Advances in Immunotherapy for Metastatic Merkel Cell Carcinoma: A Clinician’s Guide

Kelly G. Paulson, MD, PhD,a,b,c and Shailender Bhatia, MD,a,b,c

Abstract
Merkel cell carcinoma (MCC) is a neuroendocrine skin cancer. The clinical impact of MCC has been increasing due to steadily rising incidence rates. Since 2001, more than 24,000 cases of MCC have been reported to the US National Program of Cancer Registries database, and in 2018, more than 2,500 incident cases are expected. MCC is highly aggressive, and one-third of patients will either present with or develop metastatic disease. Outcomes in patients with metastatic MCC have historically been poor; median time to progression with cytotoxic chemotherapy is only 3 months. MCC has long been appreciated to be immunogenic, with reports of spontaneous regression and responsiveness to immunotherapy. However, the mechanisms of this immunogenicity have only been understood over the past decade, with approximately 80% of cases in the United States associated with the Merkel cell polyomavirus (MCPyV) and expression of viral antigens (virus-positive [VP] MCC), and the remaining 20% of cases caused by UV radiation–induced damage leading to a high mutational burden and expression of neoantigens (virus-negative [VN] MCC). These insights have led to multiple successful trials of immunotherapies for MCC. PD-1 axis checkpoint inhibitors are now regarded as the preferred frontline systemic therapy in eligible patients (including both VP- and VN-MCC), with impressive frequency, durability, and depth of objective responses, which compare favorably to those of most solid tumors. This article reviews the safety and efficacy data from the key clinical trials of immune checkpoint inhibitors for metastatic MCC, and discusses several issues relevant to the clinical use of these agents. Finally, emerging immunotherapies for MCC, including cellular therapies and adjuvant systemic therapies, are reviewed.

J Natl Compr Canc Netw 2018;16(6):782–790
doi: 10.6004/jnccn.2018.7049

Merkel Cell Carcinoma Presentation and Incidence
Merkel cell carcinoma (MCC) typically presents as a rapidly enlarging red nodule on sun-exposed skin.1 Risk factors include UV radiation exposure, age >65 years, and infection with the Merkel cell polyomavirus (MCPyV). Chronic systemic immune suppression (from HIV, hematologic malignancies, or use of immunosuppressive medications) is associated with increased MCC risk and significantly poorer outcomes1–3; however, most MCCs occur in individuals without underlying immunodeficiency. The reported incidence of MCC has been increasing rapidly, with approximately 25,000 cases recorded in the United States since 2000, including >2,200 incident cases reported in 2014 to the National Program of Cancer Registries/SEER combined registries, which captures >98% of the US population (Figure 1A).4 Incidence is expected to continue to briskly increase due to aging of the baby boomer generation, with >3,000 US cases estimated in 2025.5

The characteristic microscopic appearance for MCC is tightly packed, small, round, blue cells with high mitotic activity; immunohistochemistry is classically positive for cytokeratin 20 (CK20) in a dot-like pattern and

…

*Division of Medical Oncology, Department of Medicine, University of Washington; ‡Fred Hutchinson Cancer Research Center; and §Seattle Cancer Care Alliance, Seattle, Washington.

Submitted February 4, 2018; accepted for publication May 15, 2018.

Dr. Paulson co-developed the described MCPyV serology assay, but receives no compensation related to this. She is also a coinventor on a patent related to a transgenic TCR in development for MCC. Dr. Bhatia reports research funding to his institution (University of Washington) from Merck, BMS, EMD-Serono, Oncosec, ImmuneDesign, and NanKwest, and has received honoraria for participation in advisory boards for EMD-Serono and Genentech.

This work was fully supported by the NCI of the NIH under award numbers T32CA009515 and P30CA015704. The content is solely the responsibility of the authors and does not necessarily reflect the official views of the NIH.

