

Merkel cell carcinoma masquerading as cellulitis: a case report and review of the literature

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ABSTRACT

Merkel cell carcinoma (MCC) is an uncommon malignancy of the skin arising from cells located in the deeper layers of the epidermis called Merkel cells. This malignancy rarely presents as a metastatic disease, and the field is therefore deficient in regards to management. We report the case of a 49-year-old woman who presented with a presumptive diagnosis of osteomyelitis of the left fifth digit that was resistant to treatment with antibiotics; she underwent debridement of the digit that revealed MCC and was later to have metastatic disease to her lungs, liver, and musculoskeletal system. The management of MCC, although simple in the early stage of the disease, can become challenging when it is more advanced. Multiple new modalities for its treatment have emerged over the last few years, and more recently, clinical trials are being conducted for the use of immunotherapy agents in the treatment of this malignancy.

Key Words Merkel cell carcinoma, Merkel cell polyoma virus, skin neoplasm, metastatic

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CASE DESCRIPTION

Clinical History

A 49-year-old Caucasian woman initially presented with a presumptive diagnosis of cellulitis failing outpatient oral antibiotic treatment. The patient had presented with erythema, tenderness, and swelling of the left fifth digit and was given a course of cephalexin. On presentation, the patient had progressively worsening swelling and erythema and was therefore admitted for intravenous antibiotics. Review of systems was significant for 60-pound weight loss over the last year but was otherwise negative. Prior medical history included unprovoked deep vein thrombosis and pulmonary embolism treated with warfarin, iron deficiency anemia, chronic obstructive pulmonary disease, hyperthyroidism, and a history of intravenous drug abuse. The patient was a current smoker. Family history was non-contributory. Physical exam was significant for erythema, swelling, and fluctuation of the left fifth digit. The patient also appeared cachectic. Laboratory data comprised of a blood count and chemistry were normal, with negative bacterial cultures. An X-ray of the hand (Figure 1) demonstrated advanced osteomyelitis of the fifth proximal phalanx with complete bony destruction. Due to the extensive

nature of the osteomyelitis and destruction, it was decided that the patient would undergo amputation of the affected digit. The patient had no complications from the procedure and was subsequently discharged with a peripherally inserted central catheter (PICC) to complete the course of intravenous antibiotics.

Biopsy

The pathology from the left fifth digit (shown in Figures 2 and 3) demonstrated features consistent with high-grade neuroendocrine carcinoma favouring Merkel cell neoplasm involving the soft tissue, bone fragments and marrow space, with margins positive for involvement with Merkel cell. Immunohistochemistry as shown in Table I. The programmed death (PD)-1 Ligand (PD-L1) expression status was not examined in the pathology specimen.

Due to the diagnosis of Merkel cell carcinoma (MCC) with positive margins the patient was to have surgical exploration and further amputation of the left fifth digit. However, during the intervening period the patient developed left knee pain and swelling as well as a mass on her left lower back. The patient had an outpatient *magnetic resonance imaging* (MRI) of the left knee which demonstrated findings consistent with bony destruction. Due to



FIGURE 1 X-ray image of the left hand showing an area of bone erosion of the proximal phalanx of the fifth digit.

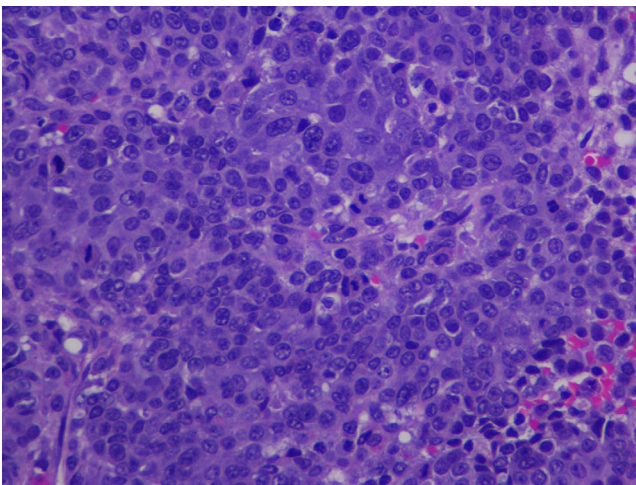


FIGURE 2 Debrided tissue of left fifth digit. Nest of hyperchromatic basophilic cells demonstrating anisonucleosis with clumped chromatin and vesicular nuclei. A high mitotic rate, with at least 4 mitotic figures within this 1 high powered field, is indicative of the malignant nature of this tumour. (400× magnification)

