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PD-L1 Inhibition with Avelumab for Metastatic Merkel Cell Carcinoma

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Abstract

Introduction: Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer that lacks durable responses to traditional chemotherapy.

Areas covered: After MCC was shown to be an immunogenic tumor, small trials revealed high objective response rates to PD-1/PD-L1 checkpoint inhibitors. The JAVELIN Merkel 200 (NCT02155647) trial tested the use of avelumab, a human IgG1 monoclonal antibody against PD-L1, in metastatic MCC. Avelumab recently became the first approved drug for metastatic MCC.

Expert commentary: By conducting broad phase I studies assessing the safety of avelumab and a small phase II study demonstrating efficacy in this rare orphan tumor type, avelumab gained accelerated approval for the treatment of metastatic MCC. Additional studies are needed to determine how the antibody-dependent cellular cytotoxicity (ADCC) competent Fc region of avelumab contributes to disease control.

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Merck Group provided a scientific accuracy review at the request of the journal editor.

8. INFORMATION RESOURCES

Avelumab (BAVENCIO®) full prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf

Merkelcell.org is an authoritative source of information on Merkel cell carcinoma for patients, physicians, and researchers. https://www.merkelcell.org/

Key publications:

Kaufman et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016 Oct;17(10):1374-1385.

Nghiem et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. N Engl J Med. 2016 Jun 30;374(26): 2542-52.

Remaining questions: Longer follow-up will determine the durability of checkpoint blockade in controlling metastatic MCC. Additional studies will assess the utility and safety of adjuvant checkpoint blockade in patients with excised MCC. How to increase response rates by combining PD-1/PD-L1 blockade with other treatment approaches needs to be explored. In addition, treatment options for MCC patients who fail or do not respond to avelumab need to be identified.

Keywords

anti-PD-1; anti-PD-L1; avelumab; Bavencio; check point inhibitor; immunotherapy; Merkel cell carcinoma; pembrolizumab

1. INTRODUCTION

1.1 Merkel cell Carcinoma

Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer with a predilection for UV-damaged skin of older and immunocompromised patients [1, 2]. MCC is rare, occurring with an incidence of 0.2 to 0.4 cases per 100,000 people per year in Europe, 0.79 in the U.S., and 1.6 in Australia [3, 4, 5]. Although rare, MCC's incidence has tripled over the past three decades [6] and it has a disease-associated mortality of 46%, three-times that of melanoma [7, 8]. Up to 80% of MCC patients eventually develop metastases [9]. On average, patients with stage IV disease treated with cytotoxic chemotherapy face an 18% 5 year survival [7], and a median progression-free survival of only 3 months [10, 11].

MCC is an immunogenic cancer arising more often and with a worse prognosis in immunocompromised patients [12]. One of the most important factors in illuminating the pathogenesis of MCC was the discovery of the Merkel cell polyomavirus (MCV). In most studies MCV is detected in 69-85% of MCC tumors, however in countries with high UV-exposure, such as Australia and New Zealand, MCC tumors are mostly MCV-negative [13, 14, 15, 16]. MCV DNA is clonally integrated into the tumor genome [13, 17], and viral T antigens are required for proliferation and survival of MCV-positive MCC tumor cells [17, 18, 19]. Antibodies against these T antigens are specifically detected in the blood of patients with MCC, and serology titers reflect tumor burden and predict recurrence [20]. MCV-associated MCC carry very few somatic mutations. In contrast, UV-induced, MCV-negative MCC are characterized by mutational loads approximately 100 times greater than MCV-positive MCC [21, 22, 23].

Early stage MCC is treated with surgical excision and radiation [24] . Until recently, effective treatments for metastatic MCC were lacking [25]. There are no FDA-approved chemotherapy protocols for managing MCC, and treatments are largely derived from those used for small cell lung cancer, a more common neuroendocrine tumor [11]. Commonly used chemotherapy regimens include platinum-containing agents combined with etoposide or cyclophosphamide, doxorubicin, and vincristine (CAV) [11]. MCC has high response rates to chemotherapy, but tumors recur within 4-15 months [25]. As a consequence, treatment guidelines recommended enrolment in a clinical trial for patients with metastatic disease [3, 24]. However, within the last year, the anti-PD-L1 immune checkpoint inhibitor

avelumab (Bavencio®) was approved for the treatment of metastatic MCC in the United States, the European Union, Canada, Australia, Israel, Japan and Switzerland.

1.2 Overview of immunotherapy and checkpoint inhibitors

Over the last decade, the use of monoclonal antibodies against immune checkpoint receptors like cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death receptor (PD-1) has changed the practice of oncology. There is an expanding catalogue of immune checkpoint inhibitors available for the treatment of human malignancies (Table 1). Immune checkpoints are signaling pathways that restrict continued immune responses, thereby preventing host autoimmunity and excessive immune reactions against certain antigens [26]. Drugs that block immune checkpoint signaling can reactivate cellular immune responses to facilitate tumor clearance. When effective, checkpoint inhibitors can provide durable clinical benefit in close to one third of cancer patients [27, 28, 29, 30]. There is particular interest in using PD-1 blockers, alone or in combination with other agents [27, 31, 32, 33], to engage anti-tumor immune responses [33, 34].

The PD-1 immune checkpoint pathway was described in 1992 as a mechanism for T cell death [35]. The PD-1 receptor is expressed on activated B, T, and NK cells, including activated tumor-infiltrating T lymphocytes (TIL) [36, 37]. Upon ligand binding, PD-1 signaling inactivates cytotoxic T cell (CTL), promotes-their apoptosis, and reduces production of pro-inflammatory cytokines [38, 39]. There are two PD-1 ligands, PD-L1 and PD-L2. These ligands can be expressed by hematopoietic cells (B, T, dendritic, and myeloid) and tumor cells [37, 39]. Upregulation of PD-L1 by tumor cells can inactivate cytotoxic effector cells, allowing tumors to evade the immune system [34, 38, 39]. Reversing this immune escape with checkpoint inhibitors allows anti-tumor immune responses to proceed (Figure 1). At the same time, use of immune checkpoint inhibitors can induce auto-immune related side effects [40, 41, 42].

1.3 PD-L1 expression

Although data is inconsistent across malignancies, expression of PD-L1on tumor cells correlates with worse prognosis and predicts a higher likelihood of response to PD-1 blockade in some cancers [10, 31, 43, 44] . A reactive pattern of PD-L1 expression has been described in melanoma cells proximate to TIL, whereas melanomas with sparse TIL infiltration were less likely to express PD-L1 [45]. These results suggest that in response to immune recognition tumor cells upregulate PD-L1 in order to inactivate effector T cells [45]. Immunohistochemical tests for PD-L1 expression were recently approved by the FDA to stratify patients with advanced non-small-cell lung cancer as being more likely to respond to anti-PD-1 therapy [46, 47]. In contrast, other studies have shown that PD-L1 overexpression is not a robust predictor for response, and investigations of its utility as a biomarker are ongoing across multiple tumor types [10, 43, 48].

Approximately 50% of MCC express PD-1 on TIL and PD-L1 on tumor cells and adjacent immune cell infiltrates [21, 49, 50]. Moreover, circulating MCV-specific CD8-positive T cells from patients with MCC express higher levels of PD-1 than T cells specific to other common human viruses. In MCC tumors, higher PD-L1 expression correlated with TIL

infiltration and a better prognosis [23, 50]. These expression patterns provided a rationale for investigating the therapeutic potential of PD-1/PD-L1 checkpoint inhibitors in MCC. In 2011 the first phase 1 clinical trial involving the PD-L1 antibody atezolizumab in advanced solid and hematologic malignancies, including MCC was initiated. At the time of writing 17 clinical trials involving MCC and checkpoint inhibitors have been initiated (Table 2).

