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The Evolving Treatment Landscape of Merkel Cell Carcinoma

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Introduction

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer.

Common risk factors for MCC include age over 50 years, fair skin, extensive ultraviolet (UV) exposure, history of multiple skin cancers, and chronic immunosuppression such as human immunodeficiency virus (HIV), chronic lymphocytic leukemia (CLL), or solid organ transplantation [1–3]. In terms of carcinogenesis, MCC has two well-defined causes: the Merkel cell polyomavirus (MCPyV) and chronic UV-radiation exposure. MCPyV, initially described in 2008, causes approximately 80% of MCC tumors in the USA. The other 20% is caused by extensive UV-mediated damage. The incidence of MCC is increasing, with approximately 3000 new cases/year in 2020 in the USA, and a projected incidence of ~ 3200 cases in 2025. This rise is largely due to the aging population, and the fact that MCC incidence increases exponentially with age over 60 [4].

MCC often clinically presents as a non-specific cyst-like lesion. This often leads to delays in diagnosis as these tumors are often indistinguishable from benign lesions, such as cysts or lipomas [3]. Clues that can indicate a more malignant process (and warrant a biopsy),

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Compliance with Ethical Standards

Conflict of Interest

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Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

include an asymptomatic (nontender) presentation of a rapidly growing solitary red or skin-colored lesion on sun-exposed fair skin [3].

MCC has a high propensity for locoregional recurrence and distant metastasis, with 40% of patients experiencing recurrent disease after initial treatment [5]. Initial work-up, treatment, and vigilant surveillance are important for optimizing outcomes. Staging work-up of MCC includes clinical exam, sentinel lymph node biopsy (SLNB), and imaging [6••]. Baseline tumor markers such as MCPyV oncoprotein antibody titer and circulating tumor DNA (ctDNA) may help with prognostication and future surveillance, see the "Initial Staging Work-up" and the "Surveillance" sections.

Optimal treatment for MCC is often multi-modal. Therapeutic options include surgery, sentinel lymph node biopsy, radiation therapy, and systemic treatments including immunotherapy and chemotherapy. Given its rarity and complexity, multidisciplinary therapy is often warranted and should include medical, surgical, and radiation oncology. Herein, we provide a comprehensive review of current therapies for MCC including standard treatment options, immunotherapy, emerging therapies, and clinical trials.

Initial Staging Work-up

Initial staging workup should typically include histopathologic confirmation, physical exam, baseline imaging, and blood-based surveillance tests. See Fig. 1 for a flowchart detailing Merkel cell carcinoma evaluation and treatment.

Pathology

The diagnosis of MCC requires microscopic evaluation as the clinical appearance is non-specific. This is often done via punch or shave biopsy. The distinction between primary cutaneous MCC and a non-cutaneous neuroendocrine carcinoma metastasis to the skin requires immunohistochemical (IHC) and clinical pathologic correlation. MCC will typically be positive for low molecular weight cytokeratin including CAM 5.2 or AE1/AE3, CK20 (pathognomonic perinuclear dot-like pattern), neuron-specific enolase, synaptophysin, and chromogranin [9]. MCC is typically negative for CK7 or thyroid transcription factor 1 (TTF-1) (positive in SCLC), leukocyte common antigen (LCA; positive in lymphoma), S100 (positive in melanoma), and CD45 (positive in lymphoid malignancies) [9].

Physical Exam

A physical exam, ideally performed by a dermatologist, should be done on new patients presenting with MCC. This should include a focused skin exam at the known site(s) of disease. If the MCC has been excised, careful palpation on and around the scar should be done to assess for suspicious nodularity or in-transit metastases. If the MCC lesion has not been removed, palpation and subsequent marking of the tumor edges with a pen helps document the size of the lesion as MCC tumors often extend beyond the edge of the visible/elevated portion of the lesion, see Fig. 2A–C. A lymph node exam of the draining lymph node bed(s) should be performed. If a suspicious lymph node is palpated and/or detected on imaging, this would likely justify an ultrasound-guided biopsy rather than a SLNB due to lower side effects and cost.

Baseline Imaging

Baseline imaging is indicated in nearly all MCC patients, even those with clinically negative nodal disease (no enlarged lymph nodes by physical exam) as 1 in every 6 patients are upstaged by baseline imaging (compared to < 1% being upstaged in newly diagnosed invasive melanomas). PET/CT has several-fold higher sensitivity compared to CT scans alone (16.8% upstaged by PET/CT versus 6.9% upstaged by CT alone found in one large study), and thus is the favored imaging modality for baseline staging scans [6••].

Tumor Marker/Lab Orders

Baseline blood tests are important to obtain during initial workup including the AMERK (Merkel polyomavirus antibodies) and ctDNA (circulating tumor DNA) tests (see the “MCC Surveillance” section).

Localized Treatment Options

Excision of Primary Lesion

Local treatment of MCC often includes excision of the primary tumor. Current National Comprehensive Cancer Network (NCCN) guidelines recommend surgical excision with pathologically clear margins when clinically feasible for early-stage disease [10]. Several studies indicate that patients with residual tumors on surgical margins have worse survival outcomes, with positive margins noted at final excision in 4 to 57% of patients with MCC [11–14]. Historically, wide local excision (WLE) with margins of 1 to 3 cm were recommended [15–18, 19••]. However, extensive surgery may lead to delayed wound healing (more than 4–6 weeks), so it is important to balance the morbidity of surgical excision with clinical benefit. Because MCC is sensitive to radiation therapy (RT), higher risk cases often need adjuvant local radiation to lower recurrence risk (see the “RT” section). Recent studies report that narrow or even positive margins are highly effective in controlling local disease if adjuvant radiation therapy is also given [19••, 20].

WLE may be contraindicated in patients with non-operable tumors or those with certain medical comorbidities. In these patients, upfront RT may be considered. This modality provides 80% or even higher local control rates [21]. If no adjuvant RT is given to the local site, wider margins are important because surgical margins > 1 cm are associated with better local control in the absence of RT [19••]. The decision should be tailored to the patient’s preference and clinical circumstances.

Mohs Micrographic Surgery

Mohs micrographic surgery has also been used as a surgical treatment option for MCC, particularly in areas where tissue conservation is necessary due to the anatomic location of the tumor (often head/neck region). One of the major challenges of Mohs for MCC is that SLNB is often indicated for optimal management and would need to be carried out prior to the Mohs procedure in a setting with general anesthesia and nuclear medicine.

Sentinel Lymph Node Biopsy and Lymphadenectomy

SLNB is a highly sensitive test in detecting micro-metastatic MCC in the regional lymph node basin. SLNB has been shown in numerous studies to detect occult micro-metastatic disease in approximately 33% of patients presenting with clinically negative regional nodes [22, 23]. In the head and neck region, SLNB has a higher false-negative rate and is technically unsuccessful more frequently than at other body sites due to differences in lymphatic drainage in the area [24].