Correspondence: Shailender Bhatia, MD, Division of Medical Oncology, Department of Medicine, Seattle Cancer Care Alliance, 825 Eastlake Avenue E, Mailstop #CE2-102, Seattle, WA 98109. Email: sbhatia@uw.edu
neuroendocrine markers (synaptophysin, chromogranin, and/or neuron-specific enolase), and negative for CK7 and TTF-1. Consistent with its histology, MCC is aggressive, and approximately 37% of patients have nodal or distant spread at presentation (Figure 1B); sentinel lymph node evaluation is thus frequently useful to identify subclinical nodal metastases.\(^4,6\) Systemic radiologic staging is encouraged by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MCC in patients at high risk of distant metastatic disease.\(^7\) A case series of 102 patients with MCC showed improved sensitivity of whole-body FDG-PET compared with CT alone, with an added impact on management of 37% of patients.\(^8\)

**Historical Outcomes With Metastatic Disease**

Approximately 10% of patients present with stage IV MCC (Figure 1B), and 1 in 3 patients will develop distant metastatic disease.\(^9\) Metastatic sites are diverse, including lymph nodes, liver, lung, subcutaneous tissue, and nonregional skin sites, as well as unusual sites such as pancreas, heart, and parotid. Brain metastases occur in approximately 10% of patients with metastatic MCC.\(^10\)

Survival for patients presenting with stage IV MCC has been historically dismal, with a median survival of approximately 1 year and nearly 100% chance of death by 5 years.\(^9,11\) Until 2017, cytotoxic chemotherapy (typically with platinum/etoposide) was standard first-line therapy for metastatic MCC. Despite a high objective response rate (ORR) of approximately 55%, durability of disease control is poor (median progression-free survival [PFS] of ≈3 months and median duration of response ≤8 months).\(^3,12\) After development of resistance to first-line therapy, second-line and later chemotherapy regimens have been ineffective, with an ORR of 10% and median PFS of only 1.9 months.\(^3,12,13\)

**Two Distinct Immunogenic Etiologies for MCC**

Approximately 70% to 80% of MCC cases in the United States are caused by MCPyV, a small DNA tumor virus similar to human papillomavirus.\(^14\) Although MCPyV is common, with approximately 50% of US individuals infected during childhood, it must develop 2 mutations (integration and truncation) to be oncogenic.\(^15–18\) Within virus-positive (VP) MCCs, the viral oncoproteins (T antigens) are constitutively expressed and growth promoting.\(^19–22\) These nonhuman proteins are required for ongoing MCC growth,\(^19\) and are immunogens for T and B cells.\(^3,13\) Individuals with brisk immune responses to MCPyV have better...
disease outcomes, providing strong rationale for the application of immunotherapy.\textsuperscript{24-26}

The remaining approximately 20\% of MCCs are MCPyV-negative (virus-negative [VN] MCC). Because the main driver in VN-MCC is mutation from chronic UV exposure, it is more common in parts of the world with increased UV light exposure (eg, Australia).\textsuperscript{27} VN-MCC tumors carry a poorer prognosis,\textsuperscript{28} and thus a disproportionate percentage of patients who develop metastatic MCC have VN disease.\textsuperscript{29} Although they lack virus, VN-MCCs remain immunogenic due to high mutational burden from UV-induced mutations\textsuperscript{30-33}; VN-MCCs have more mutations than almost all cancers in The Cancer Genome Atlas.\textsuperscript{30} High mutational and neoantigenic burdens have been shown to be strong predictors of immunotherapy responsiveness across cancer types,\textsuperscript{34} thus supporting application of immunotherapy in both VN- and VP-MCC.