1.4 MCC as an immunogenic tumor

Many lines of evidence suggest that MCC is a highly immunogenic tumor [23, 49, 50]. MCV-positive MCC tumors express polyomavirus antigens that can serve as epitopes for immune detection. Among virus-negative MCC tumors there is an exceptionally high mutational burden [21, 22, 23] and the somatic mutation levels in tumors correlate with the production of novel peptide epitopes (neoantigens) and improved response to immunotherapy [51]. In addition to possessing candidate immune targets, expression of PD-L1 in the tumor microenvironment is evidence for immune evasion by some MCC tumors. The immunogenicity of MCC is also evidenced by the increased incidence rates observed in immune compromised populations [12, 52]. Moreover, spontaneous regression, even of metastatic MCC, has been repeatedly observed [53]. Spontaneous regression is often associated with a dense infiltrate of T cells [54, 55], suggesting an immune-mediated clearance of MCC. Furthermore, in 40% of stage IIIB patients, the primary skin tumor cannot be identified, presumably because of immunological elimination. Interestingly, these cases carry a distinctly better prognosis than stage IIIB MCC with known primary tumors [52, 56, 57]. The importance of an anti-tumor immune response in controlling MCC is also reflected in the observations that robust intratumoral CD8+ lymphocytes and a competent immune system are both independent predictors of improved survival [12, 58]. These results strongly suggest that MCC can be efficiently cleared by the immune system and supports the use of immunotherapy for this malignancy. At the same time, 8-10% of the MCC patients are immunosuppressed [12, 52], and may not respond to immunotherapy.

1.5 Immunotherapy in MCC

Immune check-point modulators are important therapies for a variety of malignancies. To date, ipilimumab (anti-CTLA-4), nivolumab (anti-PD-1), and pembrolizumab (anti-PD-1) have all been approved by the FDA and EMA as therapies against various malignancies. Avelumab, atezolizumab, and durvalumab (all anti-PD-L1) are FDA approved for the treatment of bladder cancer. Additionally, atezolizumab is also approved as therapy against metastatic lung cancer (Tables 1–3). Avelumab is the only drug that is approved for the treatment of MCC, however a number of checkpoint inhibitors have been demonstrated to be effective in MCC [30, 49, 50, 59, 60, 61, 62] .

Ipilimumab—Ipilimumab (Yervoy®, MDX-010) is a fully humanized monoclonal antibody targeting CTLA-4. Clinical trials testing ipilimumab in MCC were eagerly expected. Unfortunately, a phase 2 trial investigating the effect of ipilimumab on patients with metastatic MCC (NCT01913691) was canceled due to withdrawal of sponsor support. Winkler et al. described the use of ipilimumab in five cases of metastatic MCC. One patient experienced progressive disease, two had stable disease (SD), and two patients had complete responses (CR). Progression free survival (PFS) was between 4.8 and 23.5 months [59].

Nivolumab—Nivolumab (Opdivo®, ONO-4538, BMS-936558, MDX1106) is a fully human monoclonal IgG4 antibody directed against PD-1, disrupting the binding of PD-1 to PD-L1. A recent case report described a stable and rapid partial disease remission (> 8 months) in a patient with MCV-positive MCC treated with 3mg/kg nivolumab administered every 2 weeks [60]. Nivolumab was further tested in a recent open-label, multiple cohort, non-comparative, phase 1/2 study (CheckMate 358, NCT02488759) to evaluate its efficacy in patients with virus-associated tumors, including MCC. Among 25 MCC patients, the overall response rate (ORR) was 68% with ongoing responses in 13 of 15 (87%) patients. Responses occurred in treatment-naïve patients (71%) and in patients with 1-2 prior systemic therapies (63%) independent of MCV-status [30] (Table 3).

Pembrolizumab—Pembrolizumab (Keytruda®, MK-3475, lambrolizumab) is a fully humanized monoclonal IgG4 antibody targeting PD-1. In a single case report, a patient with etoposide-refractory metastatic MCC achieved a partial response (PR) with pembrolizumab [62]. In a phase 1 clinical trial (KEYNOTE-001, NCT01295827) of pembrolizuamb 2 mg/kg every 3 weeks in advanced tumors, one patient with previously untreated advanced MCC achieved a durable complete remission (>56 weeks) [61]. This dose regimen was therefore selected for a subsequent phase 2 clinical trial [49]. In this trial (NCT02267603) 25 patients with chemotherapy-naïve stage IIIB and IV MCC received pembrolizumab and reached an ORR of 56%, including 4 complete remissions in MCV-positive or negative tumors. Clinical responses to pembrolizumab were not correlated to PD-L1 expression on tumor cells or presence of tumor infiltrating immune cells. PD-L1 expression was more prevalent in MCV-positive tumors than in MCV-negative tumors (71% vs. 25%, p=0.049). These findings in 25 patients strongly supports PD-1/PD-L1 blockade as a therapeutic option for advanced MCC [49] .

2. INTRODUCTION TO AVELUMAB

Avelumab (Bavencio®, MSB0010718C) is a fully human IgG1 anti-PD-L1 antibody, developed by EMD Serono Inc., the biopharmaceutical division of Merck KGaA, Darmstadt, Germany. On March 23, 2017 avelumab received accelerated FDA approval for treatment of patients aged ≥12 years with metastatic MCC, Avelumab was approved by Swissmedic on September 05 (only as second line treatment), followed by the EMA on September 18. To date, it has been approved in the US, Canada, Switzerland, EU, Australia, Israel and Japan. Avelumab is administrated 10 mg/kg intravenously over 60 minutes every 2 weeks. To prevent infusion reactions, patients should be treated with acetaminophen and an antihistamine prior to treatment for the first four infusions and if necessary thereafter [63]. Approval of avelumab was based on the results of a phase 2 clinical trial including 88 patients with advanced MCC [50]. Safety data was evaluated in 1738 patients who received avelumab (JAVELIN Solid Tumor) [41, 64]. Continued approval for MCC will depend on the results of ongoing confirmatory trials.

Merck KGaA is investigating avelumab’s potential in numerous additional clinical trials. The company has partnered with Pfizer for the clinical co-development of avelumab.

2.1 Avelumab chemistry

Avelumab is a fully human monoclonal IgG1 antibody (mAb) directed against PD-L1 that inhibits PD-L1/PD-1 interactions but does not alter PD-L2/PD-1 signaling [41, 65]. In addition to disinhibiting T-cells, avelumab was designed to have the structure of a natural human IgG1 antibody. Most human or humanized antibodies directed to PD-1 or PD-L1 are of the IgG4 isotype or are IgG1 that has been mutated to minimize induction of antibody-dependent cellular cytotoxicity (ADCC) activity. Due to its native Fc domain, avelumab preserves the ability to induce natural killer-mediated ADCC *in vitro* [66]. There were initial concerns that avelumab might deplete tumor-specific PD-L1 expressing effector cells via ADCC. *In vitro* stimulation assays demonstrated that avelumab enhanced antigen-specific immune activation, indicating that avelumab did not deplete the cells required for immune stimulation [67]. In addition, when co-cultured with purified autologous NK cells, avelumab did not induce lysis of peripheral blood mononuclear cells (PBMCs) [66]. In its phase 1A dose-escalation trial, avelumab did not show any significant effect on patients' absolute lymphocyte count or on the number of circulating PD-L1 expressing immune cells [41, 64, 68], suggesting that avelumab does not measurably deplete any immune cell subsets. Although avelumab-mediated ADCC can cause direct killing of PD-L1-expressing tumor cells and immunosuppressive antigen-presenting cells, to date there is no *in vivo* evidence of an additive clinical effect from ADCC [41, 64].

