American Journal of Clinical Dermatology (2024) 25:541–557
https://doi.org/10.1007/s40257-024-00858-z

REVIEW ARTICLE

Merkel Cell Carcinoma: Integrating Epidemiology, Immunology, and Therapeutic Updates

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Accepted: 21 March 2024 / Published online: 22 April 2024

Abstract

Merkel cell carcinoma (MCC) is a rare skin cancer characterized by neuroendocrine differentiation. Its carcinogenesis is based either on the integration of the Merkel cell polyomavirus or on ultraviolet (UV) mutagenesis, both of which lead to high immunogenicity either through the expression of viral proteins or neoantigens. Despite this immunogenicity resulting from viral or UV-associated carcinogenesis, it exhibits highly aggressive behavior. However, owing to the rarity of MCC and the lack of epidemiologic registries with detailed clinical data, there is some uncertainty regarding the spontaneous course of the disease. Historically, advanced MCC patients were treated with conventional cytotoxic chemotherapy yielding a median response duration of only 3 months. Starting in 2017, four programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) immune checkpoint inhibitors—avelumab, pembrolizumab, nivolumab (utilized in both neoadjuvant and adjuvant settings), and retifanlimab—have demonstrated efficacy in treating patients with disseminated MCC on the basis of prospective clinical trials. However, generating clinical evidence for rare cancers, such as MCC, is challenging owing to difficulties in conducting large-scale trials, resulting in small sample sizes and therefore lacking statistical power. Thus, to comprehensively understand the available clinical evidence on various immunotherapy approaches for MCC, we also delve into the epidemiology and immune biology of this cancer. Nevertheless, while randomized studies directly comparing immune checkpoint inhibitors and chemotherapy in MCC are lacking, immunotherapy shows response rates comparable to those previously reported with chemotherapy but with more enduring responses. Notably, adjuvant nivolumab has proven superiority to the standard-of-care therapy (observation) in the adjuvant setting.

Key Points

Merkel cell carcinoma is an uncommon type of skin cancer that behaves aggressively. It is caused by either a virus or exposure to sunlight, making it highly likely to trigger the body's immune response.

Until recently, standard chemotherapy for advanced Merkel cell carcinoma provided only short-lived benefits, typically lasting around 3 months. However, since 2017, new drugs called PD-1/PD-L1 inhibitors, such as avelumab, pembrolizumab, nivolumab, and retifanlimab, have shown great promise in clinical trials.

Because Merkel cell carcinoma induces strong immune responses, it often develops ways to avoid being attacked by the body's immune system. This unfortunately also leads to primary and secondary resistance to PD-1/PD-L1 gene inhibitors. Researchers are now testing combinations of different treatments to overcome this problem.

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1 Epidemiology

Examining the epidemiology of Merkel cell carcinoma (MCC) poses challenges owing to its extreme rarity. Valuable population-based data regarding incidence and survival can only be reliably obtained from cancer registries covering large populations. Utilizing routine mortality statistics on the basis of ICD-10 coded causes of death is impractical for MCC, as it cannot be distinguished through the ICD-10 code C44 (pertaining to other malignant neoplasms of the skin). The evaluation of specialized disease registries at referral centers usually allows a more detailed characterization of MCC, a more precise description of the therapy and the course of the disease in terms of progression or recurrence. However, the disadvantage of such special registries is the lack of reference to a clearly defined population, which is why epidemiological measures, such as incidence, cannot be determined on this data basis. There is also a risk that the survival probabilities of MCC patients in these special registries are not representative of the population owing to potential selection bias.

In an attempt to show the current incidence of MCC worldwide and the trend in incidence over time, data from high quality population-based cancer registries from 20 nations for the period 1990–2007 and for 21 nations for the most recent period 2003–2007 were analyzed [1]. In the majority of populations, the incidence of MCC has increased over time. Exceptions were Black populations in the USA, populations in Japan, Norway, and Denmark, where the incidence remained stable over time. The rise in incidence may stem from enhanced MCC recording in cancer registries, improved histopathological diagnostics, and increased awareness among physicians and patients. A recent time trend analysis of SEER data indicates that the increase in incidence is attributable to both a period effect (reflecting changing diagnostics and awareness) and a birth cohort effect, the latter indicating an increase in MCC risk factors [2].

Nations with the highest MCC incidence (expressed as cases per million, World Standard Population) in the period 2003–2007 were Australia (men: 5.2, women: 2.2), New Zealand (4.5, women: 3.2), and the USA (white population, men: 4.2, women: 1.9). Within the US, where multiple ethnicities live and for which population-based incidence rates are available, the following ethnicities are affected by MCC in descending order: non-Hispanic white, Hispanic, American Indian, Asian & Pacific Islander, and Black [1]. The occurrence of Merkel cell carcinoma (MCC) exhibits an exponential increase with advancing age, typically manifesting between 70 and 80 years. Notably, MCC is rare in younger individuals, as evidenced by a mere 0.07% of cases under the age of 30 years in a SEER data analysis comprising 27,105 MCC cases. Among these cases, 75% were in the 20–29 year age range, and interestingly, they tended to be diagnosed at more advanced stages. The reasons behind this observation, whether linked to heightened MCC aggressiveness or diagnostic delays in younger age groups, remain unclear [3]. Moreover, consistent findings indicate a higher incidence of MCC in men compared with women, with a predilection for occurring on the skin of the head and extremities [1, 4–7].

Apart from advanced age and prolonged exposure to ultraviolet (UV) radiation, individuals with compromised immune systems face heightened risks of developing MCC. In a cohort of 309,365 patients with acquired immunodeficiency syndrome (AIDS), the risk of MCC was 13.4 times higher compared with the general population, which however dropped to 3.15 during the era of antiretroviral therapy [8, 9]. Similarly, a record linkage of the Registry of Transplant Recipients, involving 189,498 solid organ transplant recipients and data from 15 population-based cancer registries in the USA, revealed that the MCC risk after organ transplantation surged to 23.8 times higher than in the general population. Specific immunosuppressive medications such as azathioprine, cyclosporine, and mTOR inhibitors were associated with an increased risk of MCC [10]. This risk increased over time post-transplantation and varied on the basis of the organ type, with the highest risk observed after kidney transplantation. This notion may be owing to the medication patients were receiving prior to transplantation for renal insufficiency. A recent nationwide case-control study on MCC demonstrated that a cumulative dose of $\geq$ 50,000 mg of hydrochlorothiazide correlated with a 2.3-fold increased rate of MCC. Similarly, a cumulative dose of $\geq$ 2,000 defined daily doses (DDD) of furosemide was linked to a 1.9-fold increased rate of MCC [11]. Remarkably, individuals who receive organ transplants and later develop MCC tend to be approximately 10 years younger than MCC cases in the general population [12]. Additionally, individuals with a history of previous cancer are also at an elevated risk of MCC. An analysis of US SEER data, encompassing 5.4 million cancer patients, demonstrated a 43% increased risk of MCC [Statistical Information on Recidivism (SIR) = 1.43] in this group. Notably, individuals with a history of other non-epithelial skin cancers (SIR = 4.20) or lymphocytic leukemias (SIR = 6.31) faced a particularly high risk of developing MCC [13].