The immunogenicity of MCC\textsuperscript{1,15} and PD-L1 expression in the MCC tumor microenvironment\textsuperscript{36,37} have provided a strong rationale for using immunotherapy. Efforts to date have focused on a multitude of approaches aiming to render cancer cells more visible to the immune system, reinvigorate existing immune responses, or generate new anticancer immunity. Indeed, several early-phase trials, including intratumoral interleukin-12 (IL-12),\textsuperscript{38} intratumoral TLR4 agonist,\textsuperscript{39} and MCPyV-directed adoptive T-cell therapy,\textsuperscript{40,41} have all supported the potential efficacy of immune-based approaches in MCC. However, the most striking successes have been with the PD-1 axis immune checkpoint inhibitors (ICIs) (Table 1), which have been remarkably efficacious and have revolutionized systemic therapy for MCC.

### PD-1 Axis Checkpoint Inhibitors

#### Avelumab

Avelumab is a human anti–PD-L1 monoclonal antibody that maintains a wild-type IgG1 Fc region that may, in addition to blocking PD-1/PD-L1 interactions, activate antibody-dependent cell-mediated cytotoxicity. In a pivotal phase II trial, 88 patients with chemotherapy-treated metastatic MCC were treated with avelumab, 10 mg/kg intravenously every 2 weeks. The ORR was 33\% (11\% had a complete response [CR; n=10] and 22\% had a partial response [PR; n=19]).\textsuperscript{42,43} Responses occurred quickly (median, 6.1 weeks) and irrespective of MCPyV or PD-L1 status of the MCC tumors (Figure 2). Importantly, responses were durable, with 74\% lasting at least 1 year. As a result, median overall survival (OS) with second-line avelumab for metastatic MCC was 12.9 months,\textsuperscript{43} which was more than twice the historical median OS of 4 to 6 months with second-line chemotherapy.\textsuperscript{13,44} Avelumab was well tolerated. Although 70\% of patients (n=62) reported treatment-related adverse events (AEs), including most commonly fatigue (24\%) and infusion reactions (17\%), most were grade 1/2; grade 3 AEs were uncommon (5\%) and no grade 4 events were reported. Based on the impressive results from this study, avelumab received approval by the FDA, Swissmedic, and the European Medical Association in 2017 for treatment of metastatic MCC, regardless of prior chemotherapy. This trial has recently expanded to include treatment-naïve patients with metastatic MCC (ClinicalTrials.gov identifier: NCT02155647). Preliminary results of the first 39 patients enrolled in this first-line expansion cohort reported an ORR of 62\% (CR, 14\%; PR, 48\%).\textsuperscript{45}

#### Pembrolizumab

Pembrolizumab is a humanized IgG4 anti–PD-1 monoclonal antibody that is being investigated in a phase II trial for first-line systemic treatment of immune-competent patients with unresectable stage IIIB or IV MCC (ClinicalTrials.gov identifier: NCT02267603). The initial report included 26 patients (25 evaluable patients), of whom 16\% (n=4) had a CR and 40\% (n=10) had a PR, resulting in an ORR of 56\%
Although the response rate was similar to historical rates associated with first-line chemotherapy, pembrolizumab responses were remarkably more durable, with 86% ongoing at last follow-up (median follow-up ≈8 months). Treatment was well tolerated: 77% of patients (20/26) reported an AE of any grade, of which only 15% (n=4) were grade 3 or 4. An expansion cohort of 24 patients has completed accrual and the results are eagerly awaited. Nivolumab Another ongoing study (ClinicalTrials.gov identifier: NCT02488759) is investigating the anti–PD-1 antibody nivolumab in patients with virus-associated cancers including MCC. Patients with metastatic MCC are eligible regardless of MCPyV status or prior chemotherapy. Preliminary results reported an impressive 68% ORR in 22 patients. The median time to response was 2 months, and 87% of responses were ongoing at last follow-up (median follow-up, 6 months). This trial has added a second cohort investigating nivolumab plus low-dose ipilimumab (1 mg/kg) in metastatic MCC.