these suspicious findings it was determined that the patient should undergo left knee and left lower back mass biopsy. The patient had a computed tomography (CT) scan of the chest, abdomen, and pelvis for staging which demonstrated a destructive right posterior iliac bone lesion extending to the sacroiliac joint involving the right iliopsoas muscle as well as multiple enlarged bilateral paraesophageal lymph nodes with a thickened esophageal wall and multiple left

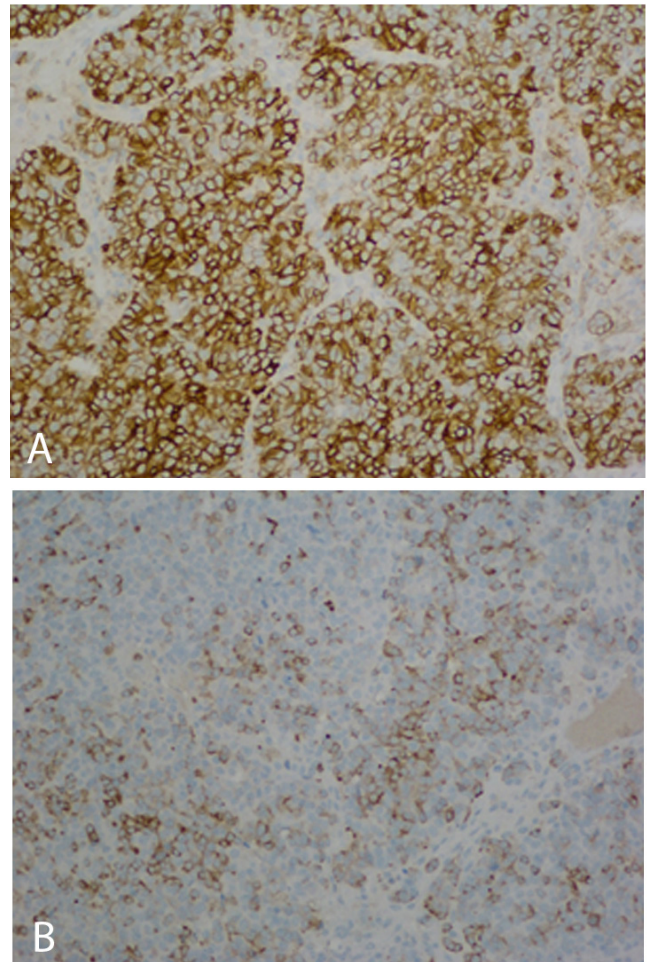


FIGURE 3 Positive immunohistochemistry markers CD56 (A) and Synaptophysin (B) consistent with neuroendocrine differentiation. (100× magnification)

supraclavicular lymph nodes with a solid right axillary node. Biopsies of the left knee and left lower back mass were consistent with MCC.

Diagnosis

Metastatic Merkel cell carcinoma

Clinical Follow-Up

With the diagnosis of metastatic MCC, the patient was treated with chemotherapy with carboplatin and etoposide. The patient's first cycle was complicated by pancytopenia and *multi-drug resistant (MDR) E. coli* urinary tract infection. She completed a second cycle of carboplatin and etoposide followed by 10 days of granulocyte-stimulating factor filgrastim (Neupogen: Amgen Inc., Thousand Oaks, CA, USA). The second cycle was well tolerated. However, the amputation site at the left fifth digit demonstrated local tumour growth and the patient received five treatments of radiation to the area. The patient was discharged home to continue outpatient chemotherapy. Later follow-up showed progression of the patient's tumour and a decision was made to start nivolumab.