Avelumab is the only therapeutic antibody which exploits immune checkpoint inhibition and ADCC-mediated killing of tumor cells simultaneously. However, compared to other checkpoint inhibitor antibodies, infusion reactions are more frequent, and this is possibly related to avelumab's native IgG1 Fc-domain.

2.2 Competing compounds in clinical development

As of June 29, 2017 140 clinical studies investigating PD-L1 inhibitors are listed on ClinicalTrials.gov including **BMS-936559** (anti-PD-L1, phase 1, BMS, NCT02576457), **LY3300054** (anti-PD-L1, phase 1, Lilly, NCT02791334), **MEDI4736** (anti-PD-L1, phase 2, Swiss Group for Clinical Cancer Research, NCT02572843), **REGN2810** (anti-PD-L1, phase 1, Regeneron Pharmaceuticals, NCT02383212), **KN035** (anti-PD-L1, phase 1, 3D Medicines (Sichuan) Co., Ltd., NCT02827968), **FAZ053** (anti-PD-L1, phase 1, Novartis, NCT02936102), **MSB0011359C** (bifunctional fusion protein targeting PD-L1 and TGF-β, phase 1, EMD Serono, NCT02517398), and **CA-170** (small molecule targeting PD-L1, PD-L2 and VISTA, phase 1, Curis Inc., NCT02812875).

Clinically available PD-L1 inhibitors include **atezolizumab** (Tecentriq®, Roche/Genentech, FDA-approval for lung cancer in April 2016 and bladder cancer in May 2016), **avelumab** (Bavencio®, Merck/Pfizer, FDA-approval for MCC in March 2017 and bladder cancer in May 2017, Swissmedic, and EMA-approval for MCC in September 2017), and **durvalumab** (Imfinzi®, Medimmune/AstraZeneca, FDA-approval for urothelial carcinoma in May 2017). Atezolizumab, a phage-derived human IgG1 monoclonal antibody, was engineered with a mutated Fc domain to prevent N-linked glycosylation and ADCC activity. Durvalumab is a human IgG1 monoclonal Ab with high affinity and specificity to PD-L1 and an Fc region modified to prevent ADCC.

2.3 Avelumab Safety and Side Effects:

Avelumab has demonstrated a manageable safety profile. Treatment related adverse events (TRAE) occurring under treatment with avelumab were similar to other agents targeting the PD-1/PD-L1 axis [69, 70, 71, 72]. Safety data was evaluated in a pool of 1738 patients from the JAVELIN Solid tumor (NCT01772004) and JAVELIN Merkel 200 (NCT02155647) trials who received 10mg/kg avelumab every 2 weeks for a median of 12 weeks [41, 64, 73]. The most common any grade TRAE included fatigue (18%), infusion related reactions (IRR) (17%), and nausea (9%). TRAE led to drug discontinuation in 107 patients (6%) and four patients (0.2%) died. The rate of IRR with avelumab is elevated relative to other monoclonal antibody immune checkpoint inhibitors (1-2%). IRR or related symptoms (e.g. chills, pyrexia, hypersensitivity) occurred in 439 patients (25%) receiving avelumab, usually at first infusion (79%) and within the first 4 doses in 99% of cases. Among patients with IRR, 14% had IRR recurrence in later cycles. IRR led to discontinuation of drug in 35 patients (2%). Autoimmune adverse events can occur in association with immunotherapy. Any grade immune-related adverse events (irAE) were seen in 247 patients (14%) treated with avelumab. These irAE were considered serious in 43 patients (2%) and led to discontinuation in 34 patients (2%). The most common any grade irAEs were thyroid disorder (6%) and rash (5%). Other irAE included colitis, pneumonitis hepatitis, adrenal insufficiency, and myositis, each occurring in <2% of patients. IrAE mostly manifested during treatment, but also occurred after discontinuation of treatment.

Anti-drug antibodies (ADA) arose after treatment initiation in 4.1% of 1558 evaluable patients. However, the emergence of ADA did not alter the pharmacokinetics (PK) of avelumab or the incidence of IRR [41, 64].

TRAE occurred in 70% of the 88 patients with MCC treated with avelumab in the JAVELIN Merkel 200 (part A) trial (66% grade 1-2, 5% grade 3). The most frequently TRAE of any grade were fatigue (24% of patients) and IRR (17% of patients). No grade 4 TRAE or treatment-related deaths occurred during the study, and only 6% of patients experienced serious TRAE (chondrocalcinosis, enterocolitis, increased aminotransferases, infusion-related reactions, intestinal nephritis or synovitis), leading to discontinuation of treatment in one patient [50]. IrAE were manageable and occurred in less than 13% of patients (grade 1 or 2: diarrhea, hyperthyroidism, hypothyroidism, nephritis, pneumonitis, rash, type 1 diabetes mellitus; grade 3: increased aminotransferase). A similar safety profile was reported for pembrolizumab when treating metastatic MCC [49].

At data cutoff on March 24, 2017, results from a separate cohort of 39 patients (112 patients planned) with chemotherapy-naïve MCC enrolled in the JAVELIN Merkel 200 (part B) trial revealed TRAE in 28 patients (72%) including grade 3-4 TRAE in 8 patients (21%). Six patient had to discontinue avelumab treatment. There were no treatment-related deaths [74].

As discussed above, the frequency of IRR with avelumab is elevated relative to other checkpoint inhibitors. IRR, such as influenza-like symptoms, are often associated with release of pro-inflammatory cytokines by direct activation of immune cells [75]. Cytokine release occurs during and shortly after therapeutic antibody infusion [76, 77]. It has been speculated that avelumab binding PD-L1 expressed on immune cells could triggering

cytokine release. The retained native IgG1 Fc-region on avelumab may also be involved in provoking cytokine release during infusion. All IRR that occurred in patients enrolled in the phase 1 dose-escalation trial [41] were medically manageable and resolved quickly with antihistamines, meperidine, acetaminophen, and rarely, corticosteroids. Patients who had an IRR subsequently had their infusions restarted at 50% reduced rate, and only one of four patients had a recurrent event, suggesting that reducing the infusion rate helps to avoid recurrence [41]. Because of the frequency of IRR, it is recommended that all patients should be premedicated with an antihistamine and acetaminophen prior to their first four infusions of avelumab. Premedication should be continued as needed, thereafter. Ongoing phase 3 trials with avelumab should further elucidate the frequency, significance, and severity of IRR and how best to manage them.

2.4 Avelumab pharmacokinetics and metabolism

The pharmacokinetics (PK) of avelumab and PD-L1 receptor occupancy (RO) were determined in samples collected from the phase 1a multi-cohort, dose-escalation JAVELIN Solid Tumor trial (NCT01772004) [41]. *In vitro* data using blood samples from healthy donors indicated that 1 μg/ml avelumab was sufficient for >95 % RO. In the dose escalation study, 53 patients with advanced solid tumors received either 1, 3, 10, or 20 mg/kg of avelumab every two weeks. There was a linear increase of both C_{max} and area under curve with dosage. Half-lives for the antibody were 66, 86, 92, and 115 hours corresponding to the four dose levels. The PK data were consistent with a two-compartment model with linear elimination of avelumab. As 10 mg/kg was sufficient for >95% RO, this dose was chosen for phase 2 and 3 trials. Steady state plasma levels of avelumab were achieved after 4-6 weeks (2-3 cycles) of treatment. In patients treated with 10 mg/kg avelumab, the mean volume of distribution at steady state was 4.72 liters, the terminal half-life was 6.1 days, and the total systemic clearance was 0.59 liters/day. The primary elimination mechanism for avelumab is proteolytic degradation. Patients with MCC demonstrated a decreased avelumab clearance over time, with a mean maximal reduction of approximately 42% (based on a post hoc analysis). Age, race, gender, tumor burden, PD-L1 expression status, and the presence of renal or hepatic impairment had no significant impact on avelumab clearance. Bodyweight and total systemic clearance of avelumab were positively correlated. The impact of severe liver dysfunction on avelumab PK is uncertain [41].

