Emerging Treatment Strategies in Merkel Cell Carcinoma: A Literature Review Comparing Novel Immunotherapy Approaches With Conventional Treatment Paradigms

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Introduction

- Merkel cell carcinoma (MCC) is an aggressive neuroendocrine malignancy characterized by high rates of local recurrence, early nodal involvement, and significant disease-specific mortality.
- Historically, treatment has relied on multimodal therapy including surgical excision, radiation therapy (RT), and cytotoxic chemotherapy.
- While surgery and RT remain central to locoregional control, systemic therapy paradigms have evolved substantially with the introduction of immune checkpoint inhibitors (ICIs), prompting reassessment of treatment durability and long-term outcomes compared with conventional systemic therapies.

This investigation reviewed emerging evidence on treatment strategies for MCC, focusing on the efficacy and durability of novel immunotherapies compared with conventional systemic treatments, and evaluating their role within modern multimodal management.

Methods

- A systematic literature review was conducted, incorporating searches of PubMed, ScienceDirect, and the Cochrane Central Register of Controlled Trials, evaluating outcomes associated with surgery, RT, chemotherapy, and immunotherapy in MCC.
- Inclusion criteria prioritized clinical trials, meta-analyses, and large population-based studies published between 2005 and 2026.
- The following markers of oncologic control were searched for:
  - Overall response rate (ORR).
  - Median progression-free survival (PFS).
  - Overall survival (OS) at 3 years.
  - Pathologic complete response (pCR).
  - Durability.
  - Presence of a survival plateau.

Discussion

This literature review highlights a shift in the management of MCC towards immunotherapy. Although cytotoxic chemotherapy can produce high initial response rates, responses are often short-lived. In contrast, PD-1/PD-L1 inhibitors demonstrate more durable responses and evidence of prolonged disease control.

In localized disease, surgery and RT remain the cornerstone of treatment by improving local-regional control and reducing recurrence risk. However, their impact on overall survival is less consistently defined compared to systemic therapies in advanced disease. However, responses to immunotherapy may be variable and reliable biomarkers are still lacking. The rarity of MCC also limits study size and consistency across trials. Overall, current evidence favors immunotherapy in advanced disease, with ongoing work needed to better devise optimized treatment strategies.

Results

Recovery Markers	Surgical Excision ± Radiation Therapy	Cytotoxic Chemotherapy	**CheckMate 358:** Neoadjuvant Nivolumab (Stage IIA–IV resectable).	**ADMEC-O:** Adjuvant Nivolumab (completely resected, any stage).	**POD1UM-201:** Retifanlimab in chemotherapy-naive patients with recurrent locally advanced or metastatic disease.	**KEYNOTE-017:** Pembrolizumab in chemotherapy-naive patients with advanced/metastatic disease.	**JAVELIN Merkel 200:** Avelumab in the second-line setting.
Overall Survival at 3 years	Mohs Surgery – RT: 87.4% Excision – RT: 84.8% Excision + adjuvant RT: 70-80%	No durable improvement in long-term survival demonstrated.	88.9% with pCR, 70.0% without pCR.	N/A	63%	N/A	32%
Median Progression Free Survival	Not a standard reported endpoint.	2–4 months	Median PFS/RFS not reached. At 24 months, recurrence-free survival was still 68.5%.	Not yet reached at 24 months.	16.0 months	16.8 months	2.7 months
Overall Response Rate	Not a standard reported endpoint.	25–60%	54.5%	No measurable disease as this study is post-resection.	54.5%	56% (24% complete response, 32% partial response).	33.0%
Pathologic Complete Response	Not a standard reported endpoint.	Not a standard endpoint.	47.2%	N/A	N/A	N/A	N/A
Durability	Greater durability for local disease control after resection, particularly with adjuvant RT.	**Not Durable**: 95% of patients experiencing progression within 1 year.	**Durable**: 0 patients with a pCR experienced tumor relapse at 19.3 months median follow-up. 24-month RFS of 68.5%.	**Durable**: DFS benefit maintained through 2 years (84% DFS).	**Durable**: 45.5% response durability at 24 months. Median duration of response was not reached.	**Durable**: 79.1% response durability at 24 months. Median duration of response was not reached.	**Durable**: Median DOR: 40.5 months. 67% response durability at 24 months.
Survival Plateau	No	No	Yes	Yes	Yes	Yes	Yes

Conclusion

Surgery with adjuvant RT remains the primary treatment for localized MCC, providing effective local-regional control. In advanced disease, immune checkpoint inhibitors offer more durable responses than chemotherapy, which is limited by short-lived benefit despite rapid tumor reduction. Ongoing efforts should focus on improving patient selection and optimizing treatment strategies to enhance durability of response.

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