For sentinel lymph node negative patients, subsequent RT to the node bed is generally not indicated.

For sentinel lymph node positive patients, there are several treatment options including complete or selective lymph node dissection, nodal radiation alone, or complete dissection followed by nodal radiation. For patients with microscopic nodal involvement, nodal dissection followed by nodal RT is generally not recommended because either modality alone confers a nearly 100% regional control rate, and the combination leads to greater morbidity, including chronic lymphedema [25]. Given their similar efficacy, the choice between these treatments may be based on the clinical scenario and anticipated side effect profiles. However, combined surgery and radiation is often the preferred approach in the setting of clinically evident nodal disease.

Radiation Therapy

MCC is a highly radiation sensitive cancer with high local control rates [26]. Therefore, RT has evolved into an essential tool in the management of MCC, primarily in earlier stages. RT is typically used in the post-operative or adjuvant setting [27, 28]. In this setting, RT has shown improvements in both locoregional control and overall survival [29–31]. Current NCCN guidelines recommend considering post-operative RT (PORT) when 1 or more of the following six prognostic risk factors are present: positive or close/narrow margins (< 5 mm), head and neck primary tumor location, T-cell immunosuppression, large primary tumor size (> 1 cm), lymphovascular invasion, or positive SLNB. The conventional PORT dose and fractionation is 50 Gy in 25 fractions, with up to 66 Gy in 33 fractions in cases of gross residual disease. For nodal (including patients with only microscopic nodal involvement), RT to the primary tumor bed and involved LN basin is typically indicated. RT dose in this setting ranges from 46 to 50 Gy (for patients with only microscopic nodal disease) up to 60–66 Gy for unresected clinically evident nodal disease. Typical fractionation in both scenarios is about 2 Gy per fraction. Definitive radiation (60–66 Gy) may be considered in inoperable cases that are extremely large or invade muscle, bone, or cartilage (T4 stage) or in patients with comorbidities that make surgery too risky [25, 32].

Hypofractionated Radiation Therapy (Special Considerations)

Hypofractionated RT is also an option that is actively being explored in MCC. This approach involves treating at higher doses in fewer fractions (e.g., 8 Gy in 1–3 fractions), see Fig. 3. Single fraction radiation therapy (SFRT, 8 Gy × 1 fraction) has been used safely for decades for the treatment of bone metastases in other cancers [33–35].

For patients with oligometastatic disease, SFRT may be used as a convenient, less toxic alternative to systemic therapy for palliation/tumor debulking. Hypofractionated RT may also be used in the post-operative setting for patients who are elderly or frail (for whom conventional RT would lead to significant time burden or toxicity), or those with low-to-moderate baseline risk. Specifically, in a study of 26 metastatic MCC patients treated in the palliative setting, SFRT demonstrated high in-field local control rates in immunocompetent patients (91%; 29/32 treated tumors). Control was somewhat less effective among immunosuppressed patients (70%; 40/57 treated tumors), suggesting an important role of the immune system in maintaining disease control following RT. Morbidity was minimal for this approach and median follow-up was 277 days [36].

In the post-operative RT setting, SFRT achieved an in-field loco-regional control rate of 96% among 46 patients with localized stage I-II MCC with a 2.3-year median follow-up [37]. Additional studies of post-operative SFRT have shown similar results, highlighting this as a promising approach that offers excellent in-field local control rates with minimal associated toxicities and travel requirements [38••]. Hypofractionated RT shows promise as an alternative to conventional RT, particularly for medium-risk patients who would otherwise not have any RT in this setting.

MCC Surveillance

Approximately 40% of MCC cases recur, with most cases occurring within the first 2 years. The AMERK (Merkel polyomavirus antibodies) and ctDNA (circulating tumor DNA) tests can be used in MCC patients to sensitively detect early recurrences.

Antibodies to Merkel Polyomavirus Oncoproteins

Eighty percent of MCC tumors are caused by MCPyV in the USA. Approximately 50% of MCC patients produce antibodies to the Merkel cell polyomavirus oncoproteins that drive tumor growth. These “sero-positive” patients have a better prognosis (about 40% lower risk of recurrence) compared to sero-negative patients [39, 40]. In sero-positive patients, the titer of viral oncoprotein antibodies can be used to detect early recurrences because these antibodies fluctuate with disease burden.

A baseline test is recommended for MCC patients within 3 months of initial treatment to determine whether or not they produce these antibodies. This timeline is recommended because antibody titers typically become undetectable by about 7 months after initial treatment. One study found the antibody test to outperform imaging in the detection of recurrent MCC among 260 patients. This test detected several recurrences before they were visible on scans [41]. This same study revealed that patients with two consecutive increasing titers had a positive predictive value for disease recurrence of ~ 99%. In some cases, however, antibody titers may increase significantly before disease becomes clinically evident, with the delay in clinical progression sometimes extending for over a year. In such cases, it is appropriate to monitor frequently as initiating therapy in the absence of clinically evident disease is not recommended. Conversely, two consecutive decreasing titers (each decreasing by at least 20%) had a negative predictive value of 99% for recurrent disease. Based on these data, NCCN guidelines now include AMERK testing as part of routine

initial workup for all patients with newly diagnosed MCC and for ongoing surveillance in seropositive patients [42].

Notably, this test is not useful in patients who do not produce antibodies to MCPyV, and thus would not be recommended for surveillance purposes.

Patients are recommended to undergo surveillance blood testing every 3 months, for at least the first 2 years after diagnosis. Over time, as a patient's risk falls (see the "Recurrence Risk Calculator" section below), it is appropriate to discuss increasing the interval between blood testing to every 4–5 months. Once patients are 5–6 years out from their initial diagnosis without any recurrences, it is appropriate to discuss discontinuation of regular surveillance.

Circulating Tumor DNA Test

ctDNA is a clinical blood test to monitor early recurrences. Although new to MCC, this test has been used in other cancer types, including colorectal cancer, non-small cell lung cancer, and breast cancer [43]. This test is not currently recommended for MCC by international or national guidelines but can be obtained through direct coordination with the company (Natera). Currently, the company is covering the cost of this test while it is being studied in the setting of MCC. However, once commercially available for MCC, it will likely be billed to insurance. For those without insurance coverage, the company will likely offer a compassionate care program.

The ctDNA assay design has two parts: (A) whole exome sequencing (WES) to identify unique clonal tumor mutations and (B) a personalized multiplex polymerase chain reaction assay to target the signature mutations found by WES. The personalized assay can then be used to test the patient's blood for the presence of ctDNA [44].

This test has several advantages: (1) The blood test can be used in essentially all MCC patients, regardless of MCPyV status. (2) It can be performed at any time point in a patient's treatment or surveillance course, unlike the MCPyV oncoprotein antibody test that requires a baseline test within the first few months of diagnosis for best test sensitivity. (3) WES can provide information on a patient's tumor mutational burden rate, from which MCPyV status can be extrapolated. (4) The test provides a more accurate reflection of current disease burden as ctDNA has a shorter half-life (minutes) compared to antibodies (~ 4–6 weeks). (5) ctDNA levels remain reliable in the setting of recurrent disease or during treatment with immunotherapy compared to antibody titers which can fluctuate.