2.5 Avelumab clinical efficacy:

As of May 2017, avelumab has been investigated in phase 1 clinical trials for various cancers, including bladder, stomach, lung (NSCLC), head and neck, ovary, kidney, and mesothelioma. For MCC, a phase 2 trial is ongoing. Numerous phase 3 trials are investigating the use of avelumab in malignancies including NSCLC, bladder, ovarian and gastric cancer. Additionally, avelumab received orphan drug designation by the EMA for the treatment of gastric cancer in January 2017.

At the point of writing, Avelumab has been under investigations in 56 different clinical trials including the following malignancies: colorectal carcinoma, NSCLC, glioblastoma multiforme, nasopharyngeal cancer, MCC, small intestinal adenocarcinoma, endometrial cancer, gestational trophoblastic neoplasia (GTN), recurrent respiratory papillomatosis,

acute myeloid leukemia, epithelial ovarian cancer, triple negative breast neoplasms, osteosarcoma, squamous cell carcinoma of head and neck, thymoma and thymic carcinoma, renal cell cancer, neuroendocrine carcinoma grade 3, relapsed and refractory T-cell lymphoma, metastatic leiomyosarcoma and metastatic liposarcoma, clear-cell renal cell carcinoma, gastric cancer, urothelial cancer, Hodgkins and Non-Hodgkins Lymphoma, prostate cancer, melanoma, diffuse large B-cell lymphoma, and pancreatic cancer.

3. AVELUMAB IN CLINICAL STUDIES

3.1 Phase I studies

The ongoing multinational, open-label, phase 1b, dose-expansion component of the JAVELIN Solid Tumor trial involves >4000 patients comprising 16 different cancers of various entities, including breast, pancreas, ovary, lung (NSCLC), urothelium as well as mesothelioma, all regardless of PD-L1 expression [64, 78]. All patients receive 10mg/kg avelumab intravenously every 2 weeks up to the point of unacceptable toxicity, disease progression, or other reason for withdrawal. Although safety is the primary endpoint of the phase 1b dose-expansion trial [64], avelumab demonstrated preliminary efficacy in various malignancies. For instance, 50% of patients of the non-treatment-naive advanced NSCLC cohort of JAVELIN Solid Tumor (184 patients, 8.8 months median follow-up) demonstrated disease control (one CR, 21 PR, and 67 SD) [64], and the confirmed ORR was 12%. PD-L1 expression or histopathological features of the tumor had no influence on the treatment responses. According to RECIST version 1.1, median PFS was 11.6 weeks and median overall survival (OS) was 8.4 months [64]. Based on the results of this trial, numerous phase 2 and 3 trials were introduced, including JAVELIN Merkel 200, which led to the FDA approval of avelumab for MCC [41].

In additional studies, interim efficacy results demonstrated different objective response rates (ORR) for the following JAVELIN Solid Tumor cohorts: advanced NSCLC (145 patients, first-line treatment, ORR 18.7%) [79], advanced gastric or gastro-esophageal junction cancer (151 patients, first-line maintenance or second-line therapy, ORR 9.7%) [80], metastatic urothelial carcinoma (249 patients, after platinum-based therapy or cisplatin-ineligible, ORR 17.6%) [81], advanced adrenocortical carcinoma (37 patients, progressed after platinum-based therapy, ORR 10.5%) [82], advanced thymic epithelial tumor (8 patients, second-line therapy, ORR 57%) [83], locally advanced or metastatic breast cancer (168 patients, refractory to or progressing after standard therapy, ORR 5.4%) [84], recurrent/refractory ovarian cancer (124 patients, refractory to or progressing after standard therapy, ORR 9.7%) [85], and advanced unresectable mesothelioma (53 patients, progressed after platinum-pemetrexed-containing regimen, ORR 9.4%) [86].

JAVELIN Solid Tumor JPN (NCT01943461) has been initiated as an open-label, phase 1b trial of avelumab in Japanese patients suffering from advanced solid tumors consisting of a dose-escalation cohort and as a dose-expansion cohort [87, 88]. So far, preliminary results of 20 patients with advanced gastric or gastroesophageal junction adenocarcinoma are available. The 20 patients were treated with 10mg/kg avelumab every two weeks in the dose expansion part of the study based on level of PD-L1 expression. [88]. Disease control rate (CR, PR and SD; median follow-up of 6 months) was 65% based on three patients with

confirmed PR. There was a trend towards higher ORR and PFS rates in patients with PD-L1-positive tumors compared with PD-L1-negative patients [88].

3.2 Efficacy in MCC - Phase II studies

JAVELIN Merkel 200 (NCT02155647)—This multicenter, international, prospective, open-label, single-group, phase 2 trial enrolled 88 patients with chemotherapy-resistant (part A) metastatic MCC measurable by RECIST criteria v1.1 [3]. All patients had distant metastatic disease (M1, defined as metastases beyond regional lymph nodes) at the time of study enrolment. Patient selection was not based on MCV or PD-L1 expression status [50, 89]. Patients received avelumab 10 mg/kg by 1 hour intravenous infusion once every 2 weeks until unacceptable toxicity, confirmed disease progression, or occurrence of any other criterion for withdrawal. All patients received premedication with an H1-antihistamine, such as diphenhydramine, and acetaminophen 30-60 min before avelumab treatment. Tumors were evaluated by an independent review committee every 6 weeks. ORR was the primary efficacy endpoint, identified as the fraction of patients with CR or PR [50, 89]. At a median follow-up of 16.4 months (primary analysis; data cut-off date of 3 September 2016), using modified immune-related response criteria, 29 patients (33.0%) had an ORR (11% CR and 22% PR; 10% SD and 36% PD);18 patients (21%) were not assessable [89]. Among responses, 76% were noted at the first post-baseline assessment (6 weeks). The median duration of response had not been reached (range 2.8-23.3 months; 95% CI 18.0 months-not estimable). Responses were ongoing in 21 patients (72% of responders). Median PFS was 2.7 months, and median OS was 12.9 months[89]. Subgroup analyses suggested a higher probability of response in patients who received fewer prior lines of chemotherapy, with a lower baseline disease burden, and with PD-L1-positive tumors. Nonetheless, durable responses occurred irrespective of baseline factors, including MCV status [89]. Insofar as patient-reported outcomes, a recent sub-analysis of the first cohort of 88 MCC patients determined that non-progression of metastatic MCC during treatment with avelumab correlated with gains in health-related quality of life [90].

As of March 24, 2017, results from a separate cohort of 39 patients with chemotherapy-naïve MCC enrolled in the JAVELIN Merkel 200 (part B) trial revealed in patients with ≥ 3 months of follow up (n=29) an ORR of 62% (14% complete response, 48% partial response). Patients with ≥ 6 months of follow up (n=14) had an ORR of 71% (29% complete response, 43% partial response). PFS rate at 3 months was 67%. These results suggest that first-line treatment with avelumab also achieves durable responses in patients with advanced MCC [74, 91].

3.3 Phase III studies:

As of May 2017, avelumab is being tested in numerous phase 3 studies e.g. patients suffering from NSCLC, bladder, gastric, renal, head and neck cancer, and ovarian cancer. Efficacy analysis has yet to be performed. The JAVELIN program is ongoing, further trials are running in solid tumors, as well as in hematologic malignancies. Running definitive phase 3 trials with chemotherapy as the comparator would be problematic for ethical reasons in an orphan disease like MCC where conventional therapies do not provide durable responses.