After the first dose of nivolumab, the patient developed a pathologic femoral fracture (Figure 4). She was transferred to a centre specializing in orthopedic oncology. She was offered amputation of the lower extremity, which she refused. It was also noted at that time that the patient had further tumour growth at the site of the left fifth digit amputation. Further surgical excision of that site as well as amputation of the fourth left digit were done. Due to obvious further tumour progression the decision was made for the patient to go into hospice care.

DISCUSSION AND REVIEW OF THE LITERATURE

Merkel cell carcinoma is an aggressive neuroendocrine cutaneous malignancy mainly involving the head and neck region of elderly males with light skin types¹. These tumours are believed to arise from the neuroendocrine Merkel cells of the skin based on their phenotypic similarities. However the cells of origin are still unknown². Merkel

cells are mostly located in the basal layer of the epidermis and are responsible for the sensation of light touch. They are present in high numbers on the lip, hard palate, palms, finger pads, proximal nail folds, and dorsa of the feet³. Recent studies have also shown involvement of polyomavirus and BCL-2 in the oncogenesis of MCC⁴.

Epidemiology

Merkel cell carcinoma is a rare but very aggressive tumour. The incidence of MCC is greater in men than in women, with the majority of patients being Caucasian aged 60 to 85. Though MCC accounts for less than 1% of cutaneous malignancies, the incidence is rising³. Analysis of 1,124 identified cases of MCC in the Surveillance, Epidemiology, and End Results (SEER) database demonstrated an increased incidence over a 15-year period (from 0.15 cases per 100,000 in 1986 to 0.44 case per 100,000 in 2001)⁵. In the United States, the estimated annual incidence of MCC is 0.23 per 100,000 in Caucasian individuals. Head and neck are the most common sites of occurrence (50%), followed by the lower limbs (30%), the upper limbs (15%), and the trunk (5%)⁶.

Risk Factors

Risk factors for MCC include fair skin, being elderly, UV exposure, and immunosuppression. An analysis of 3,870 cases of MCC recorded from the SEER database showed 94.9% of patients were Caucasian, with rare occurrence in the African American population⁷. Increased prevalence of MCC in the Caucasian population has been attributed to chronic sun exposure and UV-induced skin damage. Merkel cell carcinoma is more common in geographic areas subject to high sun^{8,9}. A cohort study conducted to analyze the association of MCC with UV radiation displayed a higher mutation rate leading to DNA damage in sun-exposed areas especially of the head and neck¹⁰. A subsequent analysis demonstrated a greater prevalence in males over the age of 65¹¹.

The risk of MCC is greatly increased among the immunosuppressed population, especially after solid organ transplant⁶. Data from the US Scientific Registry of Transplant Recipients revealed a 23.8-fold increase in the risk of MCC in those patients than in general population⁶.

Presentation

Merkel cell carcinoma generally presents as a cutaneous disease, but local recurrence, regional lymph node metastases, and systemic disease are common¹². It usually manifests as a solitary dome-shaped nodule or firm plaque, typically red, violaceous, or purple, with most lesions occurring in the head or neck³.

Merkel cell carcinoma is usually less than 2 cm in diameter, and often misdiagnosed as lipoma, cyst, or other benign lesions on presentation. However, the tumour rapidly grows within three months and has a marked propensity for regional metastasis¹³.

Histologically, it is predominantly a dermal-based lesion, composed of monomorphic small round cells with scant cytoplasm¹⁴. The malignant cells express both epithelial and neuroendocrine markers¹⁴. Among various immunohistochemical markers, neuron-specific enolase and CD56 have shown the highest frequency of positivity¹⁵.

TABLE I Immunohistochemical markers of the tumour

Pan-cytokeratin	Positive
CK 20 (cytokeratin)	Positive
CAM 5.2	Positive
EMA	Positive
BER-EP4	Positive
CD 56	Positive
Synaptophysin	Positive
Neuron-specific enolase	Positive

CK = cytokeratin; EMA = epithelial membrane antigen; CAM = cell adhesion molecule.