Population-based cancer registries primarily assess the survival probability of MCC patients at a population level. However, they are typically not optimized for determining recurrence-free or progression-free survival owing to incomplete reporting of recurrences or progressions, even in mandatory reporting cases. MCC-specific survival

Table 1 Publications reporting 5-year relative survival (%) of Merkel cell carcinoma by sex in chronological order of publication year

Publication	Population and time period	Comment	5-year relative survival %)		Multivariable-adjusted hazard ratio (95% CI)
			Men	Women	
Agelli and Clegg [4]	U.S., SEER, 1973–1999	No sex stratification of relative survival	62		0.71 (0.59–0.87)
Reichgelt et al. [123]	Netherlands, 1993–2007		55	67	0.71 (0.58–0.86)
Kukko et al. [5]	Finland, 1983–2004	No additional multivariable modelling	36 (20–54)	69 (56–82)	
Youlden et al. [7]	Queensland, 1993–2010		38 (30–47)	48 (365–60)	0.77 (0.5–1.16)
Rubio-Casadevall et al. [124]	Girona (Spain), 1994–2002	No sex stratification (26 cases only)	44 (26–74)		
Eisemann et al. [14][a]	Germany, 2007–2011	No additional multivariable modelling	58 (51–65)	84 (79–88)	
Lee et al. [64]	New Zealand, 2000–2015		43 (36–51)	47 (39–55)	0.86 (0.71–1.04)
Uitentuis et al. [125]	Netherlands, 1993–2015		62 (years 1993–2000) 65 (years 2011–2016)		0.70 (0.63–0.79)

PubMed search ["relative survival" AND Merkel cell carcinoma], May 4, 2023; all survival estimates including 95% confidence limits were rounded to zero decimal places; Multivariable, stage-adjusted hazard ratios for death from any cause for the sex effect (reference group: men)

[a]The authors themselves critically note that the relative survival probabilities may have been overestimated due to an under registration of deaths

probability can be determined using cause of death statistics or relative survival probabilities. However, cause of death statistics, based on ICD-10 codes, may be imprecise and error-prone, potentially leading to confusion with other skin neoplasms. Relative survival probabilities, comparing observed and expected survival on the basis of the general population life table, are more valid owing to their accuracy.

Eight publications provide diverse 5-year relative survival estimates from population-based registries. The 5-year relative survival probability varies significantly based on population, age, sex, and calendar time, ranging from 36% (Finland, men, 1983–2004) [5] to 84% (Germany, women, 2007–2011) [14]. Despite this variability, a consistent trend emerges: women consistently exhibit higher 5-year relative survival probabilities than men. In five of the eight publications, survival rates were adjusted for various confounders, particularly tumor stage through Cox modeling. Notably, a clear and consistent sex difference in favor of women persists in all five analyses (Table 1). In addition to sex, other prognostic factors include TNM stage and immunosuppression [15]. Immunosuppression, defined as a hematologic neoplasia, AIDS, or a condition after organ transplantation was associated with a multiple-adjusted hazard ratio (disease-specific mortality) of 2.80 in a UK-wide cohort study [6]. In another cohort study, immunosuppression was associated with an increased risk of MCC recurrence [hazard ratio (HR) = 2.40] [16].

2 Immunobiology

Initiation of MCC can result from either genetic alterations induced by UV light or infection, including the integration of Merkel cell polyomavirus (MCPyV) into the host cell genome [17]. However, not all genetic alterations or infections lead to tumor formation. Protective mechanisms exist to prevent the proliferation of nonfunctional or noncooperating cells within tissues. For instance, the DNA repair system can address many daily occurring DNA lesions [18], and intrinsic tumor suppressive mechanisms curb inappropriate cell expansion [19]. In cases where damage is extensive and irreparable, cells may undergo apoptosis or enter senescence [20]. If these mechanisms fail, the immune system poses a powerful extrinsic system to detect, prevent, and eliminate tumor growth.

2.1 Innate and Adaptive Immune Responses

Innate immunity represents the first line of immunological defense. Its cellular constituents are myeloid cells [macrophages, neutrophils, dendritic cells (DC)] and innate lymphoid cells (ILCs). ILCs are lymphocytes that do not express specific receptors and can be divided into five distinct subsets: NK cells, lymphoid-tissue inducer, and group 1, 2, and 3 ILCs (ILC1-3) [21]. For the detection of target cells they express both activating and inhibitory receptors, such as natural cytotoxicity receptors, killer cell immunoglobulin-like receptors, and the type II transmembrane C-type lectin-like receptor NKG2D, and thus their activation status depends on the cooperation of activating and inhibiting signals [21].

Innate immune cells exhibit swift cytolytic responses to tumor cells but struggle to control established solid tumors effectively [22]. Conversely, adaptive immune responses, while requiring time to develop, are specific and enduring [23]. While γδ-T cells are at the crossroad of innate and adaptive immunity, peptide-specific $CD8^+$ cytotoxic T cells (CTLs) are the ultimate effector cells of adaptive immunity [23].

However, initiation of adaptive antitumor immune responses require innate immune cells to recognize tumor cells, which will lead to their activation and acquire effector functions. For example, activated macrophages, DCs, neutrophils, and mast cells produce chemokines and cytokines like interferons and interleukins, which can recruit other immune cells to the tumor microenvironment (TME) [24]. Furthermore, activated NK cells will be the first to induce immunogenic cell death and these dying tumor cells will release antigens efficiently taken up by DCs for presentation to T cells. One DC subtype is particularly important since the initiation of cytotoxic antitumor CD8+ T cell responses by cross-priming is mainly mediated by them: type-1 conventional DCs (cDC1s) [25]. They are equipped to efficiently uptake antigen from dying cells, deliver cell-associated antigen to early endosomes, and owing to lower proteolysis show increased antigen retention [25]. Captured antigen is processed into small fragments, loaded onto MHC class I molecules, transported to the cell surface where this peptide/MHC class I complexes are presented to CD8+ T cells [26]. Those CD8 T cells, which encounter their cognate antigen presented by a cDC1 will be activated, and in the presence of additional costimulatory signals will undergo clonal expansion to form the population of antigen-specific CTLs able to recognize and eliminate cells expressing the same antigen [27, 28]. The process of CD4+ T-cell response priming is similar with cDC2s being potent stimulators, and antigen is presented as peptide/MHC class II complexes [29].

For the priming of T cells the antigen-loaded DCs will normally migrate to the tumor draining lymph node where they encounter thousands of T cells, which serves to accelerate the initiation and execution of specific immune responses (Fig. 1) [30]. Primed CD8+ T cells will translocate to the tumor to recognize, bind, and in the best case kill the tumor cells. However, adaptive immune responses can also be primed in tertiary lymphoid structures (TLSs). TLSs are characterized by an inner zone of B cells and an outer zone of T cells (Fig. 1) [31]. They can differ in their cellular composition, localization (stromal, peritumoral, and intratumoral) and maturation (lymphoid aggregate, primary follicle, and secondary follicle) [31]. In several tumor entities, including MCC, TLSs are associated with a better prognosis [32, 33]. Compared with priming in lymph nodes, an in situ priming in TLSs could offer the advantages of speed, efficiency with primed cells more likely to encounter cognate antigen, more unique immune responses owing to the effect of local tissue factors, and better survival of lymphocytes [31].

The immunoediting process, outlined in phases of elimination, equilibrium, and escape, delineates the interplay between immune responses and developing tumors [34]. The elimination phase marks the commencement of innate and adaptive immunity, aiming to eliminate malignant or transformed tumor cells before clinical detection. If tumor cells exhibit low immunogenicity, they may progress to the equilibrium phase. In this phase, the interaction between adaptive immunity and tumor cells reaches a stable balance, hindering complete tumor elimination by the immune system and preventing tumor cells from escaping immune surveillance. In the escape phase, immune response limitations allow unrestricted tumor cell proliferation, leading to clinically apparent tumors. Significantly, immune suppression and advancing age stand out as primary risk factors for MCC. The latter, likely attributed to immunosenescence, denotes the gradual decline of the immune system with age [35]. Both factors are likely contributors to the progression into the escape phase.