3.4 Comparison of checkpoint inhibitor studies in MCC:

When considering the two published studies on treating MCC with checkpoint inhibitors, there are differences between the JAVELIN Merkel 200 trial (part A) using avelumab [89] and the first-line pembrolizumab study [49] (Table 3). The patients in the first-line pembrolizumab study had treatment-naïve stage IIIB and stage IV disease, whereas the patients in the avelumab study had chemotherapy-refractory stage IV MCC. The more advanced, treatment-resistant disease in the avelumab study may have contributed to the lower ORR (33% versus 56%). Consistent with this idea, preliminary data from the chemotherapy-naïve (part B) MCC cohort of the JAVELIN Merkel 200 trial showed a confirmed ORR of 62% in 29 patients with ≥ 3 months of follow up and an ORR of 71% in 14 patients with ≥ 6 months of follow up [74, 91]. In addition, preliminary analysis of the phase 2 study of nivolumab in 25 patients with MCC, patients with treatment-naïve disease had a better ORR (71%) than treatment-resistant disease (63%) [30]. Similar trends have been observed with other malignancies, suggesting that immunotherapy achieves better results in patients who have not received prior chemotherapy. This could be due to treatment-resistant tumors being more aggressive in addition to host immune system impairment by chemotherapy [92, 93].

All studies of checkpoint inhibitors in MCC have shown durable responses, albeit with relatively short median follow-up times. All studies have also reported responses in patients regardless of tumor PD-L1 expression and MCV-status. When considering virus status, it is noteworthy that the percentage of MCV-negative tumors among patients enrolled in these studies was slightly higher than would be expected from previous reports [94].

4. REGULATORY AFFAIRS

In late 2015, avelumab obtained orphan drug, fast track, and breakthrough therapy designations from the FDA for the treatment of MCC. On March 23, 2017, after priority review, the FDA granted accelerated approval to avelumab for the treatment of adults and pediatric patients ≥12 years with metastatic MCC, irrespective of prior treatments. Approval was based on data from part A of the JAVELIN Merkel 200 trial. The ongoing part B of this trial will confirm the clinical efficacy of avelumab in treatment-naïve advanced MCC, a required condition of accelerated approval.

According to Merck KGaA, the wholesale price for avelumab is $13,000 US dollar/month. Avelumab is co-commercialized by EMD Serono, the biopharmaceutical business of Merck KGaA in the US and Canada, and Pfizer.

In mid-2016 avelumab received EMA orphan drug designation for the treatment of MCC. In July of 2017 the Committee for Medicinal Products for Human Use (CHMP) of the EMA recommended approval of avelumab for the treatment of adults with metastatic MCC. On September 5, 2017 avelumab was approved by Swissmedic for MCC treatment. On September 18, 2017 avelumab was approved by the EMA for treatment of MCC. To date, it has been approved in the US, Canada, Switzerland, EU, Australia, Israel and Japan.

5. EXPERT COMMENTARY

Avelumab is the first approved therapy for MCC, and it is the first therapy to offer durable treatment responses to a meaningful portion of patients with metastatic disease. The immunogenicity of MCC and its notably high response rates to single agent checkpoint inhibitors draw interest to this rare malignancy. As immunotherapy is adopted as the primary treatment for metastatic MCC, more will be learned about the characteristics and durability of responses in MCC, and perhaps about the nature of immunotherapy in the treatment of solid tumors.

5.1 Adjuvant immunotherapy treatment of resected MCC

Patients with stage I-III MCC who are free of disease after surgical resection are being recruited to a clinical trial in Germany testing checkpoint inhibition as an adjuvant treatment to prevent disease recurrence (NCT02196961; CA184-205; ADMEC). Initially, patients were randomized to either receive ipilimumab 3 mg/kg every 3 weeks for 12 weeks or to an observation arm. However, the treatment arm was changed, and now patients receive nivolumab 480 mg every 4 weeks for up to one year.

A placebo-controlled clinical trial testing the efficacy of avelumab as an adjuvant treatment for patients with resected stage III MCC is currently being planned in the US. These studies will hopefully quantify the utility of adjuvant checkpoint blockade in preventing progression of resected MCC so that it can be weighed against the risks associated with treatment.

5.2 Seeking predictors of response to immunotherapy

To date, all the studies of checkpoint inhibition in MCC have been relatively small. This limits what can be learned from subgroup analyses to identify predictors of treatment response. As discussed above, chemotherapeutic-naïve patients are more likely respond more frequently than patients who have been treated with multiple lines of chemotherapy. However, with avelumab being used as a first-line therapy, going forward, it is likely that patients with MCC will primarily get chemotherapy after failing a checkpoint inhibitor.

Although no difference was detected, it is possible that avelumab might achieve differential therapeutic benefits in patients whose MCC is driven by different underlying mechanisms. Specifically, MCV-positive tumors that express viral antigens and have low somatic mutational burdens are likely to be immunogenic in a different way than MCV-negative tumors that have a high burden of UV-mutagenesis driven neoantigens [21, 22, 23]. Results demonstrating clinical activity in both, virus-related and UV-radiation-induced MCC tumors provide an impetus for investigating avelumab in other tumor types with similar causes. However, tumor markers that suggest impaired ability to present immune antigens such as low predicted neoantigen levels, lack of viral protein expression, or reduced major histocompatibility complex I (MHC I) expression levels may help identify less immunogenic tumors.

Theoretical treatment response differences between virus positive and virus negative MCC might be confounded by the fact that MCV-positive tumors tend to express PD-L1 more frequently than MCV-negative tumors [23, 49]. Similar to most tumor types, there has been a

trend in MCC whereby tumors that stain positively for PD-L1 have slightly higher response rates, especially when using more stringent testing thresholds (>5% tumor cells staining positive versus >1%) [49, 50]. In September 2015, Merck and Pfizer started a cooperation with Dako (Agilent Technologies), for the development of a companion diagnostic test for use with avelumab [72]. This test uses immunostaining to analyze PD-L1 expression within the tumor as well as the tumor microenvironment, including tumor-associated immune cells. The investigational assay is being assessed as part of ongoing trials [72]. When considering the potential utility of PD-L1 staining as a predictor of response to anti PD-1/PD-L1 immunotherapy, it is important to define the staining protocol and thresholds being used. A recent comparison of four PD-L1 assays (28-8, 22C3, SP142, SP263) on lung carcinoma samples showed that, with the exception of the SP142 antibody in the Ventana automated staining system (which was less sensitive), the remaining assays yielded similar results [95]. Although PD-L1 appears to have some prognostic value, there will need to be a standardized assay and interpretation for tumor PD-L1 protein expression before it can be effectively tested as a biomarker to predict the probability of response to checkpoint inhibitors in MCC or other malignancies.

The fact that complete responses are also achieved in patients whose tumors were negative for PD-L1 staining suggests that high levels of PD-L1 are not needed on tumor cells to maintain immune quiescence once it is established. However, blocking the PD-L1 that is upregulated in response to inflammation is a potential mechanism to prevent the reestablishment of tumor immune evasion. It is possible that the presence of detectible PD-L1 within a tumor reflects an active anti-tumor immune response that is being inhibited - the so called “hot tumor”. In contrast, a tumor with no PD-L1 may have achieved immune quiescence and is now a “cold tumor”. There are efforts to identify combinations of biomarkers that will better distinguish hot from cold tumors, including PD-L1 expression and the presence of CD8 T cells along the tumor margins [32], or quantifying markers of activation and immune exhaustion on lymphocytes. The hope is that such combinations will be effective in predicting response to immunotherapy.

