Merkel Cell Carcinoma: Therapeutic Update and Emerging Therapies

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare but highly aggressive neuroendocrine skin cancer whose incidence has almost doubled in recent decades. Risk factors for MCC include age > 65 years, immunosuppression, sun exposure and infection by Merkel cell polyomavirus. MCC usually presents as rapidly growing, firm, red to violaceous nodule localized on the sun-exposed skin. Surgery followed by radiation therapy is considered to be the first-line treatment for primary or loco-regional MCC in order to prevent recurrences and lymph node metastasis, while chemotherapy has always been used to treat advanced forms. However, responses to chemotherapy are mostly of short duration, and the associated clinical benefit on overall survival is still unclear. The use of checkpoint inhibitors (CPIs) has shown good results in the treatment of advanced MCC and, consequently, CPIs are considered emerging immunotherapeutic options for these patients, although there are still no standardized treatments for patients with metastatic disease. Here we present a complete overview of the different possibilities for the treatment of MCC according to the stage of the disease, focusing on the emerging immunotherapies used for treating advanced MCC.

Keywords: Avelumab; Chemotherapy; Immunotherapy; Immune checkpoint inhibitor; Merkel, skin cancer; Surgery

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare but highly aggressive neuroendocrine skin cancer associated with frequent recurrences, metastasis and highly mortality rate [1–4]. The incidence of MCC in the USA almost doubled between 2000 and 2013 and is expected to exceed 3000 cases per year by 2025, with similar increases expected in Australia and many European countries [5–8]. This increase may be related to an aging population and improvement in diagnostic recognition. The risk factors include age > 65 years [9], immunosuppression [10–12], sun exposure and infection by Merkel cell polyomavirus (MCPyV) [13]. MCPyV infection has been detected in almost 80% of MCC cases [14–16], whereas the other 20% with no detectable MCPyV levels were triggered by ultraviolet-mediated mutations [17, 18]. MCC
classically presents as a rapidly growing, firm, red to violaceous nodule on sun-exposed skin, including the head–neck region and limbs, of an elderly, fair-skin individual [19–22]. However, up to 15% of patients will present with a tumor-positive lymph node without a visible cutaneous manifestation; these cases probably represent metastatic disease with regression of the primary skin tumor. Histopathological and immunohistochemical examinations (including chromogranin A, and/or synaptophysin and cytokeratin-20) are necessary to confirm the diagnosis [23–26]. A wide local excision followed by radiation therapy (RT) is considered to be the first-line treatment for primary or loco-regional MCC in order to prevent recurrences at the primary site and lymph node metastasis (stage I and II), while cytotoxic chemotherapy with platinum-based regimens, etoposide, anthracyclines and taxanes, in different combinations or alone, has always been used to treat patients with metastatic MCC [26, 27]. However, recent advances in the understanding of the biology of MCC, for example the discovery of MCPyV, have created opportunities for the development of novel therapeutic strategies that may improve treatment efficacy. The use of checkpoint inhibitors (CPIs) has shown good results in the treatment of advanced MCC and, consequently, CPIs are considered to be emerging immunotherapeutic options for these patients [28]. Since MCC, especially in its advanced form, is frequently refractory to adequate systemic treatment, a long-term treatment is often required to control the burden of the disease, prevent flare-ups and achieve better patient quality of life outcomes. This has led to large variations in systemic treatment approaches worldwide; this situation is further exacerbated by the lack of international standardized guidelines [13, 29].

In this review, we analyze the existing literature and present a complete overview of the different possibilities for the treatment of MCC according to the stage of the disease, focusing on the emerging immunotherapies used to treat advanced MCC.

METHODS

We searched the English-language literature on the management of MCC and its treatment in the following databases through to 20 December 2018: PubMed, Embase, The Cochrane Library, Google Scholar, EBSCO and Scopus. The following key words were used: “Merkel cell carcinoma,” “Merkel,” “surgery,” “radiotherapy,” “immunotherapy,” “avelumab,” “ipilimumab,” “targeted therapy,” “advanced Merkel cell carcinoma.” All of the published articles identified (case report, case series, prospective and retrospective studies, clinical trials, reviews, guidelines and consensus) were reviewed to provide a complete overview of and detailed data on new targeted therapies, which represent an exciting perspective for the management of advanced forms of MCC.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Current Treatment Options in MCC

The choice of treatment depends on the tumor characteristics, such as the stage at presentation, regional lymph node involvement, location of the disease, comorbidities and performance status of the patient [29–31]. Current treatment strategies that incorporate surgery and/or radiotherapy achieve high rates of locoregional control, but they are commonly associated with the development of distant metastases. Chemotherapy has demonstrated limited efficacy in the treatment of metastatic disease, but advances in immunotherapeutics are likely to have a major impact on the management and outcomes of MCC. As treatment options for the loco-regional form have already been standardized, there are no therapeutic agents specifically approved for the treatment of the advanced form of MCC, and treatment choice is often based on data available from retrospective series and prospective randomized controlled trials [32]. In the metastatic setting, chemotherapy has limited efficacy, but advances in immunotherapeutics are likely to have a
major impact on the management and outcomes of MCC.

**Locoregional Primary MCC**

**Surgery**
Surgery has typically been the first-line treatment for patients with locoregional primary MCC. However, just how much of the surrounding normal-appearing skin should be excised around the tumor during surgery is still controversial [32, 33]. Complete surgical excision, with the goal of establishing clear margins, is the mainstay to treat local MCC. Although surgical margins have not yet been defined, a wide excision with 1 to 3 cm of clinically free margins is generally recommended, regardless of tumor size [34]. A correlation between margin size and the recurrence risk has not been established, with some studies suggesting that wide margins of 2–3 cm are associated with a reduction of recurrence risk [35–37] and others showing no difference in recurrence risk with margins that are > 1 cm [38]. According to the current National Comprehensive Cancer Network (NCCN) guidelines, for local disease excision should be done with margins of 1–2 cm and down to the fascia or peristeum [26]. The recurrence risk of MCC after a wide excision ranges from 25 to 40% [35, 39, 40]. When tissue sparing is critical, due to the anatomic location of the tumor with complete peripheral and deep margin control, Mohs micrographic surgery (MMS) and modified Mohs surgery are also considered [41–43]. Several retrospective studies have demonstrated Mohs surgery to be effective, although prospective studies comparing MMS to wide local excision have not been performed [44]. Some authors report that MMS is related to an increased risk of developing in-transit metastases. Patients with clinical nodal-positive disease should undergo complete lymph node dissection (CLND) followed by radiotherapy on a case-by-case basis [45]. For clinical node-negative cases, sentinel lymph node biopsy (SLNB) is required [29], concurrent with primary MCC excision, in order to define microscopic lymph node status [46]. If the SLNB is positive, patients should undergo lymph node dissection and/or RT, as MCC is responsive to the latter [47, 48].