2.2 MCC is an Immunogenic Tumor

Considering that immunosuppression is a major risk factor for MCC [8, 10, 15, 36], and given the occurrence of spontaneous regression, including complete regression, with over 40 documented cases to date, MCC is viewed as an immunogenic cancer [37, 38]. In this regard, both the UV- and viral carcinogenesis readily explain MCC's immunogenicity (Fig. 2A). For UV-associated MCC the etiologic factor is UV-induced mutagenesis. Thus, in contrast to the virus-associated MCC, these tumors display a high tumor mutational burden [39, 40], which should translate into numerous neoantigens. Indeed, in a recently published case report, Church et al. were able to identify and characterize tumor-specific Th1-skewed CD4+ T cells targeting several different neoantigens in a patient with a UV-associated MCC [41].

After the identification of MCPyV in 2008 [42], more than 35 publications verified an overall combined prevalence rate of MCPyV in MCC of 80% [43]. Importantly, virus-associated MCC are not only characterized by the expression of virally encoded oncoproteins, i.e., the small and large T antigen (TA) [44], but they are actually dependent on TA expression for their growth [44, 45]. Notably, viral proteins presented by MHC molecules are often immunogenic [46], thus viral proteins appear to be eminent antigens shared between patients with virus-associated MCC [47, 48]. Indeed, numerous immunogenic MCPyV TA-derived epitopes, tailored to various HLA haplotypes, have been identified [49, 50]. This discovery not only enables the

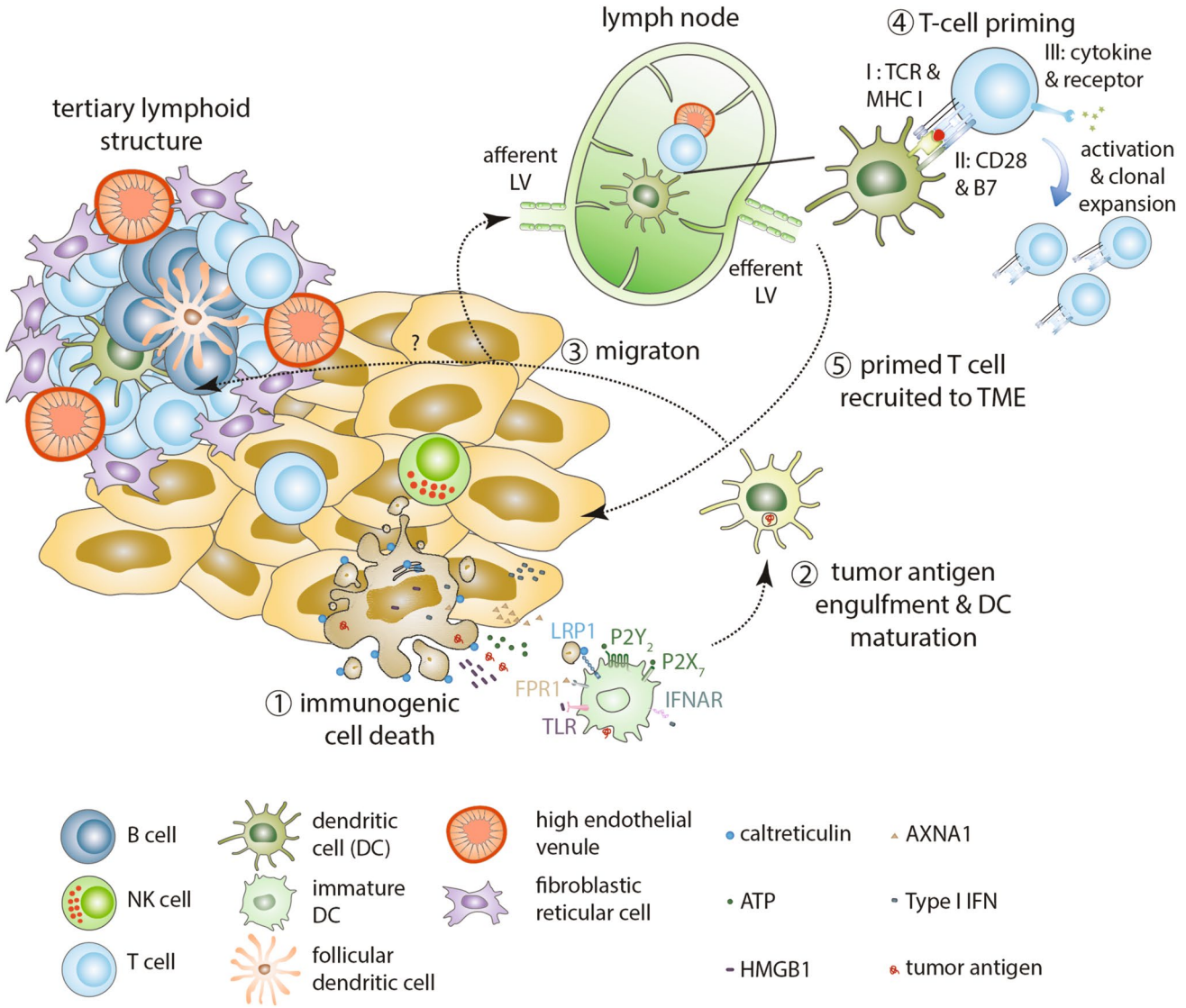

Fig. 1. Tumor antigen cross-presentation for priming of tumor-specific T cells. (1) Upon immunogenic cell death, damage-associated molecular patterns (DAMPs) are presented or released by the tumor cells. For example, dying cells will translocate calreticulin to the cell surface, release high-mobility group box 1 (HMGB1) protein, Annexin A1 (AXNA1) and adenosine triphosphate (ATP) and secrete type I interferons. (2) Immature dendritic cells (DCs) sense these DAMPs by pattern recognition receptors. This leads to maturation of the DCs and increased phagocytosis of released tumor antigens, which are subsequently processed and presented to T cells. (3) DCs migrate to the lymph node via the afferent lymphatic vessels. They might also migrate into tertiary lymphoid structures present at the tumor (in this case a peritumoral location is depicted). (4) In the lymph node and maybe also in TLS priming of T cells will take place. Depicted for cross priming of CD8+ T cells, full activation and clonal expansion of the T cells require three signals: (1) recognition of the MHC class I/peptide complex by the TCR, (2) costimulation of CD28 by B7 ligand, and (3) cytokines binding to cytokine receptor. (5) Primed T cells will leave the lymph node via efferent lymphatic vessel and are recruited to the tumor microenvironment where they can attack tumor cells expressing their cognate peptide

monitoring of immune responses, but also presents potential new targets for T-cell-based therapies. Intratumoral infiltration by MCPyV-specific T cells was associated with significantly improved MCC-specific survival, suggesting that augmenting the number or avidity of virus-specific T cells may have therapeutic benefit [51]. Moreover, a close interaction between MCPyV-specific T cells and MCC tumor cells can be deduced by the observation that the frequency of MCPyV-specific T cells correlated with tumor burden, i.e., increased upon tumor progression and decreased upon efficient therapy rendering the patient tumor free [52]. MCPyV large T antigen seems to be the major tumor-specific antigen present in virus-associated MCC: when tumor-infiltrating lymphocytes (TILs) obtained from MCC tumors were analyzed for specificity against three viral proteins, 80% of