FIGURE 4 X-ray image of the left knee showing a lytic lesion of the medial epicondyle region with an overlying fracture.

Recent studies have also shown that MCCs are CK20-positive, which helps in distinguishing it from other small cell carcinomas¹⁶. Expression of p63 has been shown to be associated with poor survival and can be useful as a prognostic tool¹⁷.

Pathophysiology

The Merkel cell polyomavirus (MCV) has been found to be linked to the development of MCC, most commonly in the northern half of the globe. Merkel cell polyomavirus is a non-enveloped double-stranded DNA virus that is found in the skin flora of up to 80% of the normal adult population. The virus's genetic material contains coding genes for the large and small T antigens (LT and sT). These two genes are responsible for its oncogenic potential. The LT mainly exhibits its function by binding and suppressing the activity of the anti-neoplastic retinoblastoma protein (RB1) and by suppressing the expression of TLR9, a receptor implicated in the immune response to viral and bacterial dsDNA rendering infected cells protected for the host's immune system¹.

On the other hand, the sT antigen exhibits more prominent oncogenic activity by affecting the function of many signalling pathways, including the PI3K/AKT/mTOR pathway and the SKP1/CULLIN1/F-box (SCF) protein ubiquitin ligase complex that eventually leads to the upregulation of cellular proto-oncogenes such as cMYC and Cyclin E¹⁸.

Conversely, epidemiologic studies have demonstrated that, in some Australian populations, MCV was present in less than one fourth of cases of MCC, despite the higher prevalence of this malignancy. It has been speculated that the mechanism of oncogenesis in this situation is DNA damage caused by exposure to UV radiation. Sequencing of the TP53 gene in this context revealed C to T transition mutations that are commonly found in other skin cancers¹.

Additionally, mutations in tyrosine kinase signalling pathways, namely PDGFRA and KIT were found to be expressed in more than 60% of MCC tumours in multiple studies¹⁹. Although there is no evidence of a direct role for these mutations in the oncogenesis of MCC, it is believed that they may play a role in tumour cell proliferation and may have prognostic significance.

Diagnosis and Histology

Merkel cell carcinoma is typically diagnosed by histologic and immunochemical studies done on a tissue sample. Three histologic subtypes of MCC have been described; they differ according to cellular and architectural characteristics. The most common is the intermediate variant, which shows diffuse sheets of basophilic cells with powdery chromatin in the nucleus containing a small nucleolus. The second type is the small-cell variant, which consists of solid sheets or clusters of small round cells that have a scant cytoplasm and oval dense nuclei containing large nucleoli. The third variant is the trabecular, which consists of a ribbon-like or trabecular arrangement of round to polygonal cells that have an abundant cytoplasm with central nuclei and inconspicuous nucleoli¹⁴.

Merkel cell carcinoma cells have a multitude of immunochemical characteristics owing to their neuroendocrine and epithelial features. These immunohistochemical markers are summarized in Table II. It is worth noting that TTF-1 is

typically negative in MCC^{12,20,21}. The PD-L1 marker was found to be expressed in 42% to 69% of cases of MCC. However its clinical significance, in terms of prognostic value and prediction of response to therapy, is yet to be uncovered¹⁵⁻¹⁷.

Staging of a newly diagnosed MCC is done by imaging and sentinel lymph node biopsy (SLNB). F-fluorodeoxyglucose-positron emission tomography (FDG-PET) CT scanning may be the preferred modality of imaging when available, alongside a brain MRI with contrast to detect lymphatic and distant metastatic disease, and can also aid in differentiating MCC from small-cell lung cancer that is metastatic to the skin (esp. if CK20 negative). The National Comprehensive Cancer Network (NCCN) also recommends SLNB for nodal staging of MCC¹⁰. Staging of MCC is shown in Table III.