**Radiotherapy**
Merkel cell carcinoma is a radiosensitive tumor [49], and RT should be considered either as adjuvant treatment to surgery or as palliative treatment for inoperable cases of MCC. In some studies, adjuvant RT was recommended for patients with loco-regional tumor in order to reduce the recurrence rate, although the impact on the overall survival is still unclear [50–52]. However, the outcomes of radiation monotherapy may be inferior to those of complete surgical resection [49, 52, 53]. There are few published studies reporting the outcomes of RT and its effects on MCC relapse and disease-specific survival. A retrospective study of 57 inoperable patients treated with localized RT reported an overall survival rate at 5 years of 39% [51]; similar results have been reported in a retrospective study involving 43 patients in which an overall survival rate of 37% was reported [52]. The NCCN guidelines recommend doses of 60–66 Gy for curative-intent radiation, with a wide treatment margin (5 cm) around the primary site [48]. Radiation doses to the primary site after surgical resection should range from 50 to 60 Gy depending on the presence or absence of microscopically positive margins [33, 48].

**Localized MCC**
Adjuvant RT to the tumor bed for local control after wide excision may be associated with lower recurrences [54], although the benefits to overall survival remain controversial. An analysis of 185 patients with localized MCC and margin-negative excision found that adjuvant radiation to the surgical bed did not improve the rate of local control [38]. Conversely, other studies have found that adjuvant radiation in early-stage MCC is beneficial and should be administered expeditiously after surgery [55–57]. In 2016, Bhatia et al. conducted a retrospective analysis on 6908 patients with MCC treated with surgery and adjuvant RT. For localized MCC (stage I: 3369 patients, stage II: 1474 patients), surgery plus adjuvant RT was associated with statistically significant better overall survival than with
surgery alone in the multivariable analyses (stage I: hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.64–0.80, \( P < 0.001 \); stage II: HR 0.77, 95% CI 0.66–0.89, \( P < 0.001 \)). In patients with regional nodal metastases (stage III: 2065 patients), neither adjuvant RT nor chemotherapy was associated with statistically significant improved or worsened overall survival [58]. The standard practice is to consider radiation to the primary site alone if the SLNB is negative, but to include the nodal basin if the SLNB is positive [59].

**MCC with Nodal and Metastatic Disease**

Although most studies lack standardized treatment protocols for patients with clinically or pathologically positive nodal disease, standard treatment options include complete lymph node dissection, definitive nodal radiation or a combination of the two [60–63]. Two independent studies comparing these two treatment options found no difference in terms of regional recurrence or overall survival between groups treated with CLND, definitive RT or combination therapy. The NCCN guidelines recommend adjuvant radiation to the draining nodal basin after CLND in the presence of multiple involved nodes or extracapsular extension of the tumor [26]. RT can be used to palliate symptoms in patients with metastatic disease. It contributes to cancer control by directly damaging the DNA of tumor cells and by immunomodulation [64, 65]. A retrospective study evaluating 26 patients with advanced MCC treated with radiation treatment as a single fraction of 8 Gy reported complete response (CR) in 47% of the tumors treated, as well as durable responses in the “in-field” treated lesions [63]. This treatment may improve the patient’s quality of life compared to multiple RT sections. However, another analysis found much higher rates of durable local control with three fractions of 8 Gy [66]. Despite the specific regimen used, short-course radiation represents a valid palliative treatment option for metastatic MCC [65]. Moreover, short-course RT has been shown to be effective in patients with metastatic MCC who do not respond to immune checkpoint inhibitors [66].

**Chemotherapy**

Although cytotoxic chemotherapy has been commonly used to treat patients with advanced MCC, its role remains unclear in the literature; responses are rarely durable, and few studies have shown a survival benefit. The most common regimens recommended in the NCCN guidelines are carboplatin (or cisplatin) and etoposide or a combination of cyclophosphamide, doxorubicin (or epirubicin) and vincristine. MCC is very sensitive to chemotherapy [67–70], and initial response rates range from 53 to 76%; however, this high response rate is not durable, and tumors often recur within 4–15 months. A retrospective study of 6908 patients found that chemotherapy was not associated with an overall survival benefit in patients who presented with either local or nodal MCC [58]. Chemotherapy is also associated with a high risk of toxicity, particularly in patients aged > 65 years. Myelosuppression, sepsis, fatigue, alopecia, nausea and renal failure are the most common adverse events reported [67, 71]. Given the toxicity and lack of durable responses associated with chemotherapy, for each patient, the potential short-term benefit should be compared to the potential risks [45, 72].

**Emerging Therapies**

Genetic and epigenetic alterations lead many cancers to produce antigens that may be recognized by the immune system. Immunotherapy is one of the most recent and expanding treatment modalities for metastatic MCC because (1) MCPyV-positive tumors express viral oncoproteins, and (2) MCPyV-negative tumors have a high mutational burden associated with neoantigen production. Both of these characteristics are used as key therapeutic targets in reactivating immune responses [72, 73]. However, no treatment directly targeting the tumor is available for use in combination with these checkpoint inhibitors (CPIs) to enhance their efficacy. We identified only one study in our literature search that characterized MCC line sensitivity to cellular lysis, with the authors identifying cell surface antigens that they used to carrying out direct targeting of this tumor.
More studies to better define these new therapeutic targets are required.