One study analyzed 167 patients (total of 562 blood samples); 66 had clinically evident MCC at baseline and a majority (63/66) were ctDNA positive (sensitivity 95%; 95% CI: 87–99%) [45]. This same study found that primary tumor diameter (median tumor size 2.2 cm; range 0.4–12) was strongly correlated with ctDNA levels (median: 17.2 MTM/mL, range 0.08–4490; $r = 0.82$, $p < 0.001$). Additionally, a positive test conferred a nearly sevenfold higher rate of recurrence during surveillance (HR = 6.8, 95% CI: 2.9–16, $p < 0.001$) compared to a negative ctDNA test [45].

Overall, ctDNA shows promising potential as a surveillance tool for MCC patients. This test can reduce the number scans needed to track especially when patients have negative ctDNA, see Fig. 4.

Recurrence Risk Calculator

Once a patient is fully staged, determining their risk of recurrence is important for appropriately planning surveillance. Currently, no detailed guidelines for surveillance frequency in MCC exist. The NCCN recommends imaging studies “as clinically indicated” and the consideration of routine scans for high-risk patients [42].

Personalized MCC recurrence risk depends on sex, disease stage at diagnosis, immunosuppression status, site of primary tumor, age, and time since diagnosis [46, 47••]. A cohort of 618 patients with MCC were studied to generate a personalized recurrence risk calculator https://merkelcell.org/recur/ [47••]. This calculator determines overall risk of recurrence (encompassing locoregional and distant recurrence risk). It provides a recurrence risk estimate at the time of completing initial treatment as well as at any given follow-up time. The majority of recurrence risk is within the first 2 years; therefore, patients should be followed most closely during this time. More accurate estimation of risk can provide important perspective for decisions relating to surveillance frequency.

Scans

Routine surveillance scans are indicated in high-risk patients who are not followed regularly with blood tests. For the first few years after initial treatment, scans should typically be performed every 3–6 months. The decision to carry out scans less frequently should be individualized based on the patient’s disease status and recurrence risk.

In terms of imaging modality, surveillance scans are typically performed via CT scans with contrast. Although PET scans are more sensitive at baseline, they are more expensive and are typically not approved by insurance for surveillance. PET-CT imaging is also logistically difficult as patients need to be fasting and cannot have exercised muscles near the time of the test to avoid false positive results.

Systemic Treatment Options

Immune Checkpoint Inhibitors

MCC is a highly immunogenic cancer. This is supported by the many reports of spontaneous regression, as well as the increased risk of developing MCC in immunocompromised populations (HIV, organ transplant, CLL) [48]. Indeed, immunotherapy became the treatment of choice for advanced MCC.

The dominant immunotherapy pathway targeted for MCC is programmed cell death (PD)-1/PD-ligand(L)1. Cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitors are also used [49••]. These are collectively known as immune checkpoint inhibitors (ICI) [50, 51]. Avelumab (anti-PD-L1) was the first agent approved by the US Food and Drug Administration (FDA) for MCC in 2017, with an objective response rate (ORR) of 62% in first-line setting [52, 53]. Then, pembrolizumab (anti-PD-1) was approved in 2018, which

has an ORR of 56% [54, 55•]. Retifanlimab (anti-PD-1) was recently approved for MCC on March 22, 2023. It has an ORR of 52% in the first-line setting for advanced MCC [56].

Combination ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) are not currently FDA approved in the first-line setting. However, in one randomized phase 2 trial, all immunotherapy-naïve patients (22/22) showed an objective response to ipilimumab plus nivolumab with or without SBRT [57–61].

Standard Dosage

Avelumab is infused at 800 mg every 2 weeks. Premedication with acetaminophen and antihistamine for the first 4 infusions is recommended by FDA guidelines to reduce infusion reactions [62]. Pembrolizumab has two standard infusion regimens, either 200 mg every 3 weeks or 400 mg every 6 weeks [63]. Retifanlimab is infused every 4 weeks, at 500 mg per dose [56].

Nivolumab monotherapy dosing is detailed below under “neoadjuvant immunotherapy.” Ipilimumab monotherapy is not recommended for advanced MCC. It is typically used in PD-(L)1 refractory MCC as a combination therapy with nivolumab. Combination therapy dosing is detailed in the “Treatment Options for PD-(L)1 Refractory Disease” section.

Neoadjuvant Immunotherapy

Neoadjuvant therapy is given while cancer is still clinically present, prior to other planned definitive therapy. The Checkmate 358 trial studied neoadjuvant nivolumab (240 mg infusions for two doses every 2 weeks) in 39 patients with stage IIA-IV MCC, with subsequent surgical resection planned. Seventeen of 36 (47%) patients who had surgery had a pathologic complete response (CR). Recurrence-free survival (RFS) significantly correlated with a pathologic CR and radiographic response at the time of surgery [64]. Ongoing studies of neoadjuvant immunotherapy are detailed in Table 1.

Adjuvant Immunotherapy

Adjuvant immunotherapy in MCC is under active investigation, see Table 1. The ADAM (ADjuvant Avelumab in Merkel) trial (NCT03271372) is evaluating this approach in stage III MCC. This phase III trial aims to randomize 100 patients to either placebo or avelumab for 2 years [65]. The STAMP (Surgically Treated Adjuvant Merkel cell carcinoma with Pembrolizumab) trial (NCT03712605) has just completed enrollment with 280 stage I–III patients randomized to either pembrolizumab or observation for 1 year [66]. A European phase II clinical trial, ADMEC-O (NCT02196961), is investigating adjuvant nivolumab monotherapy versus observation. This is the first adjuvant ICI trial with published data. Preliminary findings show a 44% reduction in recurrences in the nivolumab arm compared to the observation arm with a hazard ratio of 0.56; however, this has not reached statistical significance ($p = 0.109$) [67].

Main Side Effects

Side effects of ICI in MCC are comparable to other diseases treated with ICIs. Most adverse reactions are mild, but 11–28% patients may have grade 3 + toxicities [68]. The more

serious reactions are often due to the development of autoimmunity or the rejection of a renal allograft. Therefore, special consideration by a multidisciplinary team should be made for patients with a history of autoimmune disease or a kidney transplant. Overall, a patient's preferences for quality of life and their comorbidities must be carefully weighed when considering ICI therapy.

When to Discontinue Immunotherapy in Patients with a Good Response?

There are no clear guidelines on when to discontinue ICI in patients who respond well to therapy. Most ICI clinical trials had patients on therapy for 1–2 years; however, recent data suggests that there is a 35–60% recurrence risk following immunotherapy cessation [69•, 70].