TABLE II Immunohistochemical markers found in Merkel cell carcinoma

Marker	Type
Cytokeratin (CK) 7	
CK 20	
BER-EP4	Epithelial
CD 200	
Pancytokeratin	
Chromogranin	
Synaptophysin	Neuroendocrine
Neuron-specific enolase (NSE)	
Neurofilaments	
CD 56	
CD 117	

TABLE III TNM staging of MCC

This	Carcinoma <i>in situ</i>		
T1	Tumour ≤2 cm in greatest dimension		
T2	Tumour >2 cm but not >5 cm in greatest dimension		
T3	Tumour >5 cm in greatest dimension		
T4	Tumour invades deep extra-dermal structures		
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph nodes		
N1	Regional lymph node metastasis		
Mx	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage 0	This	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

TNM = tumour node and metastasis; MCC = Merkel cell carcinoma.

Treatment

Definitive management of MCC depends on the clinical and pathological stages of the disease. Surgical resection is the mainstay treatment for localized disease (N0 and M0). Tai recommends Mohs micrographic surgery along with wide local excision with negative margins of 1 to 2 cm for good disease-free survival⁵. The use of radiation therapy following surgical treatment remains controversial given the lack of adequate evidence to support or contradict its use. A randomized clinical trial done by Jouary *et al.* showed no survival benefit but a decrease in the rate of recurrence of MCC following adjuvant radiation therapy at the site of the excised tumour¹¹. Conversely, a large retrospective study of the SEER database showed a longer survival in patients who received radiation therapy after surgery, especially if the tumour was more than 2 cm wide²².

For node-positive disease, Fang *et al.* found that radiation alone was able to provide adequate regional control and a comparable overall survival at two years compared with lymph node dissection²³. The NCCN recommends RT with lymph node dissection if there is extensive lymphatic involvement, with adjuvant chemotherapy in some cases.

When it comes to metastatic MCC, the terrain remains vague and the evidence remains sparse. There are no guidelines for chemotherapy for MCC, and treatment strategies are based on recommendations mostly derived from case series. The majority of regimens used are extrapolated from those used for small-cell lung cancer. In a case series of 101 patients, Voog *et al.* found response rates of 47% and 100% with polytherapeutic regimens using platinum and etoposide or cisplatin and doxorubicin, respectively⁷. Similarly, the NCCN recommends using platinum-based regimens along with etoposide¹⁰.

More recent advancements in the use of immunotherapeutic agents for a multitude of malignancies have led to trials looking at their efficacy in the setting of MCC. Lipson *et al.* analyzed patients for PD-L1 expression and demonstrated tumour cells and immune infiltrates expressed PD-L1, with 97% of PD-L1-expressing MCC cells associated with these immune infiltrates¹⁶. A multicentre phase II trial was conducted by Nghiem *et al.* on treatment of naïve patients, using pembrolizumab. Four of 26 patients had a complete response and 10 had a partial response. Progression-free survival at six months was reported as 67%²⁴. Pembrolizumab is currently the only immunotherapeutic agent recommended by the NCCN. However, there are some case studies in the literature which explore the utility of other agents such as nivolumab for the treatment of MCC. Walocko *et al.* demonstrated marked partial metabolic response as seen on PET scan with the use of nivolumab and a published stable disease burden of eight months' duration. Further studies are currently being conducted for MCC treatment with nivolumab⁶. Avelumab is an additional anti-PD-L1 monoclonal antibody that was recently approved by the United States Food and Drug Administration (FDA) for the treatment of metastatic MCC¹⁴. A phase II multicentre international trial conducted by Kaufman *et al.* showed an objective response in 31.8% of a cohort of 88 patients who had metastatic MCC and who were treated with at least one line of cytotoxic chemotherapy. A sustained response at

six months was seen in the vast majority (approximately 92%) of patients who at least had a partial response after treatment with avelumab. The drug was well tolerated, the most common adverse events being fatigue and infusion-related reactions (grade 1 to 2). A minority of patients had grade 3 adverse events (including metabolic disturbances and lymphopenia in about 5% of patients). Otherwise, no grade 4 or 5 events were reported²⁵.