**Immune Checkpoint Inhibitors** The programmed cell death receptor 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathways contribute to local immune evasion by inhibiting T-cell response. PD-L1 is an immune checkpoint molecule that binds to its main receptor, PD-1, which is expressed by activated T lymphocytes. The complex PD-L1/PD-1 inhibits the signaling pathway involved in T-cell proliferation and cytotoxic activity, thereby preventing the stimulation of immune responses. Therefore, blocking the interaction between PD-L1 and PD-1 is a key therapeutic target in the reactivation of the immune response for the treatment of many tumors, including MCC [75]. PD-L1 is frequently expressed on MCC tumor cells and peritumoral immune cells while circulating MCPyV-specific T cells express PD-1. This characteristic makes these tumors excellent candidates for immunotherapy, and clinical trials evaluating checkpoint inhibitors therapy in metastatic MCC patients are ongoing [76–79].

Avelumab is a fully human PD-L1 inhibitor which blocks human immunoglobulin G1 (IgG1) lambda monoclonal antibody on the tumor cell, inhibiting the interaction between the PD-1 on T lymphocytes with the PD-L1 on the tumor cell, thereby preventing the inactivation of the T lymphocyte and keeping it available for tumor-cell destruction [75, 80]. Avelumab was approved in September 2017 by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a first-line treatment for patients (aged > 12 years) with metastatic MCC. These approvals were based on data from an open-label, single-arm, multicenter clinical trial [81, 82], in which 88 patients with metastatic MCC unresponsive to chemotherapy received at least one dose of avelumab (10 mg/kg body weight intravenously every 2 weeks). Patients were followed up for a median of 10.4 months, at which time 28 of the 88 patients (31.8%; 95% CI 21.9–43.1) had achieved an objective response, including 8 CR and 20 partial responses (PR). Avelumab also demonstrated a good safety profile [83]: no treatment-related grade 4 adverse events or treatment-related deaths were reported. Serious treatment-related adverse events were reported in five patients (6%), namely, enterocolitis, infusion-related reaction, increase in levels of aminotransferases, chondrocalcinosis, synovitis and interstitial nephritis; five grade 3 treatment-related adverse events occurred in four (5%) patients, namely, lymphopenia in two patients, blood creatine phosphokinase increase in one patient, aminotransferase increase in one patient, and blood cholesterol increase in one patient. This positive response was also reported in an human immunodeficiency virus (HIV)-positive patient treated with avelumab [82]. In December 2018, Kratzsch et al. described for the first time the occurrence of immune thrombocytopenia and anemia in a 77-year-old man treated with avelumab (10 mg/kg body weight every 2 weeks) for a metastatic MCC [84].

Pembrolizumab is a humanized IgG4 anti-PD-1 monoclonal antibody. It was the first immune CPI to demonstrate effective tumor regression in patients with metastatic MCC [85, 86]. Nghiem et al. conducted a multicenter phase 2 non-controlled study involving 26 with advanced MCC who had received no previous systemic therapy [73]. All patients received pembrolizumab at a dose of 2 mg/kg body weight every 3 weeks. The objective response rate among the 25 patients with at least one evaluation during treatment was 56% (95% CI 35–76); four patients had a CR and ten had a PR. With a median follow-up of 33 (range 7–53) weeks, relapses occurred in two of the 14 patients who had a response (14%). The response duration ranged from at least 2.2 months to at least 9.7 months. Pembrolizumab was effective in both MCPyV-positive and MCPyV-negative MCCs. It was well-tolerated; grade 3 or 4 adverse events occurred only in 15% of the patients [73]. Based on this result pembrolizumab was added to the 2017 NCCN treatment options for metastatic MCC. In another study, Winkler et al. reported the case of a 80-year-old patient with metastatic MCC who was successfully treated with the reintroduction of pembrolizumab after disease progression during a 4-month period without therapy [87].
Nivolumab is another fully human IgG4 anti-PD-1 antibody with clinical activity in advanced MCC still under investigation [88]. A phase 1/2 trial (CheckMate358) is currently investigating the safety and effectiveness of nivolumab and nivolumab combination therapy in virus-associated tumors, including MCC. Two earlier cases of a good response have been reported. In 2016, Walocko et al. described the case of an 80-year-old man with advanced MCC who achieved a significant and durable response to nivolumab (3 mg/kg body weight intravenously every 2 weeks for 6 cycles) [89, 90]. In 2015, Mantripragada and Birnbaum reported the case of a young patient with advanced MCC who obtained an impressive response to nivolumab [86].

Several immunotherapies that act through mechanisms other than inhibition of PD-1 and PDL-1 are currently under investigation for the treatment of metastatic MCC. Therapeutic combinations that include the CTLA-4 antibody ipilimumab [91] are currently being studied. A phase II randomized trial investigating ipilimumab as adjuvant therapy after excision versus observation is currently underway [92]. In 2017, a case series of five patients with metastatic MCC treated with ipilimumab (3 mg/kg body weight every 3 weeks) reported controversial results for ipilimumab in advanced MCC. Previous to that case series, only one report on a patient who achieved a reduction in cutaneous MCC lesions during combined therapy of ipilimumab and chemotherapy had been described [93]. Autoimmune toxicity, which most commonly affects the skin, gastrointestinal tract, liver and endocrine system represents the most frequent side effects of immunotherapy and is the consequence of T-cell activation against the host tissue. Colitis, myositis, hypothyroidism and autoimmune insulin-dependent diabetes mellitus are the most frequently described immune-related adverse events in patients with MCC treated with immunotherapeutics agents. Therefore, patients with autoimmune disorders, HIV infection and hematologic or solid malignancies are commonly excluded from participating in clinical trials except for clinical case reports and small cohort studies [94, 95]. Furthermore, resistance to this therapy is frequent due to the activation of adaptive resistance, with upregulation of alternative immune checkpoints. An interesting strategy for treating patients advanced MCC not responding to the classic immune CPIs is the use of other immunotherapies, such as intratumoral interferon, interleukin-12 DNA electroporation and Toll-like receptor 4 agonists; these therapies are still under investigation [96–98].

The main trials which have investigated immune CPIs are shown in Table 1.