Given the high risk of recurrence after discontinuing immunotherapy, extending the duration of treatment can be considered. ICIs have demonstrated activity outlasting current dosing intervals. For example, nivolumab has shown sustained PD-1 receptor occupancy for 60 + days following a single infusion [71]. This supports the use of a reduced frequency ICI regimen in those who pursue an extended treatment duration. However, data is needed to determine whether or when immunotherapy should be electively discontinued in MCC patients.

Chemotherapy

Since 2015, chemotherapy is no longer the first choice for advanced MCC due to its short-lived efficacy and immunosuppressive effects. However, it can be a useful short-term palliative option, given its relatively high response rate and ability to debulk extensive disease [72]. The most common regimen used in MCC is carboplatin plus etoposide. Alternatives include cyclophosphamide, doxorubicin, and vincristine.

Treatment Options for PD-(L)1 Refractory Disease

Unfortunately, over half of patients with advanced MCC will eventually experience disease progression despite PD-(L)1 pathway blockade. Treatment options for ICI-refractory MCC are limited, and without clear guidelines.

Combination Therapy with Ipilimumab and Nivolumad

The combination therapy of ipilimumab and nivolumab has recently become the default option for PD-(L)1 refractory MCC. This combination has shown a ~ 30% response rate in this setting [57–61].

This regimen is associated with increased risk of all- and high-grade irAEs including pruritus, rash, diarrhea, colitis, hypo/hyperthyroidism, hypophysitis, hepatitis, and pneumonitis [73].

A typical dosing regimen is 1 mg/kg of ipilimumab and 3 mg/kg of nivolumab every 3 weeks for the first 4 cycles, followed by nivolumab monotherapy. An alternative dosing regimen is 3 mg/kg of ipilimumab and 1 mg/kg of nivolumab every 3 weeks, although this regimen is used less frequently.

MDM2 Inhibiton

MDM2 inhibitors can suppress growth of MCC by stabilizing the p53 tumor suppressor, hence promoting p53-mediated cell death. In patients with virus-positive disease, the MCPyV small T antigen activates MDM2 protein expression (an E3 ubiquitin ligase) which in turn binds and ubiquitinates p53, leading to its degradation [74, 75]. A current phase 1b/2 clinical trial is assessing the efficacy of MDM2 inhibitor, navtemadline, in patients who have failed treatment with at least one anti-PD-(L)1 agent or in combination with avelumab in MCC patients who are ICI treatment naïve. A recently published update from this trial revealed an overall response rate (ORR) of 25% and disease control rate of 63% in ICI-refractory patients receiving 180 mg of navtemadline for 5 days on and 23 days off (n = 8). Median time to treatment response was around 4 months. Notably, 1 patient achieved CR after 2 years of treatment [76•]. This early data supports the potential role for treatment with MDM2 inhibitors in patients with ICI-refractory MCC (n = 29).

ATTAC Trial

MCPyV proteins are shared across patients with MCC, allowing targeting of this tumor using a T cell receptor that can work across patients with a shared HLA type. The Autologous Transgenic T cells, Avelumab and Class I MHC upregulation for Advanced Checkpoint-inhibitor resistant MCC (ATTAC) trial was designed for patients with advanced or unresectable MCPyV-associated disease who had progressed despite ICI therapy. Patients with a history of a significant irAE are permitted to receive the same regimen, in the absence of an ICI. Treatment includes genetically modified T cells (autologous MCPyV-specific HLA-A02-restricted TCR-transduced CD4 + and CD8 + T-cells), interferon gamma (IFN-y), and a PD-(L)1 inhibitor.

Preliminary data revealed no dose limiting toxicities [77]. Four of five patients developed progressive disease (PD), but the fifth patient had a significant partial response (PR) with 11/12 MCC lesions resolving. The single persistent lesion was treated with RT, and the patient has experienced RFS for over one year. The unresponsive lesion had lost expression of major histocompatibility complex (MHC) class I. To address this, patients are now pretreated with IFN-y to promote MHC class I expression. This trial is still actively recruiting.

Emerging Treatments of Interest

Targeted Therapies

Targeted therapies are systemic treatment options that are focused on a cancer-specific mechanism [78]. Typically, these are indicated in patients with PD-(L)1 refractory disease, or for those with contraindications to ICIs.

Somatostatin Analogs

The cyclic peptide hormone somatostatin controls a variety of functions via binding to somatostatin receptors (SSTR). Many organs and some tumors, including neuroendocrine tumors (NET) like MCC, express SSTRs [79].

Somatostatin analogs (SSAs) such as octreotide have well-established antitumor effects in NETs via the inhibition of SSTRs and are generally well tolerated [80]. Approximately 85% of MCC tumors express SSTR. This contrasts with other high-grade NETs, where SSTR expression is uncommon [81]. To determine whether a MCC tumor would likely be responsive to an SSA, SSTR expression can be evaluated by somatostatin receptor scintigraphy such as 68-Gallium DOTATATE PET-CT or Octreotide scintigraphy. SSAs can have clinically significant efficacy in MCC, providing disease control in ~ 43% of patients, but they seldom produce a CR [81].

Peptide Receptor Radionucleotide Therapy

Peptide receptor radionucleotide therapy (PRRT) is another therapy that can be used in the ICI-refractory setting or in patients with advanced inoperable tumors [82].

This radiopharmaceutical agent enables the delivery of targeted radiation to cancer cells by binding a radionuclide to a peptide molecule, typically a somatostatin receptor agonist. Therefore, PRRT is effective in treating NETs with high expression levels of SSTRs, like MCC. In one systematic review, 37 patients with metastatic MCC received PRRT with ^{177}Lu- and/or ^{90}Y-labeled somatostatin analogs. Six out of 19 patients (31.6%) with available imaging showed objective responses (including partial and complete responses), and no severe adverse events were reported [83]. PRRT has also demonstrated efficacy when used in combination with ipilimumab and nivolumab [84]. This combination treatment (ICI + PRRT) is currently being explored in the prospective Australian GoTHAM study (Targeted Therapy and Avelumab in Merkel Cell Carcinoma; NCT04261855).

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) target many growth factors (vascular endothelial, platelet-derived, and fibroblast growth factors) which are often involved in angiogenesis and/or tumor cell growth. Angiogenesis in particular is important for cancer growth as it promotes the ongoing development of a sufficient blood supply. By inhibiting angiogenesis, tumor growth can be reduced [85]. TKIs include drugs like pazopanib, imatinib, cabozantinib, and idelalisib. When TKIs show efficacy, they typically result in stable disease (SD) [78].