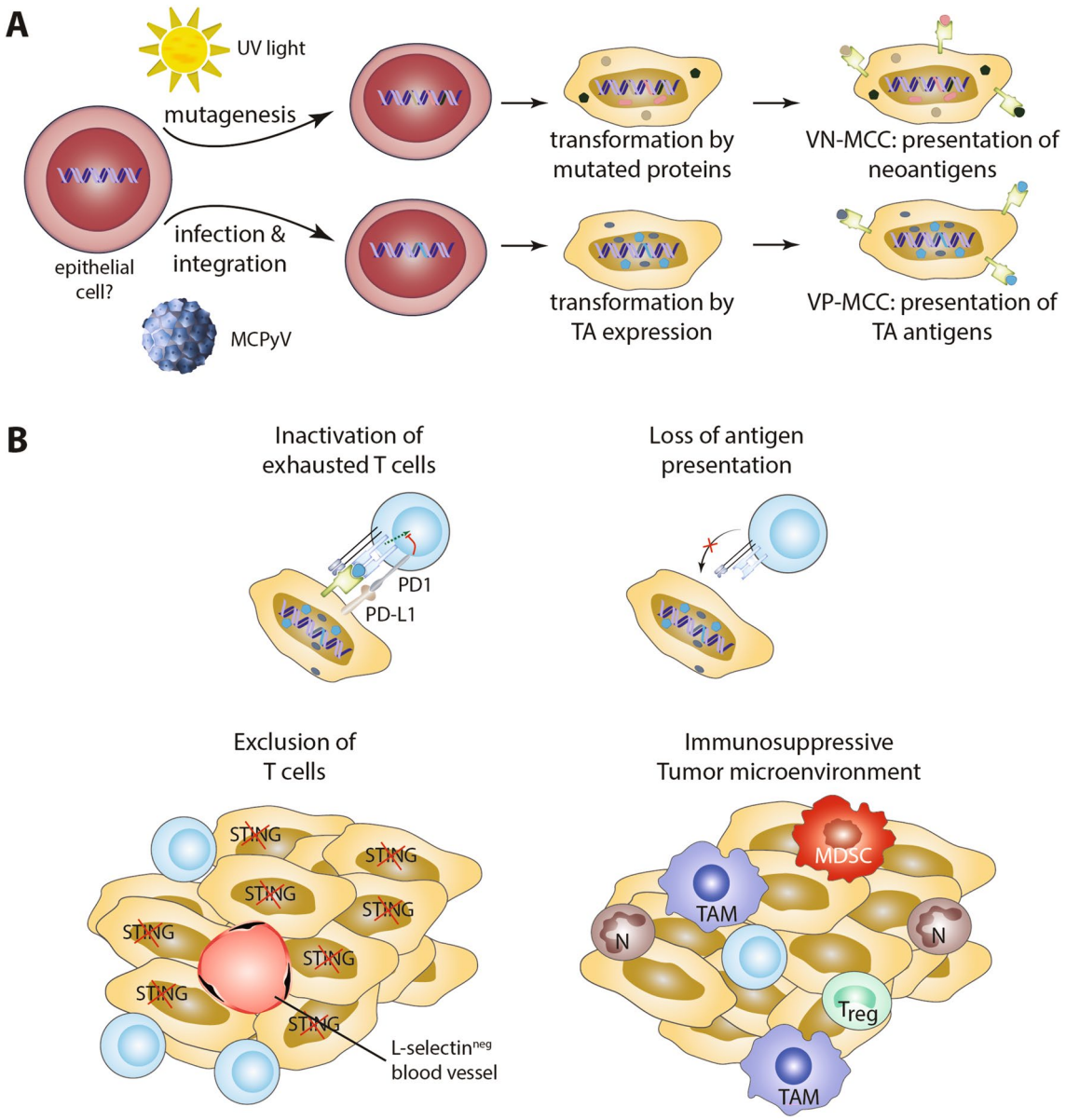

Fig. 2. Antigenicity and immune escape in MCC. **A** On the basis of the different etiological factors leading to MCC development, VN-MCC should be able to present neoantigens while VP-MCC present TA-derived antigens. **B** Several immune escape mechanisms have been described for MCC. *MDSC* myeloid derived suppressor cell, *N* neutrophil, *TAM* tumor-associated macrophage, *Treg* regulatory T cell

identified T-cell responses were reacting to the large T antigen [53].

2.3 Immune Escape Mechanisms of MCC

Therefore, both etiologies of MCC lead to an immunogenic tumor, with a more robust immune response noted in virus-associated MCC. Consequently, an improved prognosis is linked to both increased numbers of intratumoral CD8+ T cells and the quality of the infiltrate [54, 55]. However, the number of cases with a high intratumoral CD8 infiltration is rather low, implying that immune evasion mechanisms are present in MCC.

A physiological mechanism to avert harm from excessive immune responses involves inducing an exhausted state when T cells face chronic inflammation or prolonged exposure to antigens [56]. This process unfolds gradually, transitioning from PD1+TCF1+ precursor exhausted T cells (T_{pex}) with retained proliferation capability to a fully exhausted state (T_{ex}; PD1+TCF-) [57]. T_{ex} is distinguished by elevated expression of co-inhibitory receptors, such as PD1, LAG3, CTLA-4, and TIM3. While T_{ex} lacks proliferation capacity, it appears to regain cytotoxic potential when compared

with T_{pex} [57, 58]. The process involves the dysregulation of multiple signaling pathways, transcriptional programs, and epigenetic alterations. It is not only triggered by persistent antigen encounter but is also shaped by the tumor microenvironment (TME). For instance, factors such as nutrition restrictions, hypoxia, and immunosuppressive cells and signals render the TME immunosuppressive [59, 60]. T cell exhaustion is an important immune escape mechanism in MCC: a significant proportion of TILs express PD-1 and TIM-3, which are not only regarded as the exhaustion markers, but actually promote T-cell dysfunction [52, 61]. Activation and proliferation of T cells are inhibited through PD-1 signaling. When PD-1 is stimulated by binding to its ligands (PD-L1 or PD-L2), it undergoes phosphorylation, enabling the recruitment and activation of Src homology region 2 domain-containing phosphatase (SHP-2). This, in turn, results in the dephosphorylation of critical signaling molecules downstream of the T cell receptor (TCR). The downstream signaling pathways activated by TIM-3 involve the coupling of TIM-3 to TCR signaling pathways, leading to the modulation of T cell function [62]. On binding to galectin 9 or CEACAM1, Tyr256 and Tyr263 in the intracellular domain of TIM3 are phosphorylated. This phosphorylation releases BAT3 and facilitates the recruitment of the tyrosine kinase FYN. Consequently, immune synapse formation is disrupted and phosphatase recruitment ensues. Ultimately, the cell becomes anergic or undergoes apoptosis, mediated by intracellular calcium release. Additionally, phosphatidylserine released from apoptotic cells can bind to the FG–CC′ cleft-binding site on TIM3.

Another prominent immune escape mechanism in MCC is the downregulation of MHC class I molecules. To attack tumor cells, primed T cells have to recognize their target cells via binding of the TCR to cognate antigen presented on MHC complexes. Hence, tumor cells with impaired antigen presentation become unnoted by T cells. In a study with MCC cell lines, we observed that in most of the analyzed cell lines the expression of members of the antigen presentation machinery, i.e., subunits of the proteasome required for degradation of antigen into peptides, transporters associated with antigen processing and antigen presentation molecules, is impaired [63].