**Targeted Molecular Therapy** While immunotherapy has demonstrated a high response rate in immunocompetent patients (>50% in chemotherapy-naive patients) and the overall survival is durable, alternatives to immunotherapy are needed for patients with advanced-stage MCC who are immunosuppressed, transplanted patients who are at risk of transplant rejection and patients who do not respond to classic immunotherapy [45, 72]. Several types of targeted therapies have been investigated in MCC cell lines and xenograft models, and ongoing prospective clinical trials are studying these agents [99, 100]. An interesting strategy for advanced MCC not responding to immune CPIs is the use of natural killer cell-based treatment. An ever-increasing body of evidence supports the importance of angiogenesis in the pathogenesis of MCC tumors that express vascular endothelial growth factors (VEGF), such as VEGF-A, VEGF-C, VEGF-R2, platelet-derived growth factor (PDGF)-b and C-kit [13].

Pazopanib and cabozantinib are inhibitors of multiple receptor tyrosine kinases (VEGFR-1, -2 and 3 and C-kit). Pazopanib also inhibits PDGF-α and -β. To date, little data have been reported in the literature on the utility of pazopanib and cabozantinib in MCC [101]. Tarabadkar et al. described a case series in which the VEGFR tyrosine kinase inhibitors (TKIs) pazopanib and cabozantinib were used successfully in five patients with metastatic MCC who had previously been treated with cytotoxic therapy [102]. Prior to this case series, only a single case of metastatic MCC successfully treated with pazopanib had been described [103]. Prospective clinical trials investigating either pazopanib and
Cabozantinib are undergoing [104]. To date, activating tyrosine-kinase mutations have not been detected in MCCs; consequently, there is little evidence that tyrosine kinase inhibition is an effective treatment approach for patients with MCC [105]. Complete remission following treatment with imatinib, a targeted inhibitor of some tyrosine kinase receptors, including the C-kit receptor, was reported in a patient with an inoperable MCC of the eyebrow [106], although a phase II clinical trial evaluating the efficacy of imatinib in advanced MCC was prematurely discontinued because there was no evidence of clinical efficacy [105].

Mutations which activate phosphatidylinositol 3-kinase–mammalian target of rapamycin (PI3K–mTOR) have been found in some MCPyV-negative patients, although this specific type of mutation is very rare [106, 107]. There has only been a single reported case of a patient with advanced MCC carrying a known PI3K mutation who was successfully treated with idelalisib, a PI3K inhibitor, resulting in a rapid and complete remission [108]. Several prospective studies are currently investigating the safety and efficacy of mTOR inhibition in patients with advanced MCC.

MCC is a neuroendocrine cancer that expresses somatostatin receptors (SSTs), in particular SST-2. Therefore, somatostatin analogs are being investigated for both molecular imaging and the treatment of advanced MCC [109]; however, data are currently lacking. Response following treatment with lanreotide, a somatostatin analog has been reported in only one case of MCC [110], and a phase II trial evaluating its efficacy and safety is ongoing [111]. In a prospective study involving 58 patients with neuroendocrine tumors treated with octreotide, another somatostatin analog, a PR rate of only 3% was reported [112].

The cases of advanced MCC successfully treated with new targeted molecular therapies are shown in Table 2.

As, poly-ADP ribose polymerase 1 (PARP1) is overexpressed in advanced MCC, as in small lung cell cancer. Trials on the efficacy of PARP inhibitors are ongoing with the aim to explore other novel therapeutic options for inoperable MCC [113].

| Drug                        | Authors                     | Number of cases | Dosage                                   | Objective response |
|-----------------------------|-----------------------------|-----------------|------------------------------------------|--------------------|
| Avelumab (PD-L1 inhibitor)  | Kaufman et al. [80, 81]     | 88              | 10 mg/kg intravenously every 2 weeks     | 28 (31.8%): 8 CR   |
|                             |                             |                 |                                          | 20 PR              |
| Pembrolizumab (PD-1 inhibitor) | Nghiem et al. [73]       | 26              | 2 mg/kg intravenously every 3 weeks      | 14 patients (56%): 4 CR |
|                             |                             |                 |                                          | 10 PR              |
| Nivolumab (PD-1 inhibitor)  | Topalian et al. [88]       | 25              | 240 mg every 2 weeks                     | 64% objective response |
| Ipilimumab (anti CTLA-4)    | Schadendorf et al. [92]    |                 | 3 mg/kg every 3 weeks                    | –                  |

CTLA-4 Cytotoxic T-lymphocyte–associated antigen 4, CR complete response, PD-1 programmed cell death receptor 1, PD-L1 programmed cell death ligand 1 PR partial response
DISCUSSION

Merkel cell carcinoma is a rare and aggressive skin cancer with a neuroendocrine phenotype. Incidence varies according to geographic region, but is increasing worldwide, with higher incidence rates among older males and subjects with light skin [1, 3]. Infection with MCPyV, ultraviolet radiation exposure and immunosuppression are the main factors associated with the pathogenesis of MCC. Most frequently, MCC presents as local disease, but up to 30% of cases may involve regional lymph node and distant metastases. Surgery is the first-line treatment for localized disease, followed by adjuvant radiation or chemoradiation [9]. In the advanced form of MCC, chemotherapy is considered to be the standard treatment, despite the high rate of adverse events associated with the chemotherapeutic regimens. In addition, the majority of regimens used are associated with toxicity and worsening of the immunosuppression status. The therapeutic landscape for metastatic MCC is evolving rapidly [28, 114], and recent advances in the development of well-tolerated immunotherapy agents [30, 115] have the potential to provide effective treatment options for patients with advanced MCC. Immune checkpoint blockade is an exciting treatment option for patients with metastatic MCCs. Avelumab (anti-PD-L1) and pembrolizumab (anti-PD-1) have shown promising results in clinical trials performed on patients with advanced MCC. In this context, given its therapeutic response and safety profile, avelumab was approved in September 2017 by the US FDA and EMA as a first-line treatment for patients (aged > 12 years) with metastatic MCC [80]. Despite these successes several immune-related adverse events during treatment with immune CPIs have been reported, and approximately 50% of patients with metastatic MCC do not respond or experience disease progression after their initial response to treatment with CPIs, underscoring the need for novel strategies to broaden antitumor immune responses in these patients [94, 95, 116]. A growing body of literature suggests an increased rate of response in patients with metastatic MCC treated with short-course RT combined with immune CPIs [117]. There is also increasing evidence supporting the importance of angiogenesis in the pathogenesis of MCC tumors that express VEGFs, such as VEGF-A, VEGF-C, VEGF-R2, PDGF-b, and C-kit [13]. Several therapeutic agents acting on these factors have been studied, and trials evaluating their efficacy are ongoing. According to the NCCN Clinical Practice guidelines, continuous follow-up for patients with diagnosed MCC is recommended. A complete physical exam, including lymph node evaluation, is required.