PD-1 Axis Blockade

The striking and concordant results from the aforementioned trials of 3 different immunotherapies blocking the PD-1/PD-L1 interaction have offered powerful new options for managing advanced MCC. Responses to ICIs occur rapidly (Figure 2) and at a frequency similar to that expected with frontline chemotherapy, but are more durable, have been shown to be associated with improved quality of life, and are expected to lead to a meaningful improvement in OS, with perhaps even a chance at cure for an otherwise terminal disease. Importantly, response rates are higher in treatment-naive patients and lower in those treated with prior chemotherapy, likely due to the well-characterized immunosuppressive effects of chemotherapy. Rates of grade ≥3 treatment-related AEs have been low, and compare favorably with those of cytotoxic chemotherapy. Thus, PD-1/PD-L1–based immunotherapy should be considered as the new standard of care for first-line treatment of patients with metastatic MCC. This consideration is reflected in the recent listing of avelumab, pembrolizumab, and nivolumab as the recommended options for disseminated MCC in the 2018 NCCN Guidelines, although a clinical trial should still be the preferred choice, whenever available and appropriate. Avelumab is currently the only FDA-approved therapy for patients with metastatic MCC. For patients eligible for a PD-1 axis ICI, no clear data favor one drug over another; ORR looks comparable in the first-line setting. Avelumab has been tested most extensively so far and has also demonstrated a quality-of-life benefit. However, both pembrolizumab and nivolumab are reasonable alternatives, with pembrolizumab administered every 3 weeks (vs every 2 weeks for nivolumab and avelumab) if a less frequent dosing schedule is preferred. Rates of toxicity also appear similar for the drugs, as does toxicity management. Management of immune-related AEs has been extensively detailed in the recent ESMO and Society for Immunotherapy of Cancer (SITC) guidelines.
Contraindications to ICIs include ongoing immune suppression (likely to reduce efficacy), prior solid organ transplant, and/or prior autoimmune disease. Experience with ICIs in these settings is absent for MCC and limited for other malignancies. ICIs post–solid organ transplant have been reported to be associated with organ rejection and death. For autoimmune disease, a systematic review collated the effects of ICI therapy in 123 patients and found that 75% of patients with autoimmune disease developed flare of autoimmune disease and/or immune-related AEs. Most AEs were manageable with treatment discontinuation and steroids, but some were severe and fatal. Therefore, in these settings, the unique toxicity risks must be weighed against the risks of progressive MCC, particularly with the paucity of effective nonimmunotherapy options for such patients.

**Predictors of Response**

Nearly half of MCCs do not respond to PD-1 axis blockade. Thus, an urgent need exists to identify tumor or host characteristics that might predict nonresponse in order to prioritize clinical trials for these patients. Patients with both VP- and VN-MCCs (with markedly different tumor mutational burdens) appear to respond similarly to ICI therapy, reflecting the immunogenicity of both subsets, albeit through different mechanisms. Therefore, testing for MCPyV status (by immunohistochemistry or serology) or tumor mutational burden has limited utility in patient selection for PD-1 blockade. Similarly, ICI responses do not correlate with PD-L1 expression in the MCC tumor microenvironment, and thus PD-L1 expression testing by immunohistochemistry is not routinely supported. As for many other cancers, including melanoma, research is ongoing to identify new response biomarkers for ICIs in MCC because predictive biomarkers represent an unmet need.

**Metastatic MCC Resistant to PD-1 Axis Blockade**

In addition to identifying predictive biomarkers, mechanistic studies to understand both primary and acquired mechanisms of resistance are critical to uncover new rational therapies. A substantial need exists for effective therapies for MCC that does not respond to PD-1/PD-L1 blockade. Fortunately, several immunotherapy and nonimmunotherapy approaches are being pursued.

**Immunotherapy**

Early-phase trials and case reports have reported responses to a number of additional immunotherapies in MCC. Excitingly, several trials of novel immunotherapeutic approaches for MCC (both innate and adaptive) are underway.