Intratumoral Therapies

Talimogene Laherparepvec—Talimogene Laherparepvec (T-VEC) is a modified herpes simplex virus that elicits local and systemic antitumor responses via viral replication and granulocyte–macrophage colony-stimulating factor (GM-CSF) production [86]. T-VEC is FDA-approved for the treatment of melanoma [87], but its use in MCC is less frequent. T-VEC may benefit patients with underlying comorbidities that either prevent them from receiving systemic immunotherapy or have locoregionally advanced, ICI-refractory disease. Impressive clinical responses, including both partial and/or complete responses, have been observed in patients with locoregionally advanced MCC treated with intralesional T-VEC [88–91]. Treatment is generally well tolerated; the most commonly reported side effects include transient flu-like symptom(s), erythema, and pain at injection site [88–91].

Intratumoral Cytokines—Several intratumoral cytokines have been explored in MCC including Toll-like receptor 4 (TLR-4) agonists, Toll-like receptor 9 (TLR-9) agonists, and Interleukin 12 (IL-12). Each of these small trials has shown evidence of efficacy in MCC [92, 93]. These agents are not currently clinically available, but these therapies will likely undergo further testing and may eventually become available more broadly.

Therapeutic Vaccine Trial

MCPyV positive MCC patients experience a decline in their virus-targeted B and T cell responses, beginning shortly after successful treatment of their tumor [94]. By 6 to 18 months after treatment, antibody titers and cancer-specific T cells have significantly diminished.

MCC is most likely to recur within the first 2 years following treatment. Perhaps, this is not a coincidence, and a therapeutic vaccine designed to target MCPyV oncoproteins may improve anti-tumor B and T cell function and thereby prevent recurrences [94]. Such a vaccine is being studied in the adjuvant setting with a phase I trial. Patients are eligible if they had MCPyV-induced MCC, no history of systemic cancer treatment, and no evidence of disease for over 1 year. MCPyV-specific immune responses to this vaccine are currently under evaluation, the results of which will determine next steps.

Factors Impacting Response to Immunotherapy

While immunotherapy initially benefits ~ 60% of patients, many do not respond and there is no way to predict this ahead of treatment. Discovering the underlying mechanism behind “non-responders” may suggest approaches to enhance the efficacy of immunotherapies.

One study collected MCPyV-specific CD8 + T cells from patients who were treated with neoadjuvant anti-PD-1 (nivolumab) therapy to study resistance mechanisms [95]. Those with detectable circulating MCPyV-specific CD8 + T cells before treatment ($n = 11$) had longer RFS (75% at 2 years) compared to patients without such cells ($n = 5$; 0% RFS at 2 years; $p = 0.0018$). Furthermore, MCC-specific CD8 + T cells in the blood exhibited characteristics of an earlier stage of exhaustion than their intratumoral counterparts. These data are further supported by an analogous study of advanced MCC patients treated with first-line pembrolizumab [96]. This suggests that cancer-specific T cells in blood may act as a reservoir of T cells that are more likely to be reinvigorated by anti-PD-1 therapy.

Another study evaluated the circulating cancer-specific T-cell response of a patient with virus-negative MCC that had a durable PR to avelumab [97]. All identified cancer-specific T cells were CD4 + , contrasting with prior findings in virus-positive MCC where most identified cancer-specific T cell responses were CD8 + . CD4 + T cells increased within weeks after initiating avelumab. However, several months after the PR, CD4 + T cell responses became undetectable. This decrease in immunity is following elimination of the cancer is consistent with other studies of MCPyV-specific T cell activity in MCC patients [94].

These recent findings suggest that adoptive T cell therapy or vaccines that improve cancer-specific T cell numbers or function may benefit patients that are refractory to anti-PD-(L)1 therapy.

Conclusions

Merkel cell carcinoma is a complex disease that benefits from multidisciplinary care to optimize management. In the last decade, significant advancements have been made in MCC management. These include an enhanced understanding of the roles of surgery and radiation, the emergence of immunotherapy, and the development of highly sensitive and specific blood tests for disease surveillance.

Prior to immunotherapy, chemotherapy was the sole systemic treatment option available for metastatic MCC. Responses to chemotherapy are typically brief (less than 3 months), whereas patients who respond to immunotherapy often experience benefits lasting for several years. However, approximately half of advanced MCC patients do not persistently benefit from immunotherapy due to primary or acquired resistance. This is the most pressing challenge facing MCC patients. For PD-(L)1 refractory patients, combination ICIs (ipilimumab plus nivolumab) and ICI synergistic treatments (RT, targeted therapies, T cell therapies) are under investigation. The next few years in MCC research hold great potential to bring further benefit to these patients.

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Abbreviations

ADAM	ADjuvant Avelumab in Merkel
AE	Adverse effect
ATTAC	Autologous Transgenic T cells, Avelumab and Class I MHC upregulation for Advanced Checkpoint-inhibitor resistant Merkel cell carcinoma
CLL	Chronic lymphocytic leukemia
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic T lymphocyte-associated protein 4
CI	Confidence interval
CR	Complete response
CT	Computed tomography

FGF	Fibroblast growth factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HR	Hazard ratio
HIV	Human immunodeficiency virus
ICI	Immune checkpoint inhibition
irAEs	Immune-related adverse events
IHC	Immunohistochemical
IFN-y	Interferon gamma
IL-12	Interleukin 12
IT	ntratumora
AMERK	MCPyV antibody test
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
MHC	Major histocompatibility complex
mMCC	Metastatic Merkel cell carcinoma
NCCN	National Comprehensive Cancer Network
NED	No evidence of disease
NET	Neuroendocrine tumors
OS	Overall survival
ORR	Overall response rate
PR	Partial response
PET-CT	Positron emission tomography and computed tomography
PFS	Progression-free survival
PD	Progressive disease
PDGF	Platelet-derived growth factor
PRRT	Peptide receptor radionucleotide therapy
PORT	Post-operative radiation therapy
PD-(L)1	Programmed cell death (ligand) 1
RT	Radiation therapy

RFS	Recurrence-free survival
SFRT	Single fraction radiation therapy
SLNB	Sentinel lymph node biopsy
SSAs	Somatostatin analogs
SSTR	Somatostatin receptors
SRS	Somatostatin receptor scintigraphy
SD	Stable disease
T-VEC	Talimogene Laherparepvec
TKIs	Tyrosine kinase inhibitors
TLR4	Toll-like receptor-4
TLR9	Toll-like receptor-9
UV	Ultraviolet
FDA	US Food and Drug Administration
VEGF	Vascular endothelial growth factor
VP	Virus positive
WES	Whole exome sequencing
WLE	Wide local excision