MYC-L and the non-canonical polycomb repressive complex 1.1 (PRC1.1) have been recognized as HLA-class I repressors in MCC [64]. In virus-associated MCCs, the recruitment of MYC-L by the small T antigen to the EP300 complex appears to be responsible. On the other hand, in UV-associated MCC, amplification of the *LMYC* gene may lead to heightened MYC-L expression and subsequently result in suppressed HLA class I expression. In accordance with these in vitro observations, MHC class I expression is absent or low in most MCC cases [63–66]. However, downregulation of MHC class I enhances the immunogenicity for NK cells. Notably, MCC cells prevent activation of NK cells by downregulating the expression of MICA and MICB, i.e., the ligands for the activating NKG2D receptor [65]. Downregulation of HLA class I and MICA/B expression is owing to epigenetic silencing and thus can be restored by histone deacetylases, interferons, and inhibitor of USP7, a component of the PRC1.1 complex [63–66].

The interaction between tumor cells and T cells can also be prevented by spatial separation. Indeed, CD8+ T cells are often found only in the vicinity of MCC, but not infiltrating into the tumor [54, 67]. For T cells to infiltrate tumors from the bloodstream, the presence of E-selectin on blood vessel walls is crucial. In MCCs, however, intratumoral vascular E-selectin was predominantly downregulated, and the frequency of E-selectin-positive vessels within the tumor correlated with the extent of intratumoral CD8+ infiltrate [68]. Consistent with studies highlighting the favorable impact of intratumoral CD8+ T cell infiltration on prognosis, the patient group with a low fraction of E-selectin-positive vessels exhibited the poorest MCC-specific survival.

The cGAS-STING pathway plays a crucial role in regulating innate and adaptive immunity by sensing cytosolic pathological DNA, where STING serves as a key adaptor for inducing interferon type I and other proinflammatory cytokines [69]. In MCC, STING expression is suppressed. Restoring STING expression in MCC cells and using a STING agonist reactivates their antitumor inflammatory cytokine production. Additionally, MCPyV-specific T cells exhibit enhanced migration and tumor cell killing when cocultured with MCC cells with restored STING [70]. Finally, intratumoral injection of a STING agonist resulted in a lasting clinical response in MCC patients. This was accompanied by expansion of cancer-specific T cells [71].

2.4 Immunological Effects of Immune Checkpoint Inhibition

On the basis of the observations that MCCs are immunogenic and TILs expedite the activation and exhaustion markers PD-1 on the one hand and PD-L1 on tumor and stromal cells on the other [61, 72, 73], it was postulated early on that this tumor entity should be well susceptible to immune checkpoint inhibitor (ICI) therapy, especially antibodies that block the PD-1/PD-L1 signaling pathway. However, the economic viability of introducing a therapy in a rare type of cancer is relatively limited; thus, it took some time for this hypothesis to be put to the test. As we will explore further, once conducted, these studies revealed that first-line anti-PD-(L)1 therapies elicited objective responses in over half of the patients with advanced MCC.

TCR repertoire analysis of TIL revealed an association of low T-cell clonality but high TCR diversity with response to ICI, while in nonresponders terminally differentiated

effector cells (most likely T_{ex}) with a constrained TCR repertoire prevailed [74]. Upon ICI therapy, responders demonstrated a more pronounced and diverse clonal expansion of TILs. Expanding this study demonstrated that dense CD8+ T cells infiltrate near tumor cells in lesions obtained before treatment was associated with a favorable response to ICI [75]. Moreover, the infiltrate of patients experiencing disease control upon ICI was predominated by cells co-expressing CD45RO, CD27, and TCF1, which are markers for central memory cells (but also for T_{pex}). In murine tumor models anti-PD-1 treatment led to an increase in the population of T_{pex} among TILs and facilitated their differentiation into T_{ex}, the cell type able to kill tumor cells in direct cytotoxicity assays [58]. In a study involving melanoma and MCC patients, the presence of PD-1+TIGIT+CD8 T cells in the blood post-treatment initiation was identified as a predictor of anti-PD-1 therapy efficacy [76]. The PD-1+TIGIT+CD8 T cells appeared to be heterogeneous probably consisting of activated, exhausted, and cytotoxic follicular T cells characterized by the expression of CXCR5. This is in line with a report demonstrating that CXCR5 served as a marker for PD-1+ T cells with self-renewal capacities responsible for the proliferation in the blood upon anti-PD-1 therapy [77]. Accordingly, increased frequency and absolute number of TCR-beta clonotypes emerging on PD-1 blockade in the PD-1+TIGIT+CD8 T cell population correlated with clinical benefit [76].

PD-1 therapy has the potential to replace exhausted clonotypes by their contraction and by activation of new highly tumor-reactive clonotypes, i.e., by the de novo priming of cytotoxic T cells [76, 78, 79]. Alternatively, the expansion pre-existing clonotypes have also been described [80–82]. As discussed above, priming and expansion of new T cell clones occur in secondary lymphoid organs or TLSs. Evidence for both scenarios have been reported: (1) subsets of T_{pex} cells found in tumor-free draining lymph nodes were clonally related to T_{ex} present in the tumor [83]. Moreover, upon anti-PD-1 therapy, the frequency of T_{pex} observed in close proximity to DCs decreased while the more differentiated intermediate-exhausted T cells became more abundant. This change in the lymph node correlated with an increase of proliferating intermediate-exhausted T cells in the blood implying an important role for the lymph nodes in mediating responses to ICI. (2) For several cancer entities the presence of TLSs is predictive for patients' responses to anti-PD-1 therapy [84, 85] and induction of TLSs upon ICI therapy was observed after neoadjuvant therapy [86].

It's crucial to emphasize that while half of patients with advanced MCC benefit from ICI therapy, the remaining half do not. This lack of persistent benefit can be attributed to either no response at all (primary resistance) or relapse after an initial positive response (secondary resistance). The resistance has been attributed to the extent or the induction/amplification of the immune escape mechanisms mentioned earlier—namely, dysfunctional T cells, inhibition of the interaction between MCC and T cells, and the immunosuppressive TME. For example, analyses of pre- and posttreatment tumor lesions of a MCC patient with acquired resistance to adoptive MCPyV-specific T cell therapy revealed transcriptional suppression of the HLA genes [87]. This transcriptional suppression was owing to epigenetic regulation since treatment with hypomethylating agents reinduced HLA expression. Similarly, treatment with histone deacetylase inhibitor could also overcome HLA class I downregulation in ICI-resistant MCC patients, but the effect on clinical response has yet to be determined in a larger cohort [88]. Concerning the immunosuppressive TME, one myeloid population stands out as particularly noteworthy: tumor-associated macrophages (TAM), identified by the expression of CD163, CD14, and S100A8. In a study involving 54 MCC patients, a greater prevalence of TAMs was linked to resistance to PD-1 blockade [89].

Numerous additional mechanisms to evade the immune system have been identified in various tumor types. These mechanisms include, for example, the loss of immunodominant antigens or the insensitivity of tumor cells to cytokines secreted by T cells. The latter is achieved by the downregulation or mutation of proteins responsible for recognizing and responding to immune effector signals [90–93]. At present, it has not yet been described that these immune escape mechanisms are also active in MCC.