Patients with known immunosuppression were not included in the trials of avelumab, as functional cellular immunity is necessary for anti-cancer immunotherapy to be effective. Immune senescence, intercurrent disease, medications, and prior cancer therapies can weaken immunity in cancer patients. Developing assays to detect impaired immunity may help in determining patients’ chances of responding to checkpoint inhibitors. A panel of *in vitro* tests, including flow cytometric measurements of PBMC subpopulations, T cell responsiveness to antigenic stimuli, and tests for NK activity may provide biomarkers for the immunocompetence of the patients and possibly explain some of the treatment failures of immune checkpoint inhibition.

5.3 Understanding and overcoming resistance

In addition to the patients who fail to respond, some individuals develop resistance to immune checkpoint inhibitors. In tumors progressing after initial response to anti-PD-1 therapy, an upregulation of the immune checkpoint receptor TIM-3 has been observed on cytotoxic T cells, and addition of a TIM-3-blocking antibody reversed the treatment

resistance [96]. Identifying and blocking alternative immune checkpoints in combination with PD-1/PD-L1 inhibition will likely improve response rates and prevent resistance. However, the safety risk of routinely using combination immunotherapy will need to be weighed against the improved benefits. The benefit and risk of combining PD-1 and CTLA-4 inhibition in MCC patients is presently being investigated in the phase I/II clinical trial CheckMate 358 which compares monotherapy with nivolumab to the combination of nivolumab and ipilimumab in metastatic MCC (NCT02488759). Patients with other virus-associated tumors, that is, Epstein-Barr virus and HPV-positive tumors, are also being included.

Genomic and transcriptomic investigations seek to define additional mechanisms of response or resistance. Tumors resistant to checkpoint inhibitors have been shown to exhibit some recurrent alterations, such as mutations in beta 2 microglobulin, loss of Phosphatase and Tensin homolog (PTEN), modifications on the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway, upregulation of WNT signaling, and elevated expression of co-inhibitory molecules [65]. Efforts to identify and countermand the changes that confer tumor resistance are ongoing.

5.4 Approaches to improve response to immunotherapy

It has been reported that the combination of immunotherapy and radiotherapy (RT) for the treatment of melanoma can have synergistic effects [97, 98]. Melanoma cells destroyed by RT release tumor antigens, induce inflammation, and reverse immune escape mechanism such as the down-regulation of MHC I. These radiation-induced changes could enhance immune checkpoint therapy. Down-regulation of MHC I expression has also been observed in MCC, notably in MCV-positive MCC. Therapies such as interferon, etoposide, and RT have been proposed as interventions to re-establish MHC I expression in MCC. Thus, combining these therapies with checkpoint inhibitors is worthy of further study [99].

Because avelumab has the ability to induce ADCC, co-administration of effector NK cells may result in synergistic anti-tumor responses. Similarly, studies combining checkpoint blockade with other cell-based immunotherapies such as autologous TIL infusion or chimeric antigen receptor T cells are being explored. The combination of checkpoint inhibition with cytokine-based immunotherapy (e.g. IL-2, IFN, IL-12, or IL-15), tumor vaccines, or oncolytic viruses may also prove to be effective.

Finally, the patient's microbiome may influence antitumor immunity. The introduction of commensal bacteria (*Bifidobacterium*) to mice caused spontaneous antitumor immunity as well as an improved response to checkpoint blockade [100]. Interindividual variations in the microbiota could potentially predict response to immunotherapy. Future studies may demonstrate a potential benefit of enhancing the microbiota prior to treatment with immunotherapy.

5.5 Conclusion

MCC is a rare and aggressive skin cancer that lacked highly effective therapies for advanced disease. Recent studies have demonstrated that metastatic MCC responds to immunotherapy with PD-1/PD-L1 checkpoint inhibitors with surprisingly high response rates and

manageable safety profiles. The largest study of immunotherapy in MCC was the JAVELIN Merkel 200 trial that demonstrated the efficacy and safety of PD-L1 inhibition with the human monoclonal antibody avelumab. Based on this study, avelumab became the first FDA approved treatment for metastatic MCC. This change in the first-line management of MCC brings the possibility of durable disease management to affected patients, and will likely impact the natural history of MCC going forward.

6. FIVE-YEAR VIEW

Immune checkpoint inhibitors like avelumab can be life extending drugs for patients with metastatic MCC, however not every patient responds and their use comes with the risk of adverse events. Overall, the available data support the early use of immune checkpoint inhibitors over chemotherapy in MCC. With the exception of patients with immunosuppression or autoimmune disease, who were excluded from the studies, most patients benefited from first-line use of PD-1/PD-L1 blocking antibodies. Future studies will investigate primary and secondary therapeutic resistances in addition to examining drug combinations that may improve response rates and limit resistance. It will also be important to define the utility of adjuvant checkpoint blockade in patients with resected MCC. To ensure optimal MCC patient treatment, there remain questions in terms of patient selection, treatment strategies in immunosuppressed patients, and how to best combine checkpoint inhibitors with radiation therapy and other treatment modalities.

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7.

KEY ISSUES

- Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin tumor with high relative mortality.
- MCC is an immunogenic tumor that responds exceptionally well to PD-1/PD-L1 checkpoint inhibitors (objective response rates > 50%).
- PD-L1 blockade with avelumab is the first and only approved treatment for patients with metastatic MCC.
- Avelumab is unique in its ability to target PD-1/PD-L1 signaling and also induce ADCC.