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Opinion statement

Merkel cell carcinoma (MCC) has a high risk of recurrence and requires unique treatment relative to other skin cancers. The patient population is generally older, with comorbidities. Multidisciplinary and personalized care is therefore paramount, based on patient preferences regarding risks and benefits. Positron emission tomography and computed tomography (PET-CT) is the most sensitive staging modality and reveals clinically occult disease in ~ 16% of patients. Discovery of occult disease spread markedly alters management. Newly diagnosed, localized disease is often managed with sentinel lymph node biopsy (SLNB), local excision, primary wound closure, and post-operative radiation therapy (PORT). In contrast, metastatic disease is usually treated systemically with an immune checkpoint inhibitor (ICI). However, one or more of these approaches may not be indicated. Criteria for such exceptions and alternative approaches will be discussed. Because MCC recurs in 40% of patients and early detection/treatment of advanced disease is advantageous, close surveillance is recommended. Given that over 90% of initial recurrences arise within 3 years, surveillance frequency can be rapidly decreased after this high-risk period. Patient-specific assessment of risk is important because recurrence risk varies widely (15 to > 80%: Merkelcell.org/recur) depending on baseline patient characteristics and time since treatment. Blood-based surveillance tests are now available (Merkel cell polyomavirus (MCPyV) antibodies and circulating tumor DNA (ctDNA)) with excellent sensitivity that can spare patients from contrast dye, radioactivity, and travel to a cancer imaging facility. If recurrent disease is locoregional, management with surgery and/or RT is typically indicated. ICIs are now the first line for systemic/advanced MCC, with objective response rates (ORRs) exceeding 50%. Cytotoxic chemotherapy is sometimes used for debulking disease or in patients who cannot tolerate ICI. ICI-refractory disease is the major problem faced by this field. Fortunately, numerous promising therapies are on the horizon to address this clinical need.

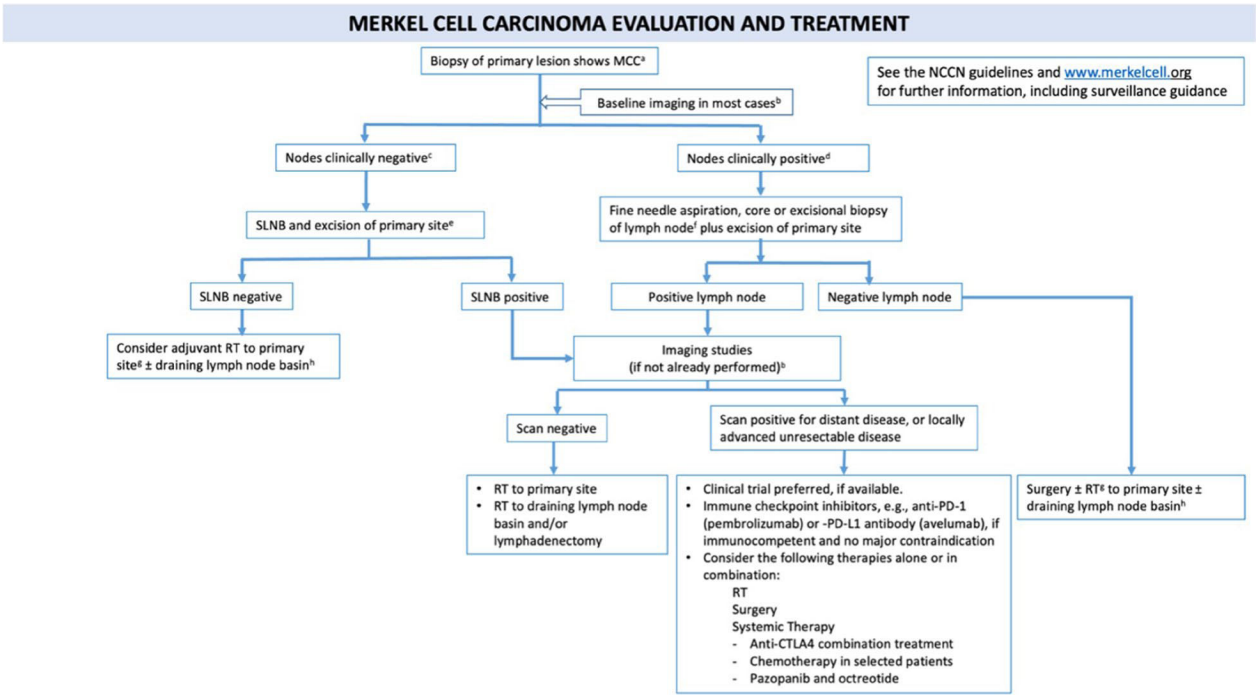

Fig. 1.

Flow chart for Merkel cell carcinoma evaluation and treatment management. **a** Consider baseline Merkel cell polyomavirus serology test for prognostic significance and surveillance (for seropo-*/ + -*itive patients). **b** Whole body FDG-PET/CT (preferred at baseline) or CT of chest, abdomen, pelvis with/without neck with contrast; brain MRI if symptomatic. **c** No enlarged/concerning nodes on physical examination and by imaging study. **d** Enlarged/concerning nodes on physical examination or by imaging study. **e** SLNB may not be indicated if a patient would not benefit from the prognostic information, if it would not alter management of the regional nodes, or if a patient is not a good candidate for surgery/anesthesia. **f** Consider excisional biopsy primarily or after negative needle/core biopsy to exclude false-negative biopsy result. **g** Adjuvant RT is often indicated unless the following low-risk features are present: primary lesion ≤ 1 cm, primary site not on head/neck, no lymphovascular invasion, widely negative pathologic margins, negative SLNB, and patient not immunosuppressed. **h** Consider RT to the nodal basin in high-risk patients (e.g., profound chronic immune suppression). Adapted, with permission, from Park et al., Future Oncol 2021 [7] and Akaike et al., Journal of Dermatological Science 2022 [8].