| Drug                                      | Authors                | Number of cases | Dosage        | Objective response |
|-------------------------------------------|------------------------|-----------------|---------------|--------------------|
| Pazopanib (anti-VEGFR-1,2,3 and C-kit)    | Tarabadkar et al. [102] | 4               | 800 mg daily  | 1 CR               |
| Cabozantinib (anti-VEGFR-1,2,3 and C-kit) | Tarabadkar et al. [102]| 1               | 60 mg daily   | PR                 |
| Imatinib (tyrosine kinase inhibitor)      | Loader et al. [106]    | 1               | 400 mg daily  | CR                 |
| Idelalisib (PI3K-inhibitor)               | Shiver et al. [108]    | 1               | 150 mg twice daily | CR               |
| Lanreotide (somatostatin analog)          | Fakiha et al. [110]    | 1               | 15 mg i.m. injection every two weeks | CR               |

PI3K Phosphoinositide 3-kinase, VEGFR vascular endothelial growth factor
every 3–6 months for the first 3 years after diagnosis and every 6–12 months thereafter. The follow-up should also include the screening of adverse events related to treatment with immune CPIs. Contrast-enhanced brain magnetic resonance imaging and contrast-enhanced neck/chest/abdomen/pelvis computed tomography are also recommended to identify and quantify regional and distant metastases [118].

CONCLUSIONS

Evidence on the efficacy and safety of immunotherapy and targeted molecular therapy is still limited, and long-term data are lacking [13, 28]. Consequently, physicians usually have to rely on experiences reported in case reports and case series. Hence, in everyday practice clinicians must follow a general approach maximizing the benefit–risk ratio. More prospective, multicenter studies are needed to evaluate further treatment options to develop international guidelines on metastatic MCC treatment.

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REFERENCES

1. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol. 2008;58(3):375–81.

2. Albores-Saavedra J, Battich K, Chable-Montero F, et al. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: A population based study. J Cutan Pathol. 2010;37:20–7.

3. Toker C. Trabecular carcinoma of the skin. Arch Dermatol 1972;105(1):107e10.

4. Houben R, Schrama D, Becker JC. Molecular pathogenesis of Merkel cell carcinoma. Exp Dermatol 2009;18(3):193e8.

5. Fitzgerald TL, Dennis S, Kachare SD, Vohra NA, Wong JH, Zervos EE. Dramatic increase in the incidence and mortality from Merkel cell carcinoma in the United States. Am Surg 2015;81(8):802e6.

6. Youlten DR, Soyer HP, Youl PH, Fritschi L, Baade PD. Incidence and survival for Merkel cell carcinoma in Queensland, Australia, 1993e2010. JAMA Dermatol 2014;150(8): 864e72.

7. Zaar O, Gillstedt M, Lindelöf B, Wennberg-Larkö AM, Paoli J. Merkel cell carcinoma incidence is increasing in Sweden. J Eur Acad Dermatol Venereol. 2016;30(10):1708–13.

8. Hodgson NC. Merkel cell carcinoma: changing incidence trends. J Surg Oncol. 2005;89(1):1–4.

9. Pulitzer M. Merkel cell carcinoma. Surg Pathol Clin. 2017;10(2):399–408.

10. Clarke CA, Robbins HA, Tatalovich Z, et al. Risk of Merkel cell carcinoma after solid organ transplantation. J Natl Cancer Inst. 2015;107:2.
11. Lanoy E, Costagliola D, Engels EA. Skin cancers associated with HIV infection and solid-organ transplantation among elderly adults. Int J Cancer. 2010;126(7):1724–31.

12. Howard RA, Dores GM, Curtis RE, Anderson WF, Travis LB. Merkel cell carcinoma and multiple primary cancers. Cancer Epidemiol Biomark Prev. 2006;15(8):1545–9.

13. Amaral T, Leiter U, Garbe C. Merkel cell carcinoma: Epidemiology, pathogenesis, diagnosis and therapy. Rev Endocr Metab Disord. 2017;18(4):517–32.

14. Gonzalez-Vela MD, Curiel-Olmo S, Derdak, et al. Shared oncogenic pathways implicated in both virus-positive and UV-induced Merkel cell carcinomas. J Invest Dermatol. 2017;137(1):197–206.

15. Liu W, MacDonald M, You J. Merkel cell polyomavirus infection and Merkel cell carcinoma. Curr Opin Virol. 2016;20:20–7.

16. Goh G, Walradt T, Markarov V, et al. Mutational landscape of MCPyV-positive and MCPyV-negative Merkel cell carcinomas with implications for immuno-therapy. Oncotarget. 2016;7(3):3403–15.

17. Harms PW, Vats P, Verhaegen ME, et al. The distinctive mutational spectra of polyomavirus-negative Merkel cell carcinoma. Cancer Res. 2015;75(18):3720–7.

18. Becker JC, Stang A, DeCaprio JA, et al. Merkel cell carcinoma. Nat Rev Dis Primers. 2017;3:17077. https://doi.org/10.1038/nrdp.2017.77.

19. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: The AEIOU features. J Am Acad Dermatol. 2008;58(3):375–81.

20. Smith VA, Camp ER, Lentsch EJ. Merkel cell carcinoma: identification of prognostic factors unique to tumors located in the head and neck based on analysis of SEER data. Laryngoscope. 2012;122(6):1283–90.

21. Hussain SK, Sundquist J, Hemminki K. Incidence trends of squamous cell and rare skin cancers in the Swedish national cancer registry point to calendar year and age-dependent increases. J Investig Dermatol. 2010;130(5):1323–8.

22. Nguyen AH, Tahseen AI, Vaudreuil AM, Caponetti GC, Huertier CJ. Clinical features and treatment of vulvar Merkel cell carcinoma: a systematic review. Gynecol Oncol Res Pract. 2017;4:2.

23. Wong HH, Wang J. Merkel cell carcinoma. Arch Pathol Lab Med. 2010;134(11):1711–6.

24. Bobos M, Hytiroglou P, Kostopoulos I, Karkavelas G, Papadimitriou CS. Immunohistochemical distinction between merkel cell carcinoma and small cell carcinoma of the lung. Am J Dermatopathol. 2006;28(2):99–104.