3 Immunotherapy

Until recently, recommendations for the systemic therapy of advanced MCC primarily relied on data derived from single-center retrospective analyses. Additionally, recommendations were drawn from data extrapolated from other tumor types and individual experiences. Despite advancements in comprehending the disease's biology and the availability of systematic retrospective data collections, along with various prospective therapeutic trials, the absence of prospective randomized studies has limited the ability to compare different systemic therapies. Nevertheless, a comparison of key parameters, such as response rates, response duration, survival times, and toxicity suggests that immunotherapy with PD-1/PD-L1 checkpoint inhibitors stands out as the most promising systemic treatment. Chemotherapy and alternative treatments may be considered as secondary options.

In this respect it is important to acknowledge some of the particularities of MCC patients with respect to

Table 2 PD-1/PD-L1 blockade in metastatic MCC

Clinical Trial	NCT0215567A	NCT0215567B	NCT02267603	NCT02488759	NCT03599713
Antibody	Avelumab	Avelumab	Pembrolizumab	Nivolumab	Retifanlimab
Target	PD-L1	PD-L1	PD-1	PD-1	PD-1
Median follow-up time	40.8 months	21.2 months	14.9 months	12.0 months	17.6 months
Number of prior therapies (PrT)	≥ 1	0	0	0 to ≥ 1	0
Patient count	88	116	50	25	101
Median age	73 years	74 years	71 years	66 years	71 years
Stage	IV	IV	IIIB/IV	III/IV	III/IV
Objective response rate [CR]	33 % [11 %] 1 PrT 43% ≥ 2 PrT 20 %	40 % [16 %]	56 % [24 %]	64 % [32 %] 0 PrT 73 % 1–2 PrT 50 %	54% [17%]
24-month PFS	26 %	Not reported	48 %	Not reported	56%
24-month OS	36 %	Not reported	69 %	Not reported	Not reported
Reference	[97]	[98]	[107]	[107]	[101]

outcome measures, specifically overall versus disease-specific survival [94]. Overall survival (OS) refers to the duration from the date of initiation of therapy until death from any cause. It is a comprehensive measure that considers all causes of death, not just those related to the specific disease being studied. In contrast, disease-specific survival (DSS) focuses solely on the duration from start of therapy until death owing to the specific disease, i.e., MCC, under investigation. It excludes deaths from unrelated causes, providing a more targeted measure of how well patients are surviving with that particular disease. While OS is universally accepted measure of direct benefit as it is easily measurable and provides a comprehensive view by considering all causes of death, in an elderly population, however, it may be influenced by comorbidities, potentially complicating result interpretation. In this respect, DSS excludes deaths from unrelated causes, offering a clearer picture of disease-specific outcome; however, it may not capture the overall impact of the treatment on patient health and well-being, especially in cases where treatment related factors, e.g., myelodepression caused by chemotherapy or autoimmune events by ICI, contribute to mortality. Thus, more limited in scope compared with OS, DSS is potentially overlooking broader health considerations in elderly patients [95].

3.1 PD-1/PD-L1-Directed Immune Checkpoint Inhibition

PD-1 and its ligand PD-L1 play a pivotal role in immune evasion by cancer cells. MCC often exhibits overexpression of PD-L1, creating an immunosuppressive microenvironment [75]. PD-1 inhibitors, such as pembrolizumab and nivolumab, or PD-L1 inhibitors, such as avelumab, disrupt this interaction, reactivating T cell responses against MCC cells.

Clinical trials evaluating PD-1 inhibitors have demonstrated remarkable efficacy in MCC. Prospective single-arm studies are available for both PD-1 (pembrolizumab, nivolumab, and retifanlimab) and PD-L1 (avelumab) blocking targeted antibodies (Table 2). Pembrolizumab was the first immune checkpoint inhibitor investigated in MCC patients, and has shown durable responses, leading to accelerated FDA approval for metastatic MCC. Nivolumab as well as avelumab have also shown promising results, highlighting the therapeutic potential of targeting the PD-1/PD-L1 axis.

The first published phase-II trial on checkpoint immunotherapy for MCC reported on 50 treatment-naive metastatic patients, who were treated with pembrolizumab [96]. The objective response rate was 56% (complete response 24%; partial response 32%). After a median follow-up of 15 months, the median response duration had not been reached. The progression-free survival (PFS) rate at 24 months was 48%, with a median PFS of 16.8 months. The overall survival (OS) rate at 24 months was 69%, with the median OS not reached. Interestingly, the MCPyV status determined in the patients' tumor tissue samples did not correlate with the objective response rate, PFS, or OS of the respective patients under pembrolizumab. However, a trend toward improvement in PFS and OS was described in patients with PD-L1-positive tumors compared with PD-L1-negative tumors. On the basis of these encouraging study results, pembrolizumab was approved by the FDA for the treatment of advanced MCC.

A further phase-II trial evaluated the PD-L1 antibody avelumab in advanced non-resectable MCC patients who had previously received at least one cytostatic pretreatment [97]. Among 88 patients, an objective response rate of 33%

was achieved after a median follow-up of 40.8 months, with a median response duration of 40.5 months. The median progression-free survival (PFS) was 2.7 months, with a PFS rate at 24 months of 26%. The median overall survival (OS) was 12.6 months, and the OS rate was 31% after 42 months. Subgroup analyses suggested a higher likelihood of response for patients with fewer prior systemic therapy lines, lower tumor burden, and PD-L1-positive tumors. However, sustained response occurred independently of these baseline factors, including MCPyV status. The study was subsequently expanded to include patients in the first-line setting [98]. In 29 evaluable patients with more than 3 months of follow-up, a response rate of 62% was observed; 16 of the 18 responders were already observed at the first staging after 6 weeks. On the basis of these positive study data, avelumab was approved by the FDA and EMA for the treatment of advanced MCC.

The latest FDA approval was granted to retifanlimab on the basis of data from the POD1UM-201 trial [99, 100]. This open-label, multiregional, single-arm study assessed retifanlimab in adults with metastatic or recurrent locally advanced MCC who had not undergone prior systemic therapy for their advanced disease. In chemotherapy-naive patients (n = 101), retifanlimab monotherapy demonstrated an objective response rate (ORR) of 54%, as independently evaluated by central review using RECIST v1.1. Notably, 17% achieved a complete response, and 37% achieved a partial response. In contrast to the other trials, patients with a tumor PD-L1 expression greater than 1% showed a significantly better response than those with lower PD-L1 expression. Among the responding patients, the duration of response varied from 1.1 to 24.9+ months. Three-fourths experienced a response lasting more than 6 months, and 62% had a response lasting more than 12 months according to landmark analysis. Serious adverse reactions occurred in 22% of patients receiving retifanlimab, with the most frequent serious adverse reactions being fatigue, arrhythmia, and pneumonitis. Permanent discontinuation owing to adverse reactions occurred in 11% of patients [101].

All the mentioned clinical trials on PD-1/PD-L1 checkpoint inhibition share the characteristic that clinical responses were observed independent of the MCPyV status and PD-L1 expression. Although a response is possible even with a high tumor burden, the early initiation of checkpoint immunotherapy with a low tumor burden proves to be more favorable in all the mentioned studies.