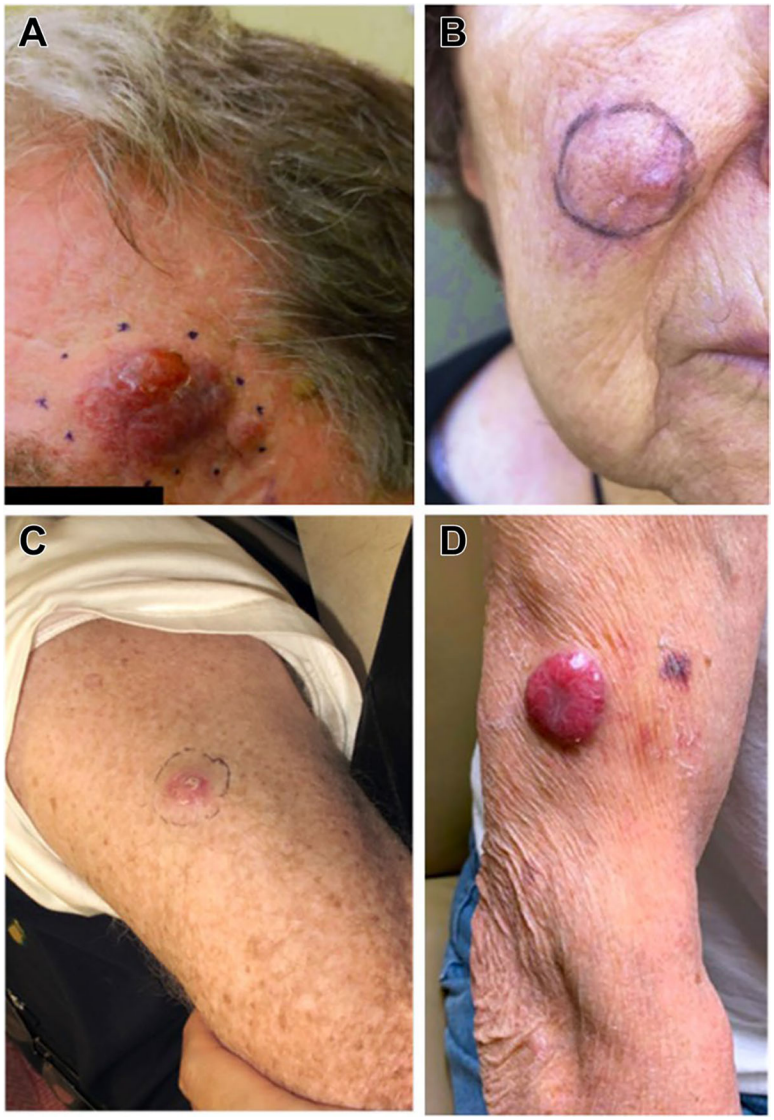

Fig. 2.

Clinical images of primary Merkel cell carcinoma tumors. The marking pen ink indicates the palpable edge of the tumors, which often extends well beyond the elevated portion of the lesion.

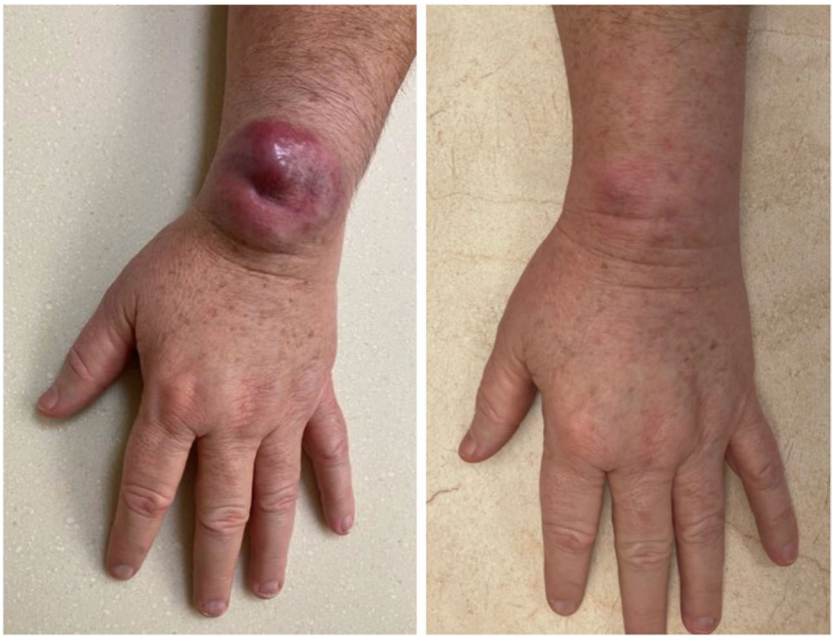

Fig. 3.
Before and after photos of MCC tumor treated with definitive hypo-fractionated radiation therapy (24 Gy in 3 fractions).

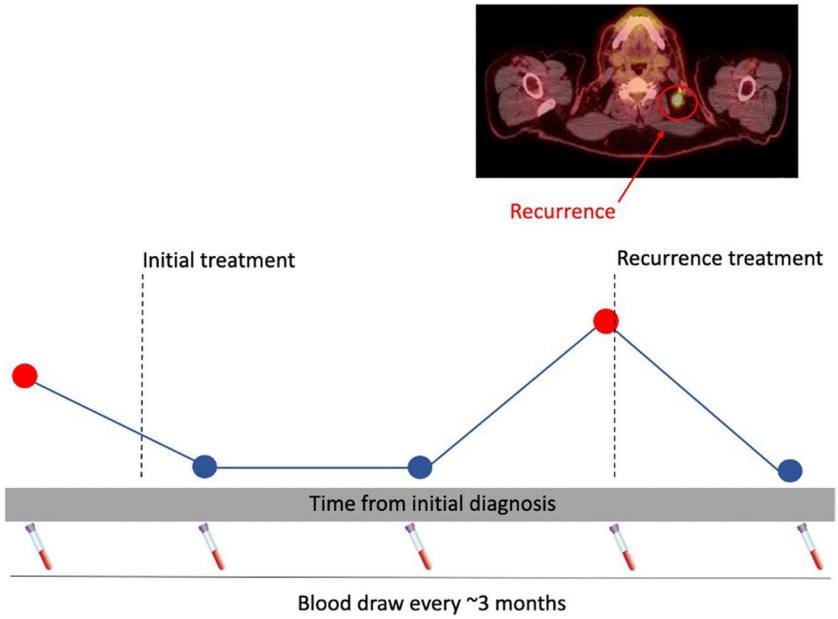

Fig. 4.

Schema for surveillance blood testing (AMERK and/or ctDNA) in MCC. X-axis represents time, with each blood vial corresponding with an approximately a 3-month testing interval. Blue dots indicate no detectable disease. The 1st red dot represents baseline lab values, reflecting the presence of disease prior to treatment. The 2nd red dot indicates early detection of a recurrence. Laboratory detection of recurrence may warrant imaging (PET/CT is significantly more sensitive than CT for detecting early recurrence) to localize the site of disease. Blood test results should decrease following successful treatment of recurrence.

Table 1.

