

Merkel cell carcinoma immunotherapy: key questions in the era of immune checkpoint blockade

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ABSTRACT

Merkel cell carcinoma (MCC) exemplifies the paradigm of immunogenic tumors that nonetheless develop sophisticated immune evasion mechanisms. This is in line with the observation that MCC exhibits remarkable susceptibility to immune checkpoint inhibitors (ICIs), with responses in approximately half of patients with advanced disease in the first-line setting. However, 40–50% of patients show primary ICI resistance, while 20–30% of patients develop acquired ICI resistance on initial disease control. Still, the advent of ICI therapy represents a revolutionary rather than evolutionary advance in MCC management, fundamentally transforming outcomes from the dismal prognosis associated with conventional chemotherapy to durable responses extending substantially beyond 2 years. Still, important questions remain: (1) Is programmed cell death protein-1 or programmed death-ligand 1 inhibition more effective? (2) How long should ICI treatment continue? (3) What is the best choice of salvage therapy for patients with primary or acquired ICI resistance? (4) Which combination regimens can increase the share of patients benefiting from ICI? (5) Which patient/tumor characteristics predict response and its duration? Finally, (6) which timing of ICI therapy, that is, the neoadjuvant, adjuvant or therapeutic setting, offers the optimal overall outcomes for patients with MCC? A number of recent studies provide initial, but unfortunately not yet definitive answers.

IMMUNOGENICITY OF MCC

The immunogenic nature of Merkel cell carcinoma (MCC) stems from its dual etiology: three-quarters of cases constitutively express the Merkel cell polyomavirus-encoded transforming antigens (ie, small and large T antigen) that function as potent tumor rejection antigens, while the remaining quarter exhibit high mutational burden from ultraviolet-induced DNA damage.¹ Despite this immunogenicity, clinically evident tumors obviously have escaped immune surveillance. Indeed, MCC tumors orchestrate complex immune escape mechanisms including tumor-intrinsic factors such as downregulation of antigen processing machinery and consequently loss of major histocompatibility complex (MHC) class I

expression, microenvironmental factors, for example, myeloid infiltration and cancer-associated fibroblast polarization, alongside tumor-extrinsic factors including immune senescence in elderly patients and hematologic malignancies, particularly B-cell chronic lymphocytic leukemia (B-CLL).¹

IMMUNOTHERAPY OF MCC

The immunogenicity aligns with the therapeutic landscape of MCC, where immune checkpoint inhibitors (ICIs) have fundamentally transformed treatment paradigms yet revealed the heterogeneous nature of immunotherapeutic responses.¹ The remarkable susceptibility of MCC to ICI therapy, demonstrated consistently across multiple clinical trials, represents one of the most compelling success stories in cancer immunotherapy, with objective response rates (ORR) ranging from approximately 50–60% in the first-line setting. However, this therapeutic triumph is tempered by the sobering reality that a substantial proportion of patients—approximately half—fail to derive meaningful clinical benefit from these agents. Moreover, among those who do achieve initial responses, a concerning subset will inevitably progress, developing acquired resistance that represents a fundamental shift in the tumor-immune ecosystem. Notably, patients with primary ICI-resistant disease face substantially poorer outcomes: Ch'en *et al* analyzed 106 patients with ICI-resistant MCC receiving salvage therapies, revealing markedly superior outcomes for acquired versus primary resistance patterns.² Median progression-free survival demonstrated more than twofold improvement in acquired resistance (9.5 vs 4.7 months; $p=0.006$). Notably, 20% of patients achieved 3-year survival through sequential, individualized multidisciplinary approaches. Nevertheless, the durability of response in those who benefit from ICI therapy is remarkable, with a 3-year progression-free survival

rate of over 70%, especially when compared with the duration of response in the chemotherapy era, which rarely lasted longer than 3 months.³