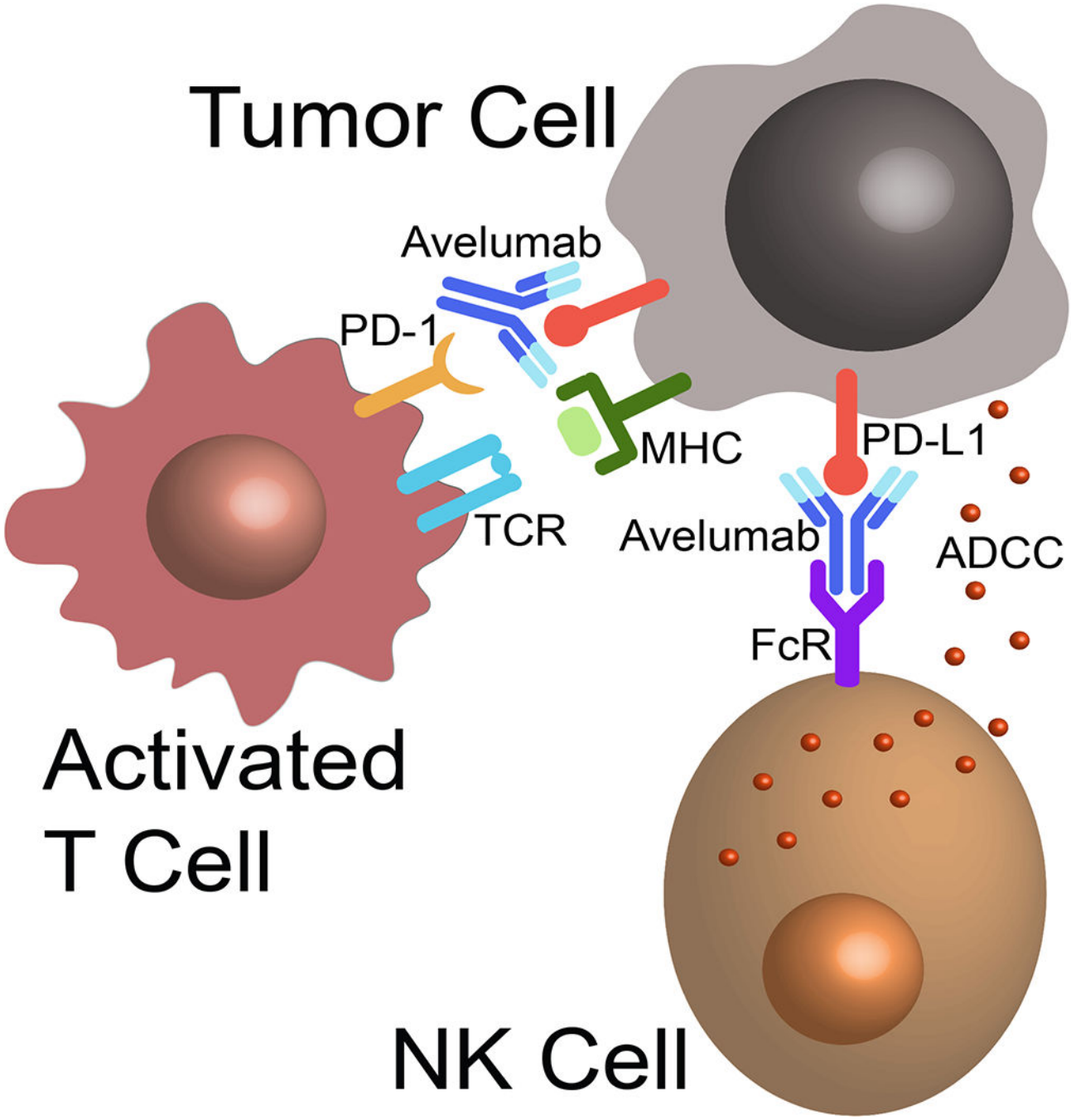

Figure 1.
Proposed mechanisms of action for avelumab. By binding PD-L1 the monoclonal antibody blocks signaling to PD-1 on anti-tumor T cells, reversing their inhibition. When bound to tumor cells, the IgG1 Fc domain on avelumab can bind Fc receptors on NK cells to activate ADCC.

Table 1.

Check-point inhibitors and their approval history as of February 14, 2018

Action	Agent/trade name/company	Antibody type	Efficacy	Ref.	Approval
Anti-CTLA4	Ipilimumab AKA: MDX-010 Trade name: Yervoy BMS	IgG1κ fully humanized	Metastatic malignant melanoma	[40]	FDA/EMA 2011
Anti-PD-1	Nivolumab AKA: Nivolumabum, ONO-4538, BMS-936558, MDX1106 Trade name: Optivo BMS	IgG4 fully humanized	Unresectable or metastatic Melanoma	[101] [102]	FDA 2014 EMA 2015
			Metastatic NSCLC		FDA/EMA 2015
			Metastatic renal cell Carcinoma		FDA/EMA 2015
			Hodgkin lymphoma		FDA/EMA 2016
			Head and neck cancer		FDA 2016 EMA 2017
			Advanced or metastatic urothelial carcinoma		FDA 2017 EMA 2016
			Hepatocellular carcinoma		FDA 2017
			Colorectal cancer		FDA 2017
			Adjuvant therapy in completely resected stage III/IV melanoma	[103]	FDA 2017
Anti-PD-1	Pembrolizumab AKA: Lambrolizumab, MK-3475 Trade name: Keytruda Merck/MSD	IgG4 fully humanized	Metastatic malignant melanoma	[104] [93]	FDA 2014 EMA 2015
			Metastatic head and neck squamous cell carcinoma		FDA 2016
			Metastatic non-small cell lung cancer		FDA 2016 EMA 2016
			Classical Hodgkin Lymphoma		FDA 2017 EMA 2017
			Locally advanced or metastatic urothelial carcinoma		FDA 2017 EMA 2017
			Any solid tumor with a specific genetic feature (microsatellite instability-high or mismatch repair deficient)		FDA 2017
			PD-L1 positive gastric/ gastroesophageal junction cancer		FDA 2017
Anti-PD-L1	Atezolizumab AKA: MPDL3280 Trade name: Tecentriq Roche Genentech	IgG1 fully humanized	Advanced Urothelial carcinoma		FDA 2016
			Metastatic lung cancer		FDA 2016 EMA 2017
			Advanced bladder cancer		FDA 2017 EMA 2017
Anti-PD-L1	Avelumab AKA: MSB0010718C Trade name: Bavencio Merck KgaA and Pfizer	IgG1 fully humanized	Merkel cell carcinoma	[50]	FDA 2017 EMA 2017
			Urothelial carcinoma		FDA 2017
Anti-PD-L1	Durvalumab Trade name: Imfinzi AstraZeneca	IgG1κ fully humanized	Advanced bladder cancer		FDA 2017

Action	Agent/trade name/company	Antibody type	Efficacy	Ref.	Approval
			Advanced non-small lung cancer		EMA 2017

Ab: antibody; ADR: adverse drug reaction; EMA: European Medicines Agency; FDA: food and drug administration; IgG: immunoglobulin G; ORR: overall response rate; PFS: progression-free survival; PD-1: programmed cell death protein 1; PD-L1: programmed cell death protein 1 ligand

Table 2.

Clinical trials including checkpoint inhibitors for treatment of Merkel Cell Carcinoma - as of September 26, 2017

Study Sponsor Collaborator	Phase	Official Title	Status	Tumor	Interventions	ClinicalTrials.gov Identifier Date of first submitted
National Cancer Institute (NCI)	II	Phase II Open-Label Trial of Ipilimumab for Metastatic Merkel Cell Carcinoma	Study withdrawn prior to enrolment	MCC	Ipilimumab	NCT01913691 July 28, 2013
JAVELIN Merkel 200 EMD Serono	II	A Phase II, Open-Label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab (MSB0010718C) in Subjects With Merkel Cell Carcinoma	Recruiting	MCC	Avelumab	NCT02155647 June 2, 2014
ADMEC Prof. Schadendorf University Hospital Essen BMS	II	Prospective Randomized Trial of an Adjuvant Therapy of Completely Resected Merkel Cell Carcinoma (MCC) With Immune Checkpoint Blocking Antibodies (Nivolumab, Opdivo®; Ipilimumab (Yervoy®) Every 3 Weeks for 12 Weeks Versus Observation	Recruiting	MCC	Ipilimumab Nivolumab	NCT02196961 June 20, 2014
National Cancer Institute (NCI)	II	A Phase II Study of MK-3475 in Patients With Advanced Merkel Cell Carcinoma (MCC)	Ongoing, but not recruiting	MCC	Pembrolizumab	NCT02267603 October 14, 2014
Fred Hutchinson Cancer Research Center National Cancer Institute (NCI) EMD Serono	I / II	Study to Evaluate Cellular Adoptive Immunotherapy Using Polyclonal Autologous CD8+ Antigen-Specific T Cells for Metastatic Merkel Cell Carcinoma in Combination With MHC Class I Up-Regulation and the Anti-PD-L1 Antibody Avelumab	Recruiting	MCC	Avelumab, Laboratory Biomarker Analysis MCPyV Tag-specific polyclonal Autologous CD8-positive T-cells, Radiation Therapy Recombinant IFN Beta	NCT02584829 October 21, 2015