In addition to the presented clinical trials since the registration of the first ICIs, real-world data have been collected and reported [75, 102, 103]. Levy at al. reported on 54 patients receiving avelumab as the first-line treatment for 74% of patients, with 15% having locally advanced disease. In line with previous experience, the overall response rate was 57%, with 24% achieving a complete response. PFS was 8.6 months and median OS was 25.8 months. Another study on a large multicenter cohort comprising 114 patients treated with different PD-1/PD-L1 inhibitors indicated that the absence of immunosuppression, a limited number of tumor-affected organ sites, and a predominance of CD8+ memory T cells among the tumor-infiltrating lymphocytes are baseline characteristics predicting a favorable response to PD-1/PD-L1 immunotherapy in patients with advanced MCC and should be considered when making treatment decisions [75]. In a recent review article, the published real-world data on the efficacy of avelumab has been summarized [103]. It is important to note that a systematic review and Bayesian network meta-analysis of ICIs in solid-organ cancers comprising 10,673 patients reported that avelumab was associated with significantly lower OS compared with nivolumab and pembrolizumab (HR 1.37, 95% CI 1.05–1.78 and HR 1.33, 95% CI 1.02–1.73, respectively) [104].

The optimal duration of treatment ICI in metastatic cancers is uncertain, especially for patients who do not achieve radiologic complete remission. Many face progressive disease after discontinuation of ICI. Extending treatment, however, often poses logistical challenges. In a retrospective study on 23 patients with advanced melanoma (n = 18) or MCC (n = 5) received ICI therapy at reduced dose frequency every 3 months after initial disease control at standard dose frequency. After frequency reduction, the 3-year progression-free survival was 73% in melanoma and 100% in patients with MCC [105]. However, among a cohort of 65 patients, those 25 who achieved a complete response (CR) on positron emission tomography–computed tomography (PET/CT) imaging seem to maintain lasting responses even after discontinuing treatment for a year. Only two patients (8%) experienced a recurrence following the cessation of avelumab treatment [106].

3.2 CTLA-4 Directed Therapies

For patients who do not respond or no longer respond to PD-1/PD-L1 blockade therapy, off-label therapy with the combination of the anti-CTLA-4 antibody ipilimumab plus nivolumab may be considered. Case reports and retrospective case series exist on this therapy combination, reporting controversial efficacy data. One report from Harvard Medical School on 13 patients with metastatic MCC who received ipilimumab plus nivolumab after failure of anti-PD-1/PD-L1 therapy found no objective responses in their patient cohort (0/13 patients achieved a complete or partial response; 3/13 achieved stable disease as the best overall response but progressed shortly thereafter) [108]. The median progression-free survival was 1.3 months; the median overall survival was 4.7 months. Subsequent multicenter retrospective study reports from German skin cancer centers indicated a high response rate of PD-1/PD-L1-refractory

MCC to combination immunotherapy with ipilimumab plus nivolumab [109].

The first prospective trial evaluating ipilimumab plus nivolumab in advanced MCC included patients in the first-line or second-line setting, treated with combined immunotherapy plus or minus stereotactic body radiation [110]. Among the 50 patients treated, 100% of the previously immunotherapy-naive patients responded (22/22), including nine (41%) complete responses. Of the patients who had previously had immunotherapy exposure, 31% (8/26 patients) had an objective response. The additional stereotyctic body radiation therapy did not improve the efficacy of combined nivolumab and ipilimumab.

On the basis of these promising results, the combination of nivolumab plus ipilimumab represents a good second-line therapeutic option for advanced MCC patients after failure of PD-1/PD-L1 fist-line treatment; however in the absence of an FDA and EMA approval status.

3.3 Novel Immunotherapy Strategies

Several strategies have been developed to induce and enhance the immunogenicity of skin tumors, mainly melanoma. Some of those have also been investigated in MCC.

Single case reports and small case series document the successful use of oncolytic virus therapy with talimogene laherparepvec (T-VEC), either as monotherapy or in combination with PD-1/PD-L1 immune checkpoint inhibiting antibodies, in advanced MCC patients [111, 112]. T-VEC is administered intratumorally and is intended to increase the immunogenicity of the treated tumors through enhanced antigen presentation and thus tumor cell recognition. In the largest reported case series of four patients, complete remission of MCC tumors was achieved in all four cases under T-VEC treatment [111]. However, prospective studies evaluating T-VEC for MCC are currently lacking. T-VEC has EMA approval only for metastatic melanoma; its use in MCC has to be considered as off-label use.

A similar approach is used in the combination of the oncolytic vaccine vusolimogene oderparepvec (RP1) plus nivolumab, which has been investigated in PD-1/PD-L1-refractory melanoma as well as non-melanoma skin cancer within the phase-2 trial IGNYTE (NCT03767348). The non-melanoma skin cancer cohort includes MCC, and the first encouraging results have been reported. Among 12 patients with nonmelanoma skin cancer resistant to PD-1/PD-L1 immunotherapy, the objective response rate for RP1 plus nivolumab was 33.3%; these responses were observed in patients with cutaneous squamous cell carcinoma, MCC, and angiosarcoma. In MCC patients treated within the same trial in first-line (immunotherapy naive), three of four patients (75%) responded to the combination of RP1 plus nivolumab [113].

In initial attempts at utilizing adoptive T cell transfer (ACT) therapy, tumor-infiltrating lymphocytes (TILs) specific to LT were expanded in vitro and reintroduced into the patient alongside high-dose IL-2. This approach led to the regression of some of the metastases in a patient with advanced Merkel cell carcinoma (MCC) [114]. In a subsequent phase I/II trial exploring this approach as part of a multimodal strategy, together with upregulation of HLA expression of the MCC cells (via intratumoral injection of IFNβ or radiation therapy) and PD-L1 inhibition, all four included patients achieved an objective response [114].

Concurrently, a significant advancement in ACT involves genetically modifying autologous T cells ex vivo by introducing T cell receptors (TCR) or chimeric antigen receptors (CAR) specific to tumor antigens. Despite CAR-T cell therapies gaining approval for hematological malignancies, their effectiveness in treating solid tumors remains limited. The ATTAC-MCC phase I/II study is investigating the safety and efficacy of engineered MCPyV-directed TCR T cells in cases of immune checkpoint inhibitor (ICI)-refractory disease (NCT03747484).

Natural killer cells, being innate immune cells with intrinsic properties, are considered ideal candidates for cellular immunotherapy in cancers that often exhibit a lack of MHC class I expression. The QUILT-3.009 phase 2 trial (registered under NCT02465957, NCT03167164) has explored the use of allogeneic activated NK cell (aNK) therapy in the treatment of patients with Merkel cell carcinoma (MCC). Clinical benefits were observed in this trial when combining aNK cell therapy with ALT-803, an IL-15 superagonist, resulting in two objective responses among 7 patients, with no reported safety concerns. Subsequently, the QUILT-3.055 trial is extending this approach by combining it with avelumab (registered under NCT03228667) [115].

A peptide receptor radionuclide therapy (PRRT) targeting somatostatin has been reported as effective in individual cases and small case series when somatostatin receptor (SSTR) expression was detected on tumors and metastases [116]. In these cases, PRRT was administered either alone or in combination with chemo- or immunotherapy. The detection of somatostatin receptors can be performed through SSTR PET/CT or SSTR PET/MRI. In a meta-analysis of somatostatin PRRT in metastatic neuroendocrine tumors across 13 studies, a pooled response rate of 28% was observed [117]. A retrospective case series of 19 patients with MCC treated with somatostatin PRRT demonstrated disease control in 43% of cases [118].