PD-1 VERSUS PD-L1 TARGETING: MECHANISTIC AND CLINICAL CONSIDERATIONS

The question of optimal checkpoint target selection remains clinically relevant given the availability of both programmed cell death protein-1 (PD-1) inhibitors (pembrolizumab, nivolumab, retifanlimab) and programmed death-ligand 1 (PD-L1) inhibitors (avelumab). Meta-analytical data across different tumor types as well as cross-trial comparisons in MCC suggest a potential advantage of PD-1 blockade, which can disrupt both PD-L1 and PD-L2 signaling pathways, whereas PD-L1 inhibitors target only the PD-1/PD-L1 interaction.⁴ However, given the rarity of MCC, most available clinical trials are either non-randomized or statistically underpowered. Thus, even small imbalances in patient characteristics could substantially influence outcomes, warranting cautious interpretation. With this in mind, one can also identify trials reporting comparable—or even numerically higher—efficacy of avelumab (anti-PD-L1; ORR 62%) relative to PD-1 inhibitors such as pembrolizumab (ORR 56%) and retifanlimab (ORR 52%), with similar response durability across agents (76–80% of responders maintaining benefit beyond 12 months).^{1,5} Thus, such cross-trial comparisons are inherently prone to selection bias, which may contribute to the apparent parity or superiority among agents. Furthermore, as observed in prior meta-analyses of chemotherapy in MCC, patient overlap across publications—particularly in real-world datasets—can also confound aggregated analyses.³

BEYOND PD-1/PD-L1 MONOTHERAPY: INTEGRATION OF CTLA-4 BLOCKADE, INTRATUMORAL IMMUNOTHERAPY, AND RADIOTHERAPY

The combination of cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and PD-1 inhibitors represents the most extensively studied dual checkpoint blockade strategy. Initial reports indicated promising results with ipilimumab plus nivolumab, which achieved an ORR of 100% in ICI-naïve patients (n=24). It should be noted half of the patients also received radiotherapy.⁶ This remarkable response rate would therefore need to be validated in larger cohorts, which was apparently not possible in more recent reports.⁷

For patients with anti-PD-(L)1 refractory disease, combination CTLA-4 blockade demonstrates more modest but clinically meaningful benefit. Retrospective case series reported ORRs of 31–32% with ipilimumab plus nivolumab in this challenging population, with complete responses in 10–15% of patients and response durations ranging from 2 to >43 months.⁸ However, toxicity remains substantial, with grade ≥3

immune-related adverse events occurring in 29–36% of patients.

Intratumoral approaches offer the potential to activate local immune responses while minimizing systemic toxicity. For example, the TLR4 agonist G100 demonstrated the ability of such an approach to transform the MCC tumor microenvironment from immunologically ‘cold’ to ‘hot’. In a first-in-human study, intratumoral G100 achieved pathologic complete response (pCR) in the neoadjuvant setting and sustained partial responses lasting >33 months in metastatic patients.⁹ Emerging intratumoral approaches include stimulator of interferone genes (STING) agonists, which can work indirectly through immune and stromal cells in the tumor microenvironment.¹⁰

The combination of radiotherapy with immunotherapy leverages the immunostimulatory effects of radiation to enhance checkpoint inhibitor efficacy by, for example, increased tumor antigen presentation, upregulation of MHC-I expression, activation of the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, and modulation of the tumor microenvironment. Anecdotal clinical evidence supports this approach in MCC. Case reports demonstrate complete responses with concurrent avelumab and radiotherapy in patients with widespread metastatic disease. A retrospective analysis of patients with limited progression on immunotherapy found that adding radiotherapy achieved disease control rates of 60% at 6 and 12 months post-radiation.¹¹

OPTIMAL TIMING: NEOADJUVANT, ADJUVANT, AND THERAPEUTIC APPLICATIONS

Neoadjuvant immunotherapy offers some advantages, including tumor downstaging for more conservative surgical approaches and the opportunity to assess pathologic (p) response as an early indicator of long-term benefit. The CheckMate 358 study established the feasibility of neoadjuvant nivolumab, with 47% of patients achieving pCR after just 4 weeks of treatment. Importantly, pCR significantly correlated with prolonged recurrence-free survival, with no patient achieving pCR experiencing tumor relapse during extended follow-up. Real-world evidence demonstrates that neoadjuvant immunotherapy in stage III MCC provides improved overall survival compared with surgery alone, with 5-year survival rates of 57% versus 44%. The pCR rate for primary tumors reaches 45.2%, with nodal pCR rates of 17.9% among patients undergoing lymph node dissection.¹²

The role of adjuvant immunotherapy in completely resected MCC continues to evolve. The ADMEC-O study randomized 179 patients with completely resected stage I–III disease to nivolumab versus observation.¹³ Nivolumab improved disease-free survival at 12 and 24 months (85% vs 77% and 84% vs 73%; HR 0.58) with manageable toxicity, establishing the first

prospective signal for adjuvant ICI in MCC, which was recently confirmed in the EA6174-STAMP study testing pembrolizumab (83% vs 71% and 73% vs 66%; HR 0.80) presented at ESMO 2025 (LBA56) by Janice Mehnert.