25. Gu J, Polak JM, Van Noorden S, Pearse AG, Marangoz PJ, Azzopardi JG. Immunostaining of neuron-specific enolase as a diagnostic tool for Merkel cell tumors. Cancer. 1983;52(6):1039–43.

26. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Merkel Cell Carcinoma. 2016.

27. Schadendorf D, Lebbe C, zur Hausen A, Avril M-F, Hariharan S, Bharml M, Becker JC. Merkel cell carcinoma: epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer 71 (2017) 53–69.

28. Pardon DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–64. https://doi.org/10.1038/nrc3239.

29. Harms PW. Update on Merkel Cell Carcinoma. Clin Lab Med. 2017;37(3):485–501.

30. Harms PW, Harms KL, Moore PS, et al. International Workshop on Merkel Cell Carcinoma Research (IWMCC) Working Group. The biology and treatment of Merkel cell carcinoma: current understanding and research priorities. Nat Rev Clin Oncol. 2018;15(12):763–76. https://doi.org/10.1038/s41571-018-0103-2.

31. Banks PD, Sandhu S, Gyorki DE, Johnston ML, Rischin D. Recent Insights and Advances in the Management of Merkel Cell Carcinoma. J Oncol Pract. 2016;12(7):637–46.

32. Frohm ML, Griffith HA, Harms KL, et al. Recurrence and survival in patients with Merkel cell carcinoma undergoing surgery without adjuvant radiation therapy to the primary site. JAMA Dermatol. 2016;152:1001–7.

33. Harms KL, Healy MA, Nghiem P, et al. Analysis of prognostic factors from 9387 Merkel cell carcinoma cases forms the basis for the new 8th Edition AJCC Staging System. Ann Surg Oncol. 2016;23(11):3564–71.

34. Chan IS, Bhatia S, Kaufman HL, Lipson EJ. Immunotherapy for Merkel cell carcinoma: a turning point in patient care. J Immunother Cancer. 2018;6(1):23.

35. Gollard R, Weber R, Kosty MP, Greenway HT, Masullo V, Humberson C. Merkel cell carcinoma: review of 22 cases with surgical, pathologic, and therapeutic considerations. Cancer. 2000;88:1842–51.
36. Yiengpruksawan A, Coit DG, Thaler HT, et al. Merkel cell carcinoma: prognosis and management. Arch Surg. 1991;126:1514.

37. O’Connor WJ, Brodland DG. Merkel cell carcinoma. Dermatol Surg. 1996;22:262–7.

38. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol. 2005;23:2300–9.

39. Ratner D, Nelson BR, Brown MD, Johnson TM. Merkel cell carcinoma. J Am Acad Dermatol. 1993;29(2 pt 1):143–56.

40. Haag ML, Glass LF, Fenske NA. Merkel cell carcinoma. Diagnosis and treatment. Dermatol Surg. 1995;21:669–83.

41. O’Connor WJ, Roenigk RK, Brodland DG. Merkel cell carcinoma. Comparison of Mohs micrographic surgery and wide excision in eighty-six patients. Dermatol Surg. 1997;23:929-933.

42. Snow SN, Larson PO, Hardy S, et al. Merkel cell carcinoma of the skin and mucosa: report of 12 cutaneous cases with 2 cases arising from the nasal mucosa. Dermatol Surg. 2001;27:165–70.

43. Boyer JD, Zitelli JA, Brodland DG, D’Angelo G. Local control of primary Merkel cell carcinoma: review of 45 cases treated with Mohs micrographic surgery with and without adjuvant radiation. J Am Acad Dermatol. 2002;47:885–92.

44. Kline L, Coldiron B. Mohs micrographic surgery for the treatment of Merkel cell carcinoma. Dermatol Surg. 2016;42:945–51.

45. Cassler NM, Merrill D, Bichakjian CK, Brownell I. Merkel cell carcinoma therapeutic update. Curr Treat Opt Oncol. 2016;17:36.

46. Su LD, Lowe L, Bradford CR, et al. Immunostaining for cytokeratin 20 improves detection of micrometastatic Merkel cell carcinoma in sentinel lymph nodes. J Am Acad Dermatol. 2002;46:661–6.

47. Medina-Franco H, Urist MM, Fiveash J, Heslin MJ, Bland KL, Beenken SW. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. Ann Surg Oncol. 2001;8:204–8.

48. Bichakjian CK, Olencki T, Aasi SZ, et al. Merkel cell carcinoma, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16:742–74.

49. Pape E, Rezvov N, Penel N, et al. Radiotherapy alone for Merkel cell carcinoma: a comparative and retrospective study of 25 patients. J Am Acad Dermatol. 2011;65:983–90.

50. Leonard JH, Ramsay JR, Kearsley JH, Birrell GW. Radiation sensitivity of Merkel cell carcinoma cell lines. Int J Radiat Oncol Biol Phys. 1995;32:1401–7.

51. Harrington C, Kwan W. Outcomes of Merkel cell carcinoma treated with radiotherapy without radical surgical excision. Ann Surg Oncol. 2014;21:3401–5.

52. Veness M, Foote M, Gebski V, Poulsen M. The role of radiotherapy alone in patients with Merkel cell carcinoma: reporting the Australian experience of 43 patients. Int J Radiat Oncol. 2010;78:703–9.

53. Fang LC, Lemos B, Douglas J, Iyer J, Nghiem P. Radiation monotherapy as regional treatment for lymph node-positive Merkel cell carcinoma. Cancer. 2010;116:1783–90.

54. Takagishi SR, Marx TE, Lewis C, et al. Postoperative radiation therapy is associated with a reduced risk of local recurrence among low risk Merkel cell carcinomas of the head and neck. Adv Radiat Oncol. 2016;1:244–51.

55. Garneski KM, Nghiem P. Merkel cell carcinoma adjuvant therapy: current data support radiation but not chemotherapy. J Am Acad Dermatol. 2007;57:166–9.

56. Rush Z, Fields RC, Lee N, Brownell I. Radiation therapy in the management of Merkel cell carcinoma: current perspectives. Expert Rev Dermatol. 2011;6(4):395–404.