Most interestingly, in a recent case report a patient whose MCC progressed on multiple lines of ICI responded well to combined therapy with ipilimumab plus nivolumab ICI and somatostatin PRRT [119]. Specifically, the patient was resistant to first-line avelumab and acquired resistance to ipilimumab/nivolumab. After confirmation of SSTR

expression, ipilimumab/nivolumab treatment was combined with two cycles of PRRT Restaging after 3 months demonstrated an exceptional response. This case demonstrates the feasibility of combined treatment with ICI and PRRT as an option for MCC patients progressing under ICI. To confirm the additive value of this combination, the GoTHAM trial (NCT04261855) was recently launched. The three-armed design compares avelumab, avelumab plus radiotherapy, or avelumab plus PRRT and stratifies patients by SSTR expression.

3.4 Neoadjuvant and Adjuvant Immunotherapy

Neoadjuvant therapy is given before surgery to help shrink a tumor or stop the disease from spreading, making it less invasive. On the other hand, adjuvant therapy is delivered after surgery to kill any remaining cancer cells in the patient. Both types of therapy aim to increase the success of the primary treatment and decrease the risk of cancer recurrence.

Even after complete resection and radiation of locoregional disease, MCCs' relapse rates are high. Given the outstanding effect of immunotherapy in the treatment of advanced MCC not-amendable to site-directed therapies, ICIs (ipilimumab, nivolumab, avelumab) are currently also being investigated in neoadjuvant and adjuvant settings. While initial reports did not find any therapeutic effects of ipilimumab monotherapy in the adjuvant use, the report of a nonrandomized neo-adjuvant trial and interim results of a prospective randomized trial indicate a benefit of the PD-1 inhibitor nivolumab regarding recurrence-free survival (RFS).

In a subgroup of the CheckMate 358 trial described above, 39 patients with MCC (AJCC Stage IIA-IV) were treated with two doses of nivolumab in a neo-adjuvant setting [120]. Of the 36 patients who underwent surgical intervention 4 weeks after therapy start, 17 (47%) achieved a complete pathological response (pCR). Among 33 patients who underwent radiological tumor evaluation before surgery, 18 (55%) showed a tumor reduction of 30% or more. Again, the clinical response was independent of MCPyV, PD-L1, or tumor mutational burden status of the respective tumors. After a median follow-up of 20.3 months, the median RFS and overall survival (OS) had not been reached; however, RFS significantly correlated with pCR and radiological response at the time of surgery. No patient with a pCR experienced tumor recurrence during the follow-up period. Three ongoing clinical trials addressing the effect of different ICI therapies, i.e., cemiplimab (NCT04975152), pembrolizumab (NCT05496036), and the combination of nivolumab and relatlimab (NCT06151236), in the neoadjuvant setting. Unfortunately, none of these prospective trials is randomized or exceeds number of patients treated in the subgroup of the CheckMate 358 trial.

In a phase 2 multicenter trial (ADMEC-O, registered under NCT02196961), patients with MCC with no evidence of disease after complete surgical resection of lesions, regardless of stage but with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, were randomly assigned in a 2:1 ratio at 20 academic medical centers in Germany and the Netherlands. The assigned treatments were either nivolumab 480 mg every 4 weeks for a duration of 1 year or observation. Stratification was based on stage (AJCC stages 1–2 versus stages 3–4), age (< 65 versus ≥ 65 years), and sex. The primary endpoint was landmark RFS at 12 and 24 months, evaluated in the intention-to-treat populations. Secondary endpoints included overall survival and safety assessments [121].

Over a span of 5 years, 179 patients were enrolled, with 65% in stages 3–4, 68% aged ≥ 65 years, and 62% being male. Stratification factors (stage, age, and sex) were evenly distributed between the nivolumab and observation groups; however, adjuvant radiotherapy was more prevalent in the control group. The interim analysis was conducted 1 year after the recruitment of the last patient. With a median follow-up of 2 years, the hazard ratio for RFS between the groups was 0.58, favoring the nivolumab group. The RFS rates in the nivolumab group were 85% at 12 months and 84% at 24 months, while in the observation group, they were 77% at 12 months and 73% at 24 months. Of note, previous adjuvant or concurrent adjuvant radiation was permitted in both groups, but more patients received it in the control group than those in the nivolumab group. Because postoperative radiotherapy is recommended in most guidelines as an effective adjuvant treatment for this radiosensitive cancer, this fact might have disadvantaged the nivolumab group. Overall survival events rates, with ten events in the active treatment group and six events in the half-the-size observation group, are not mature enough to draw conclusions [121]. Most patients allocated nivolumab completed the 1-year course of treatment. Nonetheless, nivolumab-related adverse events—most commonly, pruritus, fatigue, and serum lipase elevations—occurred in 74% (grade 3–4 events in 20%) and led to treatment discontinuation in 15%. Notably, there were no reported treatment-related deaths.

It is crucial to acknowledge that owing to the rarity of MCC, ADMEC-O is not a conventional superiority trial; rather, it is a randomized, exploratory phase-2 trial. This design was selected to address the challenge of lacking a valid reference for efficacy. Consequently, the trial did not seek statistical power to identify a significant difference, and the hazard ratios reported stem from a post-hoc analysis. The data from ADMEC-O indicate that adjuvant nivolumab is safe, well tolerated, and has promising activity in patients with MCC. Mature survival data are awaited ($> 90\%$ of patients in each group were alive at 2 years), as are results from the ongoing phase III trials of adjuvant avelumab

(NCT04291885 and NCT03271372) and pembrolizumab (NCT03712605).

4 Conclusions

Merkel cell carcinoma is characterized as an immunogenic tumor, showcasing a notable immune responsiveness. The aggressive clinical progression of the disease, however, signals the presence of immune escape mechanisms, emphasizing the complexity of tackling its immune interactions.

Clinical evidence underscores the potential of immunotherapy to enhance immune responses for effective disease control. However, the adaptive plasticity of MCC poses a challenge, as this—as already known from cytotoxic therapy approaches—enables MCC to develop early resistance to immunotherapies. Consequently, current research efforts are focused on exploring either combination therapies to counteract resistance and early treatment approaches, including adjuvant and neoadjuvant strategies.

The rarity of MCC poses a hurdle in conducting classical clinical trials that generate substantial evidence. Acknowledging this limitation, there is a growing recognition of the necessity for novel trial designs that can accommodate the unique characteristics of MCC [122]. Additionally, the use of registry and real-world data trials can collect data on patients with rare molecular alterations and outcome data of various treatments, contributing to the development of evidence for these rare conditions. This shift aims to ensure the development of more effective therapeutic strategies, given the intricacies associated with the immunogenic and highly adaptive nature of MCC.

Declarations

Funding Open Access funding enabled and organized by Projekt DEAL. Funding was provided by BMBF - DKTK (ED03).

Conflict of interest JCB is receiving speaker's bureau honoraria from Amgen, Pfizer, and Sanofi and is a paid consultant/advisory board member/data and safety monitoring board (DSMB) member for Almirall, Boehringer Ingelheim, ICON, Merck, Pfizer, and Sanofi. His group receives research grants from Merck, HTG, IQVIA, and Alcedis. SU declares research support from Bristol Myers Squibb and Merck; speaker and advisory board honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, and Novartis; and meeting and travel support from Almirall, Bristol-Myers Squibb, IGEA Clinical Biophysics, Merck Sharp & Dohme, Novartis, Pierre Fabre, and Sun Pharma. AS and DS declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethics approval, consent to participate, consent for publication Not applicable.

Availability of data and material No datasets were generated or analyzed for this review article.

Code availability Not

Author contributions All authors were involved in the literature research, writing the initial draft and the revision process. All authors read and approved the final manuscript.

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