factors again male gender, age above 70, metastases in lymph nodes at diagnosis, and no SLNB in patients without clinical nodal metastases [10].

Avelumab – adjuvant treatment

More avelumab studies are being conducted (tab. II). A multicenter, randomized, double-blinded, placebo-controlled, phase III trial of adjuvant avelumab (anti-PDL-1 antibody) in MCC patients with clinically detected lymph node metastases is currently ongoing. This is the ADAM trial: a multicenter, randomized, double-blinded, placebo-controlled, phase 3 trial of adjuvant avelumab in Merkel cell carcinoma patients with clinically detected lymph node metastases (NCT03271372). It is expected to analyze 100 MCC patients. Enrolled patients must have clinically detected nodal MCC metastases before surgery with or without concurrent adjuvant radiotherapy. Avelumab is given every 15 days for the first 120 days (induction phase 1), and later on every 30 days for the next 120 days (induction phase 2), and finally every 120 days (maintenance phase) up to 2 years in total, or until disease progression, or unacceptable toxicity. Later on patients are followed up every 6 months for 3 years. The primary objective of the study is relapse-free survival (RFS), while secondary objectives are OS, distant metastases-free survival (DMFS), disease-specific survival (DSS), and toxicity analysis. This trial is investigator-sponsored study [28, 29]. The immunotherapy adjuvant trial in patients with stage I–III Merkel cell carcinoma (I-MAT) (NCT04291885) is still in the recruitment process. This is a phase II, prospective, randomised, placebo-controlled, multi-institutional trial for patients with stage I–III Merkel cell carcinoma. Patients receive either avelumab or a placebo for 6 months. RFS is the primary outcome. Overall survival rates at 12 and 24 months are the secondary endpoints.

Conclusions

The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) immunosuppressive pathway is commonly upregula-

Table II. Current avelumab clinical trials for Merkel cell carcinoma (April 2022)

Clinical trial	Agent/interventions	Phase	Study population
NCT04261855	avelumab external beam radiation therapy (EBRT) lutetium-177 (177Lu)-DOTATATE	1 2	Merkel cell carcinoma
NCT03747484	autologous MCPyV-specific HLA-A02-restricted TCR-transduced CD4+ and CD8+ T-cells FH-MCVA2TCR avelumab pembrolizumab fludarabine cyclophosphamide	1 2	Merkel cell carcinoma
NCT04551885	FT516 avelumab cyclophosphamide fludarabine drug: IL-2	1	advanced solid tumors
NCT04792073	avelumab comprehensive ablative radiation therapy	2	Merkel cell carcinoma
NCT04393753	domatinostat in combination with avelumab	2	Merkel cell carcinoma
NCT03853317	avelumab N-803 haNK™	2	Merkel cell carcinoma
NCT03271372	avelumab	3	Merkel cell carcinoma

ted in MCC and thus ICIs offer clinicians a promising approach to treat this cancer type. Data from non-randomized phase II clinical trials in patients with MCC have demonstrated high activity of PD-1/PD-L1 blockade and improved rates of durable response compared with cytotoxic therapy. On account of this, current guidelines recommend their use as the treatment of choice for patients with metastatic MCC [12]. Avelumab (Bavencio, EMD Serono, Inc.) is a programmed death-ligand 1 (PD-L1) blocking human IgG1 lambda monoclonal antibody. It was the first immunotherapy to be approved for the treatment of MCC. In March 2017, the FDA granted accelerated approval to avelumab for the treatment of adults and pediatric patients from 12 years and older with metastatic Merkel cell carcinoma (MCC) – irrespective of prior therapy. Building on this, in July 2017, the European Medicines Agency (EMA) recommended the approval of avelumab as a monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (mMCC). These approvals were a meaningful development for patients suffering from this particularly aggressive form of skin cancer. Approvals of avelumab by the FDA and the EMA were based on the efficacy and safety demonstrated in JAVELIN Merkel 200 (NCT02155647), a multi-center, open-label, single-arm, phase II clinical trial [1].

The study was split into two parts, A and B. Part A consisted of patients treated in the second line (n = 88), with metastatic, chemotherapy-refractory MCC, life expectancy of >3 months and a follow-up of at least 18 months. Part B consisted of systemic treatment-naive patients (n = 116), who received avelumab as first-line treatment for metastatic or distally recurrent MCC. Data obtained from part A of this study, first published in 2016, resulted in the approval of this drug for MCC therapy [1]. Subsequently, the FDA approved avelumab to be used in combination with axitinib (Inlyta) for the first-line treatment of patients with advanced renal cell carcinoma (RCC) in May 2019, as well as for maintenance treatment of patients with locally advanced metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-based chemotherapy. More avelumab studies are currently running (tab. II).

Conflict of interest: none declared

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