However, extrapolating from experience with other cancers, neoadjuvant or adjuvant ICIs may not necessarily translate into improved disease-specific or overall survival, particularly given the substantial efficacy of ICIs in advanced-stage MCC.¹⁴ Indeed, pathologic pCR may be a surrogate marker for tumors exhibiting high immunological sensitivity to ICIs, potentially identifying the same patient subset that would demonstrate robust responses to immunotherapy in the more advanced setting. Therefore, the clinical benefits of ICI therapy in early-stage disease must be carefully weighed against the cumulative toxicity burden from combined immunotherapeutic, surgical, and radiotherapeutic interventions (the latter potentially deescalated by neoadjuvant ICI), the duration and intensity of treatment protocols, as well as the substantial competing risk of mortality from non-MCC causes—a particularly relevant consideration given the predominantly elderly demographics and high comorbidity burden characteristic of the patient with MCC population.

TREATMENT DURATION: BALANCING EFFICACY AND TOXICITY

The optimal duration of immunotherapy in MCC remains a critical unresolved question with significant implications for patient quality of life, healthcare costs, and long-term outcomes. Current US Food and Drug Administration approvals specify treatment ‘until disease progression, unacceptable toxicity, or up to 24 months’ for most agents, but this duration lacks robust evidence-based justification.

Recent real-world evidence provides important insights into post-discontinuation outcomes.¹⁵ In a multicenter analysis of 105 patients with advanced MCC who achieved objective responses to first-line anti-PD-(L)1 therapy, 58 patients (55%) discontinued treatment, with median treatment duration of 12 months. Among discontinuing patients, 47% experienced disease progression at a median of 11.2 months post-cessation. Critically, the depth of initial response significantly influenced post-discontinuation outcomes. Patients achieving complete response before discontinuation had substantially lower progression rates (24%) compared with those discontinuing with partial response (67%). Notably, in patients achieving a positron emission tomography/computed tomography (PET/CT)-confirmed CR, discontinuation of avelumab after 1 year was associated with durable disease control, with 88% remaining recurrence-free at 12 months and median recurrence-free survival (RFS) not reached.¹⁶ These findings align with prior evidence of differential recurrence

risk after ICI cessation and support individualizing treatment duration based on response depth rather than fixed time limits.¹⁷

AGE-RELATED CONSIDERATIONS AND IMMUNE SENESENCE

The intersection of aging and cancer immunotherapy presents particular challenges in MCC, given the disease’s predilection for elderly patients (median age 69–75 years). Immune senescence, characterized by declining immune competence and accumulation of dysfunctional T cells, may impact both treatment efficacy and optimal duration. Paradoxically, while aged patients exhibit baseline immune impairment including reduced naïve T-cell pools and increased checkpoint molecule expression, clinical outcomes with ICIs remain comparable to younger patients.¹ However, aged patients demonstrate unique response patterns, including larger cytotoxic T-cell expansions in responders and reduced regulatory T-cell dynamics, suggesting that age-tailored approaches to treatment duration may be warranted.

CONCLUSIONS AND FUTURE PERSPECTIVES

The management of MCC has been transformed by immunotherapy, yet several critical questions remain. Do PD-1 and PD-L1 inhibitors demonstrate comparable efficacy as monotherapy? Do combination approaches, particularly CTLA-4 blockade for refractory disease and radiation therapy for patients with oligometastatic disease, offer promising strategies to overcome resistance?

The timing of immunotherapy implementation should prioritize early initiation in the first-line therapeutic setting, with growing evidence supporting neoadjuvant approaches in resectable nodal disease. Treatment duration decisions require individualization based on response depth, patient age, and comorbidities, moving away from arbitrary time limits toward biomarker-guided approaches.

The unique challenges posed by immune senescence in the elderly MCC population, the complex interactions with hematologic malignancies like B-CLL, and the high plasticity contributing to acquired resistance underscore the need for combination strategies and novel therapeutic approaches. The revolution initiated by immune checkpoint blockade in MCC continues to evolve, demanding continued research into optimal sequencing, combination strategies, and personalized treatment approaches to maximize the substantial therapeutic potential of immunotherapy in this challenging disease.

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