The field is still fertile in the research effort being spent for the best treatment of MCC. Table IV, extracted from clinicaltrials.gov, displays clinical trials that have been approved for the treatment of MCC at the time of writing this article.

CONCLUSIONS

Merkel cell carcinoma is an uncommon skin cancer that generally holds a favourable prognosis if diagnosed early and resected, but cases with metastatic disease and a much poorer prognosis do exist. Therapies for similar cases are limited. However multiple new drugs are currently being investigated for the treatment of MCC, especially in the field of immunotherapy.

ACKNOWLEDGMENTS

Informed consent of the patient was obtained, and approval for the study reported here was given by the Institutional Ethics Committee of the Staten Island University Hospital.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES

- Tothill R, Estall V, Rischin D. Merkel cell carcinoma: emerging biology, current approaches, and future directions. *Am Soc Clin Oncol Educ Book* 2015:e519–26.
- Tilling T, Moll I. Which are the cells of origin in Merkel cell carcinoma? *J Skin Cancer* 2012;2012:680410.
- Wong HH, Wang J. Merkel cell carcinoma. *Arch Pathol Lab Med* 2010;134(11):1711–6.
- Eigentler TK, Hassel JC, Berking C, *et al.* Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treat Rev* 2016;45:7–18.
- Tai P. A practical update of surgical management of Merkel cell carcinoma of the skin. *ISRN Surg* 2013;2013:850797.
- Walocko FM, Scheier BY, Harms PW, Fecher LA, Lao CD. Metastatic Merkel cell carcinoma response to nivolumab. *J Immunother Cancer* 2016;4:79.
- Voog E, Biron P, Martin JP, Blay JY. Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. *Cancer* 1999;85(12):2589–95.
- Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population-based study. *J Cutan Pathol* 2010;37(1):20–7.

TABLE IV Ongoing clinical trials for the treatment of Merkel cell carcinoma

Investigator	Phase	Status	Title	Trial ID
Bhatia S <i>et al.</i>	II	Completed	IL-12 Gene and <i>In Vivo</i> Electroporation-Mediated Plasmid DNA Vaccine Therapy in Patients with Merkel Cell Cancer	NCT01440816
Becker J <i>et al.</i>	II	Unknown status	F16IL2 Plus Paclitaxel in Metastatic Merkel Cell Carcinoma	NCT02054884
Nghiem P <i>et al.</i>	II	Active, not recruiting	Pembrolizumab in Treating Patients With Advanced Merkel Cell Cancer	NCT02267603
Barker C <i>et al.</i>	II	Recruiting	A Study of T-VEC (Talimogene Laherparepvec) With or Without Radiotherapy for Melanoma, Merkel Cell Carcinoma, or Other Solid Tumors	NCT02819843
NantKwest, Inc.	II	Recruiting	QUILT-3.009: Study of aNK Infusions in Combination with ALT-803 in Patients with Stage III (IIIB) or Stage (IV) Merkel Cell Carcinoma (MCC)	NCT02465957
Kaufman HL <i>et al.</i>	II	Recruiting	Avelumab in Subjects with Merkel Cell Carcinoma (JAVELIN Merkel 200)	NCT02155647
Chung K <i>et al.</i>	II	Completed	Oblimersen in Treating Patients with Merkel Cell Carcinoma	NCT00079131
Samlowski W <i>et al.</i>	II	Completed	S0331: Imatinib Mesylate in Treating Patients With Metastatic or Unresectable Merkel Cell Cancer	NCT00068783
Kempf R <i>et al.</i>	II	Completed	S9716: Combination Chemotherapy in Treating Patients with Merkel Cell Cancer	NCT00003549
Beylot-Bary M <i>et al.</i>	II	Recruiting	Treatment of Unresectable and/or Metastatic Merkel Cell Carcinoma by Somatostatin Analogues	NCT02351128
Rabinowits G <i>et al.</i>	I/II	Recruiting	MLN0128 in Recurrent/Metastatic Merkel Cell Carcinoma	NCT02514824
Kim S <i>et al.</i>	II	Recruiting	Randomized Study of Nivolumab+Ipilimumab±SBRT for Metastatic Merkel Cell Carcinoma	NCT03071406
Rabinowits G <i>et al.</i>	II	Active, not recruiting	Cabozantinib in Recurrent/Metastatic Merkel Cell Carcinoma	NCT02036476
Schadendorf D <i>et al.</i>	II	Recruiting	Adjuvant Therapy of Completely Resected Merkel Cell Carcinoma with 3 mg/kg BW Ipilimumab (Yervoy: Bristol-Myers Squibb, New York, NY, USA) Versus Observation	NCT02196961
Bhatia S <i>et al.</i>	III	Not yet recruiting	Adjuvant Avelumab in Merkel Cell Cancer (ADAM)	NCT03271372
Chapuis A <i>et al.</i>	I/II	Recruiting	Localized Radiation Therapy or Recombinant Interferon Beta and Avelumab With or Without Cellular Adoptive Immunotherapy in Treating Patients with Metastatic Merkel Cell Carcinoma	NCT02584829