**Systemic Immunotherapy:** Ipilimumab (anti-CTLA4) has been used off-label in 5 patients with 2 successes. Prospective trials of ipilimumab (either alone or in combination with radiation and/or nivolumab) are ongoing (ClinicalTrials.gov identifiers: NCT03071406, NCT02488759) and results are eagerly anticipated. NCT02488759 includes a nivolumab plus anti-LAG3 arm, and a study of an IL-2 immunostimulatory antibody plus paclitaxel is ongoing in Europe (NCT02054884). Further, combination of anti-OX40 and nivolumab or ipilimumab has recently opened in the United States (NCT03241173). Given the subtle differences between the different drugs and in their targeted pathways, with anti–PD-1 agents targeting PD-1:PD-L1 and PD-1:PD-L2 interactions compared with anti–PD-L1 agents targeting PD-1:PD-L1 and B7.1:PD-L1 interactions, there may be a theoretical reason to consider switching drug class from an anti–PD-1 to an anti–PD-L1 agent or vice versa. However, in our experience, which is consistent with the limited data in melanoma and renal cell carcinoma, this strategy by itself is highly unlikely to be successful in overcoming MCC resistance to the PD-1/PD-L1 pathway blockade. Hence, we do not recommend trying the same outside of a clinical trial. However, there may be value in continuing the PD-1/PD-L1 pathway blockade, while adding other novel therapies on this backbone, to overcome immune evasion mechanisms.

**Cellular Immunotherapy:** The presence of viral antigens provides an ideal target for cellular immunotherapies. Endogenous T-cell therapy targeting MCPyV has been studied early-phase trials, with several responses reported, including durable CRs; additional patients are accruing (ClinicalTrials.gov identifier: NCT02584829). A trial of NK cell immunotherapies in monotherapy or in combination with IL-15 has accrued (NCT02465957), with results...
Immunotherapy for Merkel Cell Carcinoma

Review

Immunotherapy for Merkel Cell Carcinoma

**Intralesional Immunotherapy:** Multiple intralesional immunotherapies have been investigated in MCC. Case reports have indicated success with intralesional tumor necrosis factor, \(^{57,58}\) class I interferon, \(^{59-62}\) and talimogene laherparepvec (T-vec). \(^{63}\) In early-phase trials, intralesional TLR4-agonist and IL-12 delivery (via electroporation) have resulted in durable objective responses in patients with advanced MCC. \(^{38,39}\) Current active trials include T-vec alone or in combination with radiation (ClinicalTrials.gov identifier: NCT02819843) or nivolumab (NCT02978625), and TTI-621 (anti-CD47; NCT02890368). Additionally, a recently opened phase I/II trial of intralesional TLR7/8 agonist plus a modified IL-2 formulation is including patients with MCC (NCT03435640). A triple-combination study of tremelimumab (an anti-CTLA-4 antibody), durvalumab (an anti-PD-L1 antibody), and intratumoral TLR3 agonist poly-ICLC in advanced MCC is underway (NCT02643303).

**Radiation as Immunotherapy:** Single-fraction radiotherapy (SFRT) can be immunostimulatory, \(^{54}\) and such approaches have been effective for palliation/tumor control of one or a few lesions in MCC (objective in-field response rate of 94%), \(^{65}\) although abscopal effects are not commonly seen in the absence of combination with systemic agents. \(^{66}\) SFRT is included as an immune adjuvant in many of the studies described earlier.

**Nonimmune Therapies**

Chemotherapy for MCC has typically included platinum doublet regimens similar to those for small cell lung cancer. Platinum and etoposide are most commonly used, with a response rate in first-line treatment of approximately 60%, but a short PFS. \(^{1,12}\) Preliminary results from a phase II trial of pazopanib reported an ORR of 19%, but limited response durability. \(^{67}\) MCC tumors express somatostatin receptors (SSTRs), responses to somatostatin analogs have been described, \(^{68}\) and trials delivering peptide-conjugated payloads (ClinicalTrials.gov identifier: NCT02936323) and radionuclides onto SSTR-expressing neuroendocrine tumors are ongoing. Another trial (NCT02514824) is testing MLN0128, an mTOR inhibitor. \(^{69,70}\) Results from these nonimmune therapy trials are especially relevant to patients ineligible for immunotherapy.