Key active clinical trials for Merkel cell carcinoma

Trial title	NCT#	Drug regimen	Phase	Study population	Estimated enrollment	Location	Description
Neoadjuvant							
MERCURY Chemo-immunotherapy in Patients With Resectable Merkel Cell Carcinoma Prior to Surgery	NCT05594290	1 cycle of preoperative retifanlimab plus cisplatinetoposide	Phase 2	Resectable MCC (stage IIA-III)	36	Multicenter	Window-of-opportunity trial to assess the activity of 1 cycle of preoperative retifanlimab (anti-PD-1) plus platinumetoposide chemo-immunotherapy regimen in patients with resectable MCC (stage IIA-III)
Neoadjuvant PD-1 Blockade in Resectable Merkel Cell Carcinoma	NCT05496036	pembrolizumab 400 mg	Phase 2	Resectable stage I-III MCC	15	Single center (Penn | Medicine)	Study participants undergo a tumor tissue collection biopsy prior to treatment, followed by one dose of pembrolizumab 400 mg, then curative intent resection of all remaining disease 3 weeks after the initial dose of pembrolizumab. Post-operatively, subjects will receive up to 1 year of pembrolizumab 400 mg every 6 weeks
Neoadjuvant Cemiplimab in Stage I-II Merkel Cell Carcinoma: Safety and Biomarker Analysis	NCT04975152	Flat dose of cemiplimab-rwlc 350 mg IV every 3 weeks, up to 9 cycles	Phase 1	Clinical stage I-II MCC (AJCC 8th edition) either newly diagnosed or previously diagnosed with recent disease recurrence. This includes patients with a previous diagnosis of clinical Stage I-II who present with local or regional disease recurrence	30	Single center (Moffitt)	Participants will receive cemiplimab (anti-PD-1) 350 mg IV at least 3 weeks prior to surgical resection. After surgery they will continue to receive 350 mg cemiplimab every 3 weeks for up to 8 additional doses
Neoadjuvant Lenvatinib Plus Pembrolizumab in Merkel Cell Carcinoma	NCT04869137	20 mg of lenvatinib will be taken orally once daily 200 mg of pembrolizumab will be administered through IV infusion every 3 weeks	Phase 2	Stage II, III, or IV	26	Single center (Moffitt)	Participants amenable to complete resection will receive two cycles (6 weeks) of therapy with the combination of lenvatinib (tyrosine kinase inhibitor) plus pembrolizumab and then proceed to planned resection within 2–4 weeks following completion of cycle 2. Following surgical recovery and completion of adjuvant radiation therapy (if indicated), treatment will resume with pembrolizumab monotherapy with intent to complete 17 cycles total of pembrolizumab
Adjuvant							
ADAM Adjuvant Avelumab in Merkel Cell Cancer	NCT03271372	avelumab	Phase 3	Stage III MCC patients	100	Multicenter	Phase III trial of randomly assigned adjuvant avelumab or placebo treatment arms for up to 2 years
STAMP Testing Pembrolizumab Versus Observation in	NCT03712605	pembrolizumab	Phase 3	Stage I-III MCC patients	280	Multicenter	Phase III trial of randomly assigned adjuvant pembrolizumab or observation treatment arms for up to 2 years

Trial title	NCT#	Drug regimen	Phase	Study population	Estimated enrollment	Location	Description
Patients With Merkel Cell Carcinoma After Surgery							
I-MAT Immunotherapy Adjuvant Trial in Patients With Stage I-III Merkel cell carcinoma	NCT04291885	avelumab	Phase 2	Stage I-III MCC patients	132	Multicenter (Australia only)	6 months of avelumab at a dose of 800 mg as a 60-min intravenous (IV) infusion once every 2 weeks (13 doses) or 6 months of placebo as a 60-min intravenous (IV) infusion once every 2 weeks (13 doses)
Hypofractionated Radiation Therapy for Merkel Cell Carcinoma	NCT05100095	Radiation therapy	Phase 2	Stage I-III MCC patients	52	Single center (MD Anderson)	Patients receive radiation therapy in 10 daily fractions (M-F) over 2 weeks
First-line							
Gotham A Phase Ib/II Study of Combination Avelumab With Peptide Receptor Radionuclide Therapy or Conventional Fractionated Radiotherapy in Patients With Metastatic Merkel Cell Carcinoma	NCT04261855	avelumab External Beam Radiation Therapy (EBRT) Lutetium-177 (177Lu)-D0TATATE	Phase Ib/II trial	Patient with metastatic MCC that is treatment naïve (no prior systemic therapy for unresectable or metastatic MCC)	65	Multicenter (Australia)	Prospective, open-labeled, multi-institutional, three-arm, phase Ib/II trial that will evaluate the safety and anti-tumor activity of 177Lu-D0TA-octreotate (LuTate) or external beam radiation therapy (EBRT) in combination with avelumab in patients with metastatic MCC
Evaluating Length of Treatment With PD-1/PD-L1 Inhibitor in Advanced Solid Tumors	NCT04157985	Continue or discontinue PD-1/PD-L1 inhibitors treatment	Phase 3	All patients must have an advanced solid tumor malignancy treated with PD-1/ PD-L1 inhibitor	578	Single center (UPMC Hillman Cancer Center)	Continued standard of care treatment with PD-1/PD-L1-1 checkpoint inhibitor after 12 months of checkpoint inhibitor treatment or discontinued standard of care treatment with PD-1/PD-L1-1 checkpoint inhibitor after 12 months of checkpoint inhibitor treatment
PD-(L)1 refractory							
Kartos Navtemadlin (KRT-232) With or Without Anti-PD-1/Anti-PD-L1 for the Treatment of Patients With Merkel Cell Carcinoma	NCT03787602	KRT-232 Avelumab	A Phase 1b/2,	Patients With p53 Wild-Type MCC recurred or progressed on anti-PD-(L)1 therapy, or are anti-PD-(L)1 naïve	115	Multicenter	A phase Ib/II, open-label study evaluating KRT-232 +/−Avelumab (given in ICI naive patients)
ATTAC Gene-Modified Immune Cells (FH-MCVA2TCR) in Treating Patients With Metastatic or Unresectable Merkel Cell Cancer	NCT03747484	MCPyV-specific HLA-A02-restricted TCR-transduced CD4+and CD8 + T-cells FH-MCVA2TCR avelumab Interferon Gamma-1b	Phase 1/2	Metastatic MCC/ unresectable Merkel cell polyomavirus positive MCC patients not benefiting from an ICI	16	Single center (University of Washington)	phase I/II trial infusing genetically modified T cells, interferon gamma,+/-PD(L)1 inhibitor (depends on irAE history)
iPRRT Phase II Study of Peptide Receptor Radionuclide Therapy in Combination With Immunotherapy for Patients With Merkel Cell Cancer (iPRRT)	NCT05583708	pembrolizumab 400 mg IV Lutetium Lu 177 dotatate	Phase 2	Must have progressed on treatment with an anti-PD-l/Ll mAb administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies	18	Single center (not yet recruiting)	All patients will receive pembrolizumab once every 6 weeks + Luteti um Lul77 dotatate once every 2 months Pembrolizumab cycle = 6 weeks (for up to 2 years) Luteti um Lul77 dotatate Cycle = 2 months (4 doses total)

Trial title	NCT#	Drug regimen	Phase	Study population	Estimated enrollment	Location	Description
Special populations							
ARTACUS A Phase 1B/2 Study of RP1 in Solid Organ Transplant Patients with Advanced Cutaneous Malignancies	NCT04349436	RP1	Phase 1/2	Patients with either previous renal, hepatic, heart, or lung allograft transplantation and experiencing subseguent documented locally advanced or metastatic cutaneous malignancies	65	Multicenter (United States)	Study of RP1 (a novel oncolytic viral therapy) to investigate the objective response rate, safety, and tolerability of RP1 for the treatment of advanced cutaneous malignancies in up to 65 evaluable organ transplant recipients. This will include patients with either previous renal, hepatic, heart, or lung allograft transplantation and experiencing subseguent documented locally advanced or metastatic cutaneous malignancies