57. Lok B, Khan S, Mutter R, et al. Selective radiotherapy for the treatment of head and neck Merkel cell carcinoma. Cancer. 2012;118(16):3937–44.

58. Bhatia S, Storer BE, Iyer JG, et al. Adjuvant radiation therapy and chemotherapy in Merkel cell carcinoma: survival analyses of 6908 cases from the National Cancer Data Base. J Natl Cancer Inst. 2016;108:djw042

59. Jouary T, Leyral C, Dreno B, et al. Adjuvant prophylactic regional radiotherapy versus observation in stage I Merkel cell carcinoma: a multicentric prospective randomized study. Ann Oncol. 2012;23:1074–80.

60. Fields RC, Busam KJ, Chou JF, et al. Recurrence after complete resection and selective use of adjuvant therapy for stage I through III Merkel cell carcinoma: recurrence in Merkel cell carcinoma. Cancer. 2012;118:3311–20.

61. Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD81 T
cells: changing strategies for cancer treatment. Blood. 2009;114:589–95.

62. Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015;520:373–7.

63. Iyer JG, Parvathaneni U, Gooley T, et al. Single-fraction radiation therapy in patients with metastatic Merkel cell carcinoma. Cancer Med. 2015;4:1161–70.

64. Chen MM, Roman SA, Sosa JA, Judson BL. The role of adjuvant therapy in the management of head and neck Merkel cell carcinoma. Cancer Med. 2015;4:1161–70.

65. Poulsen M. Merkel cell carcinoma of skin: diagnosis and management strategies. Drugs Aging 2005;22(3):219e29.

66. Cimbak N, Barker CA. Short-course radiation therapy for Merkel cell carcinoma: relative effectiveness in a “radiosen- sitive” tumor. Int J Radiat Oncol. 2016;96:S160.

67. Tai PTH, Yu E, Winquist E, et al. Chemotherapy in neuro- endocrine/Merkel cell carcinoma of the sin: case series and review of 204 cases. J Clin Oncol. 2000;18:2493–9.

68. Voog E, Biron P, Martin J-P, Blay J-Y. Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. Cancer. 1999;85:2589–95.

69. Iyer JG, Blom A, Doumani R, et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma. Cancer Med. 2016;5:2294–301.

70. Crown J, Lipzstein R, Cohen S, et al. Chemotherapy of metastatic Merkel cell cancer. Cancer Invest. 1991;9:129–32.

71. Desch L, Kunstfeld R. Merkel cell carcinoma: chemotherapy and emerging new therapeutic options. J Skin Cancer. 2013;2013:327150. https://doi.org/10.1155/2013/327150.

72. Tello TL, Coggshall K, Yom SS, Yu SS. Merkel cell carcinoma: an update and review: current and future therapy. Am Acad Dermatol. 2018;78(3):445-54.

73. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. N Engl J Med. 2016;374:2542–52.

74. Ollier J, Kervarec T, Samimi M, et al. Merkel cell carcinoma and cellular cytotoxicity: sensitivity to cellular lysis and screening for potential target antigens suitable for antibody-dependent cellular cytotoxicity. Cancer Immunol Immunother. 2018;67(8):1209–19.

75. Palla AR, Doll D. Immunotherapy in Merkel cell carcinoma: role of Avelumab. Immunotargets Ther. 2018;7:15–19.

76. Paulson KG, Tegeder A, Willmes C, et al. Down-regulation of MHC-I expression is prevalent but reversible in Merkel cell carcinoma. Cancer Immunol Res. 2014;2:1071–9.

77. Topalian SL, Weiner GJ, Pardoll DM. Cancer immunotherapy comes of age. J Clin Oncol. 2011;29:4828–36.

78. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti PD-1 antibody in cancer. N Engl J Med. 2012;366:2443–54.

79. Barkdull S, Brownell L.PD-L1 blockade with avelu- mab: A new paradigm for treating Merkel cell carci- noma. Cancer Biol Ther. 2017;18(12):937–939.

80. Kaufman HL, Russell J, Hamid O, et al. Refractory Avelumab in patients with chemotherapy metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016;17(10):1374–85.

81. Kaufman HL, Russell JS, Hamid O, et al. CT079: Durable responses to avelumab (anti-PD-L1) in patients with Merkel cell carcinoma progressed after chemotherapy: 1-year efficacy update. Cancer Res. 2017; 77(13 Suppl):CT079–CT079.

82. Al Homsi MU, Mostafa M, Fahim K. Favorable response to treatment with avelumab in an HIV- positive patient with advanced Merkel cell carcino- noma previously refractory to chemotherapy. Case Rep Oncol. 2018 Jul 13;11(2):467–75.

83. Baker M, Cordes L, Brownell I. Avelumab: a new standard metastatic for treating Merkel cell carci- noma. Expert Rev Anticancer Ther. 2018;18(4):319–326.

84. Kratsch D, Simon JC, Pönttösch I, Ziemer M. Lethal thrombocytopenia in a patient treated with avelumab for metastatic Merkel cell carcinoma. J Dtsch Dermatol Ges. 2018.

85. Buder-Bakhaya K, Hassel JC. Biomarkers for clinical benefit of immune checkpoint inhibitor treat- ment—a review from the Melanoma perspective and beyond. Front Immunol. 2018;9:1474.

86. Mantripragada, K. & Birnbaum, A. Response to anti- PD-1 therapy in metastatic Merkel cell carcinoma
metastatic to the heart and pancreas. Cureus. 2015;7:e403.

87. Winkler JK, Bender C, Kratochwil C, et al. PD-1 blockade: a therapeutic option for treatment of metastatic Merkel cell carcinoma. Br J Dermatol. 2017;176(1):216–9.

88. Topalian SL, Bhatia S, Hollebecque A, et al. Non-comparative, open-label, multiple cohort, phase 1/2 study to evaluate nivolumab (NIVO) in patients with virus-associated tumors (CheckMate 358): efficacy and safety in Merkel cell carcinoma (MCC) [abstract]. Cancer Res. 2017;77(Suppl 13):CT074.

89. Walocko FM, Scheier BY, Harms PW, Fecher LA, Lao CD. Metastatic Merkel cell carcinoma response to nivolumab. Immunother Cancer. 2016;4:79. (eCollection 2016).