- Girschik J, Thorn K, Beer TW, Heenan PJ, Fritschi L. Merkel cell carcinoma in Western Australia: a population-based study of incidence and survival. *Br J Dermatol* 2011;165(5):1051–7.
- Network NCC. Merkel Cell Carcinoma 2016. [Available at https://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf; cited 12 April 2017]
- 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(4):1074–80.
- Narisawa Y, Koba S, Inoue T, Nagase K. Histogenesis of pure and combined Merkel cell carcinomas: an immunohistochemical study of 14 cases. *J Dermatol* 2015;42(5):445–52.
- Heath M, Jaimes N, Lemos B, *et al.* Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AETIOU features. *J Am Acad Dermatol* 2008;58(3):375–81.
- US Food and Drug Administration CfDEaR. Avelumab (BLA 761049) approval letter, March 23, 2017. [Available at https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2017/761049Orig1s000ltredt.pdf; cited 12 September 2017]
- Behr DS, Peitsch WK, Hametner C, *et al.* Prognostic value of immune cell infiltration, tertiary lymphoid structures and PD-L1 expression in Merkel cell carcinomas. *Int J Clin Exp Pathol* 2014;7(11):7610–21.
- Lipson EJ, Vincent JG, Loyo M, *et al.* PD-L1 expression in the Merkel cell carcinoma microenvironment: association with inflammation, Merkel cell polyomavirus and overall survival. *Cancer Immunol Res* 2013;1(1):54–63.
- Afanasiev OK, Yelistratova L, Miller N, *et al.* Merkel polyomavirus-specific T cells fluctuate with Merkel cell carcinoma burden and express therapeutically targetable PD-1 and Tim-3 exhaustion markers. *Clin Cancer Res* 2013;19(19):5351–60.
- Cimino PJ, Robirds DH, Tripp SR, Pfeifer JD, Abel HJ, Duncavage EJ. Retinoblastoma gene mutations detected by whole exome sequencing of Merkel cell carcinoma. *Mod Pathol* 2014;27(8):1073–87.
- Erstad DJ, Jr JC. Mutational analysis of Merkel cell carcinoma. *Cancers (Basel)* 2014;6(4):2116–36.
- 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.
21. Love JE, Thompson K, Kilgore MR, *et al.* CD200 expression in neuroendocrine neoplasms. *Am J Clin Pathol* 2017;148(3):236–42.
 22. Mojica P, Smith D, Ellenhorn JD. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. *J Clin Oncol* 2007;25(9):1043–7.
 23. 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(7):1783–90.
 24. Nghiem PT, Bhatia S, Lipson EJ, *et al.* PD-1 blockade with pembrolizumab in advanced Merkel cell carcinoma. *N Engl J Med* 2016;374(26):2542–52.
 25. Kaufman HL, Russell J, Hamid O, *et al.* Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol* 2016;17(10):1374–85.