Study Sponsor Collaborator	Phase	Official Title	Status	Tumor	Interventions	ClinicalTrials.gov Identifier Date of first submitted
Ludwig Institute for Cancer Research MedImmune LLC Cancer Research Institute, New York City	I / II	A Phase 1/2 Study of In Situ Vaccination With Tremelimumab and IV Durvalumab (MEDI4736) Plus the Toll-like Receptor Agonist PolyICLC in Subjects With Advanced, Measurable, Biopsy-accessible Cancers	Recruiting	MCC among other tumors	Durvalumab, Tremelimumab, Poly ICLC	NCT02643303 December 18, 2015
National Cancer Institute (NCI)	II	A Phase II Study of T-VEC Followed by T-VEC + Nivolumab in Refractory T Cell and NK Cell Lymphomas, Cutaneous Squamous Cell Carcinoma, Merkel Cell Carcinoma, and Other Rare Skin Tumors	Not yet recruiting	MCC among other tumors	Nivolumab Talimogene Laherparepvec	NCT02978625 November 30, 2016
AbbVie	I	A Multicenter, Phase 1, Open-Label, Dose-Escalation Study of ABBV-181, a Monoclonal Antibody, as Monotherapy and in Combination With Another Anti-Cancer Therapy in Subjects With Advanced Solid Tumors	Recrutiting	MCC among other tumors	ABBV-181 (anti-PD1) Rovalpituzumab Tesirine	NCT03000257 December 15, 2016
H. Lee Moffitt Cancer Center and Research Institute BMS	II	A Phase 2, Randomized, Multi-institutional Study of Nivolumab and Ipilimumab Versus Nivolumab, Ipilimumab and Stereotactic Body Radiation Therapy for Metastatic Merkel Cell Carcinoma	Recruiting	MCC Skin Cancer	Nivolumab, ipilimumab, stereotactic body radiation therapy (SBRT)	NCT03071406 March 1, 2017
AbbVie	I	A Multicenter, Phase 1, Open-Label, Dose-Escalation Study of the Safety, Tolerability and	Recruiting	MCC among other tumors	Nivolumab ABBV-368 (anti-c-Met)	NCT03071757 March 2, 2017

Study Sponsor Collaborator	Phase	Official Title	Status	Tumor	Interventions	ClinicalTrials.gov Identifier Date of first submitted
		Pharmacokinetics of ABBV-368 as a Single Agent and Combination in Subjects With Locally Advanced or Metastatic Solid Tumors				
Merck KGaA Pfizer		Temporary Authorization for Use (ATU) to Avelumab for Treatment of Adult Patients With Metastatic Merkel Cell Carcinoma (mMCC) with progress after at least one prior chemotherapy	Expanded access	MCC	Avelumab	NCT03089658 March 20, 2017
Incyte Biiosciences International Sàrl	I / II	A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01876 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies	Recruiting	MCC among other tumors	NCAGN01876 (anti-GITR) Nivolumab, Ipilimumab	NCT03126110 April 19, 2017
NantCell, Inc.	IB / II	NANT Merkel Cell Carcinoma (MCC) Vaccine: Combination Immunotherapy in Subjects With MCC Who Have Progressed on or After Anti-programmed Death-ligand 1 (PD-L1) Therapy	Not yet recruiting	MCC	Avelumab Bevacizumab Capecitabine Cisplatin Cyclophosphamide 5-fluorouracil Leucovorin nab-Paclitaxel omega-3-acid ethyl esters Stereotactic Body Radiation Therapy ALT-803 ETBX-051 ETBX-061 GI-6301 haNK	NCT03167164 May 23, 2017
Checkpoint Therapeutics, Inc. Novotech (Australia) Pty Limited	I	A Phase 1, Open-label, Multicenter, Dose-escalation Study of CK-301 Administered Intravenously as a Single Agent to Subjects With Advanced Cancers	Recruiting	MCC among other tumors	CK-301 (anti-PD-L1)	NCT03212404 July 6, 2017
Incyte Biosciences International Sàrl	I / II	A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01949 in Combination With Immune Therapies in Subjects With	Not yet recruiting	MCC among other tumors	INCAGN01949 (OX40 agonist) Nivolumab Ipilimumab	NCT03241173 August 2, 2017

Study Sponsor Collaborator	Phase	Official Title	Status	Tumor	Interventions	ClinicalTrials.gov Identifier Date of first submitted
		Advanced or Metastatic Malignancies				
Incyte Biosciences International Sàrl	I / II	A Phase 1/2 Safety and Efficacy Study of INCAGN01876 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies	Recruiting	MCC among other tumors	INCAGN01876 (anti-GITR) Epacadostat Pembrolizumab	NCT03277352 August 14, 2017
University of Washington National Cancer Institute	III	A Multicenter, Randomized, Double-Blinded, Placebo-Controlled, Phase 3 Trial of Adjuvant Avelumab (Anti-PDL-1 Antibody) in Merkel Cell Carcinoma Patients With Clinically Detected Lymph Node Metastases	Not yet recruiting	MCC	Avelumab	NCT03271372 August 31, 2017

IgG: immunoglobulin G; MCC: merkel cell carcinoma; PD-1: programmed cell death protein 1; PD-L1: programmed cell death protein 1 ligand

Table 3.

Clinical trials of checkpoint inhibitors for Merkel cell carcinoma

Drug	**Pembrolizumab**	**Nivolumab**	**Avelumab**	**Avelumab**
Checkpoint	Anti-PD-1	Anti-PD-1	Anti-PD-L1	Anti-PD-L1
Study	NCT02267603	CheckMate 358, NCT02488759	JAVELIN Merkel 200, NCT02155647 Part A	JAVELIN Merkel 200, NCT02155647 Part B
Study design	Multicenter, open-label, single arm, phase 2 study	Non-comparative, open-label, multiple cohort, phase 1/2 study	Multicenter, single-group, open-label, phase 2	Multicenter, single-group, open-label, phase 2
Inclusion criteria	Distant metastatic or recurrent locoregional MCC, chemotherapy-naïve	Advanced MCC, ≤ 2 prior therapies	Stage IV MCC, ≥ 1 prior therapy	Stage IV MCC, chemotherapy-naïve
No of patients	26 (1 without evaluation)	25	88	39
Median follow up (FU)	7.6 months	6.0 months (preliminary analysis)	16.4 months	5.1 months
ORR	14 (56 %)	22 (68 %)	31.1% (≥ 6 months FU) 33% (≥ 1 year FU)	62.1% (≥ 3 months FU) 71.4% (≥ 6 months FU)
Complete Response	4 (16 %)	3 (14 %)	9.1% (≥ 6 months FU) 11.4% (≥ 1 year FU)	13.8% (≥ 3 months FU) 28.6% (≥ 6 months FU)
Partial response	10 (40 %)	12 (55 %)	22.7% (≥ 6 months FU) 21.6% (≥ 1 year FU)	48.2% (≥ 3 months FU) 42.9% (≥ 6 months FU)
Stable disease	1 (4 %)	4 (18 %)	10.2% (≥ 6 months FU) 10.2% (≥ 1 year FU)	10.3% (≥ 3 months FU) 7.1% (≥ 6 months FU)
Progressive disease	9 (36 %)	3 (14 %)	36.4% (≥ 6 months FU) 36.4% (≥ 1 year FU)	24.1% (≥ 3 months FU) 14.3% (≥ 6 months FU)
Ongoing responses	14 (56 %)	13 (52 %)	72.4% (at data cutoff)	77.8% (≥ 3 months FU) 14.3% (≥ 6 months FU)
Progression-free	67 % (at 6 months)	86 % (at 3 months)	30 % (at 1 year)	67% (at 3 months)
Treatment-related adverse events of any grade	77 %, mainly fatigue and lab abnormalities	17 (68 %)	70 %, mainly fatigue (24 %) and infusion-related reactions (17 %)	72 %
Grade 3 treatment-related adverse events	4 (15 %) grade 3	5 (20 %) (grade 3 and 4)	4 (5 %) lymphopenia, blood creatine phosphokinase increase, aminotransferase increase, blood cholesterol increase	8 (20.5 %) elevated AST and ALT, cholangitis, paraneoplastic syndrome, gait disturbance, paraneoplastic encephalitis, polyneuropathy in malignant disease
Serious treatment-related adverse events	2 (8 %), myocarditis, elevated alanine aminotransferase and aspartate aminotranferase	na	5 (6 %), enterocolitis, infusion-related reaction, aminotransferases increased, chondrocalcinosis, synovitis, interstitial nephritis	none

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