90. Walocko FM, Scheier BY, Harms PW, Fecher LA, Lao CD. Erratum to: Metastatic Merkel cell carcinoma response to nivolumab. Immunother Cancer. 2017;5:27.

91. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015;33(17):1974e82.

92. Schadendorf D. Adjuvant therapy of completely resected Merkel cell carcinoma with 3 mg/kg BW ipilimumab (Nervy!) versus observation. 2017. https://www.druglib.com/trial/61/NCT02196961. html. Accessed 14 Dec 2017.

93. Winkler JK, Dimitrakopoulou-Strauss A, Sachpekidis C, Enk A, Hassel JC. Ipilimumab has efficacy in metastatic Merkel cell carcinoma: a case series of five patients. J Eur Acad Dermatol Venereol. 2017;31(9):e389–e391.

94. Johnson DB, Sullivan RJ, Ott PA, et al. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol. 2016;2(2):234–40.

95. Kanz BA, Pollack MH, Johnpule R, et al. Safety and efficacy of anti-PD-1 in patients with baseline cardiac, renal or hepatic dysfunction. J Immunother Cancer. 2016;4:60.

96. Chapuis AG, Afanasiev OK, Iyer JG, et al. Regression of metastatic Merkel cell carcinoma following transfer of polyomavirus-specific T cells and therapies capable of reinducing HLA class-I. Cancer Immunol Res. 2014;2:27–36.

97. Wahl RU, Braunschweig T, Ghassemi A, Rubben A. Immuno-therapy with imiquimod and interferon alfa for metastasized Merkel cell carcinoma. Curr Oncol. 2016;23:150.

98. Matzner P, Sorski L, Shaashua L, et al. Perioperative treatment with the new synthetic TLR-4 agonist GLA-SE reduces cancer metastasis without adverse effects: perioperative treatment with the new synthetic TLR-4 agonist GLA-SE. Int J Cancer. 2016;138:1754–64.

99. Dresang LR, Guastaferro A, Arora R, Normolle D, Chang Y, Moore PS. Response of Merkel cell polyomavirus-positive merkel cell carcinoma xenografts to a survivin inhibitor. PLoS One. 2013;8:e80543.

100. Verhaegen ME, Mangelberger D, Weick JW, et al. Merkel cell carcinoma dependence on Bcl-2 family members for survival. J Invest Dermatol. 2014;134:2241–50.

101. Davids MS, Charlton A, Ng SS, et al. Response to a novel multitargeted tyrosine kinase inhibitor pazopanib in metastatic Merkel cell carcinoma. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27(26):e97–100.

102. Tarabadkar ES, Thomas H, Blom A, et al. Clinical benefit from Tyrosine kinase inhibitors in metastatic Merkel cell carcinoma: a case series of 5 patients. Am J Case Rep. 2018;19:505–11.

103. Nathan PDGP, Wheatley K, Bowden SJ, et al. UKMCC-01: aphase II study of pazopanib (PAZ) in metastatic Merkel cell carcinoma. ASCO Meet Abstr. 2016;34(Suppl 15):9542.

104. Samlowski WE, Moon J, Tuthill RJ, et al. A phase II trial of imatinib mesylate in merkel cell carcinoma (neuroendocrine carcinoma of the skin): A southwest oncology group study (S0331). Am J Clin Oncol. 2010;33(5):495–9.

105. Nardi V, Song Y, Santamaria-Barria JA, et al. Activation of PI3K signaling in Merkel cell carcinoma. Clin Cancer Res. 2012;18:1227–366.

106. Loader DE, Feldmann R, Baumgartner M, et al. Clinical remission of Merkel cell carcinoma after treatment with imatinib. J Am Acad Dermatol. 2013;69(4):e181–3.

107. Davids M, Charlton A, Ng S-S, et al. Response to a novel multitargeted tyrosine kinase inhibitor pazopanib in metastatic Merkel cell carcinoma. J Clin Oncol. 2009;27:e97–100.

108. Shiver MB, Mahmoud F, Gao L. Response to idelalisib in a patient with stage IV Merkel-cell carcinoma. N Engl J Med. 2015;373:1580–2.

109. Buder K, Lapa C, Kreissl MC, et al. Somatostatin receptor expression in Merkel cell carcinoma as target for molecular imaging. BMC Cancer. 2014;14:268.
110. Fakiha M, Letertre P, Vuillez JP, Lebeau J. Remission of Merkel cell tumor after somatostatin analog treatment. Cancer Res Ther. 2010;6(3):382-4.

111. Treatment of unresectable and/or metastatic Merkel cell carcinoma by somatostatine analogues. National Institutes of Health. 2018. https://clinicaltrials.gov/ct2/show/NCT02351128 NCT02351128. Accessed Jan 2016.

112. di Bartolomeo M, Bajetta E, Buzzoni R, et al. Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors. A study by the Italian Trials in Medical Oncology Group. Cancer 1996;77(2):402e8.

113. Ferrarotto R, Cardnell R, Su S, et al. Poly ADP-ribose polymerase-1 as a potential therapeutic target in Merkel cell carcinoma. Head Neck. 2018;40(8):1676–84.

114. Tétu P, Baroudjian B, Madelaine I, Delyon J, Lebbe C.[Update in treatment for Merkel Cell Carcinoma and clinical practice guide]. Cancer. 2018. (pii: S0007-4551(18)30365-5).

115. Robert C. What’s new in oncodermatology. Ann Dermatol Venereol. 2018;145 Suppl 7:VIIS40–VIIS46.

116. Colunga A, Pulliam T, Nghiem. Merkel cell carcinoma in the age of immunotherapy: facts and hopes. Clin Cancer Res. 2018;24(9):2035-2043.

117. Xu MJ, Wu S, Daud AI, Yu SS, Yom SS. In-field and abscopal response after short-course radiation therapy in patients with metastatic Merkel cell carcinoma progressing on PD-1 checkpoint blockade: a case series. J Immunother Cancer. 2018;6(1):43.

118. Gallo M, Guarnotta V, De Cicco F, et al. Immune checkpoint blockade for Merkel cell carcinoma: actual findings and unanswered questions. J Cancer Res Clin Oncol. 2019. doi: 10.1007/s00432-019-02839-w.