**Resected MCC With High Risk of Recurrence**

Adjuvant radiation is supported in many cases of resected MCC, with strong evidence for improved locoregional control and a trend toward improved survival. \(^{5,71-74}\) However, adjuvant cytotoxic chemotherapy, despite being commonly used by clinicians, has not been associated with survival benefit. \(^{73,75,76}\) Given unclear benefit, considerable toxicity in an elderly population, and the potential negative effect on responsiveness to subsequent use of ICI, adjuvant chemotherapy should not be used routinely. Fortunately, clinical trials are underway to test the safety and efficacy of ICIs as systemic adjuvant therapy in high-risk patients with MCC. A multicenter, randomized, place-controlled phase III trial investigating adjuvant avelumab in patients with clinically detected lymph node metastases (ADAM trial; ClinicalTrials.gov identifier: NCT03271372) was recently launched in the United States. Another trial, ADMEC-O (NCT02196961), is ongoing in Germany and is testing adjuvant ipilimumab (accrued) or nivolumab versus observation in patients with resected MCC.

**Surveillance**

After locoregional disease has been adequately treated, the NCCN Guidelines\(^{11}\) reflect a general clinical consensus and recommend a complete skin and lymph node examination every 3 to 6 months for the first 2 years, then every 6 to 12 months thereafter. Although radiologic surveillance is generally considered appropriate for patients at high risk for distant metastases, there is no strong consensus regarding which patients would be appropriate for radiologic surveillance, partly due to the lack of prospective data on recurrence-free survival in MCC. In practice, we typically do not perform routine surveillance imaging in nonimmunosuppressed patients with \(<2\)-cm primary MCC tumors and negative sentinel lymph node biopsy results because these groups have a \(<25\%\) risk of recurrence. \(^{11,77}\) Choice of imaging modality should reflect the sites at highest risk of recurrence. We typically use CT scans of the chest, abdomen, and pelvis in most patients, and sometimes CT scans of the head/neck and extremities, depend-
serology to T-oncoprotein is now clinically available (AMERK; https://www.merkelcell.org/serology). The NCCN Guidelines indicate that quantitation of MCPyV oncoprotein can help inform radiologic surveillance in patients with MCC, because seronegative patients may have a higher risk of recurrence, and an increasing titer in seropositive patients may be an early indicator of recurrence. If a patient is seropositive for viral oncoproteins at diagnosis, the antibody titer typically decreases after initial treatment and can increase with subsequent recurrence, serial measurements may help inform the need for scans and reduce imaging-related radiation exposure.

Conclusions

MCC is a highly immunogenic, virus-associated skin cancer with a rapidly increasing incidence and clinical impact. Immunotheory with PD-1 axis blockade leads to quick-onset, durable responses in metastatic MCC, and thus eligible patients should receive immunotherapy as first-line systemic therapy. Current research is centered around testing immunotherapy in the adjuvant setting for high-risk disease, investigating combinations to enhance ICI efficacy, and finding salvage therapies for patients with ICI-refractory disease. Learnings from immunotherapy successes and failures in MCC have high potential to guide immunotherapy efforts more broadly for all cancers and are worth aggressive pursuit.

References

Introduction

Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer that typically occurs in older adults. MCC is characterized by the presence of polyomavirus (MCPyV) in a subset of cases. Understanding the role of the immune system in MCC is crucial for developing effective therapeutic strategies.

Immunotherapy for MCC

The immune system plays a critical role in the development and progression of MCC. The initiation of MCC by MCPyV infection highlights the importance of the immune response in the natural history of the disease. Anti-MCPyV T cells have been identified in MCC tumors, and their enumeration has been shown to correlate with disease burden.


27. **Kwiat AB, Donahue RN, Bernstein MB, Hodge JW.** In the field: exploring the untapped potential of immunogenic modulation by radiation in


