Review

Immunotherapy in Merkel Cell Carcinoma of the Skin: A 2025 Comprehensive Review

Patricia Tai *, Omar Alqaisi, Suhair Al-Ghabeesh, Lorent Sijarina, Edward Yu, Aoife Jones Thachuthara, Avi Assouline, Osama Souied, Kimberley Hagel, Kurian Joseph

Posted Date: 25 July 2025

doi: 10.20944/preprints202507.2063.v1

Keywords: Merkel cell carcinoma; skin cancer; immunotherapy; systematic review; PRISMA review; systemic therapy; cell-free DNA; database; recommendations; clinical trials

 doi:10.20944/preprints202507.2063.v1

Review

Immunotherapy in Merkel Cell Carcinoma of the Skin: A 2025 Comprehensive Review

Patricia Tai [1,*], Omar Alqaisi [2], Suhair Al-Ghabeesh [2], Lorent Sijarina [3], Edward Yu [4], Aoife Jones Thachuthara [5], Avi Assouline [6], Osama Souied [1], Kimberley Hagel [1] and Kurian Joseph [7]

[1] University of Saskatchewan, Canada
[2] Department of Nursing, Al-Zaytoonah University, Jordan
[3] Faculty of Medicine, University of Prishtina, Kosovo
[4] Faculty of Medicine, University of Prishtina, Kosovo
[5] Department of Medical Oncology, Cork University, Ireland
[6] Department of Radiation Oncology, Collège de Médecine des Hôpitaux de Paris, France
[7] Department of Radiation Oncology, University of Alberta, Canada
* Correspondence: ptai2@yahoo.com

Simple Summary

Merkel cell carcinoma is a rare and aggressive form of skin cancer. While immunotherapy has transformed its management, published data remain limited. Therefore, we conducted this review to evaluate the current landscape, with the ultimate goal of improving patient care. The cancer is known to spread to lymph nodes and distant organs. We searched four databases for publications on immunotherapy, which may be administered either before or after surgery. In cases of unresectable or advanced disease, immunotherapy can be used as a standalone treatment. Our summarized findings highlight the need for further clinical research to guide future therapeutic approaches.

Abstract

Purpose: Merkel cell carcinoma (MCC) is a rare and aggressive form of skin cancer. Although immunotherapy has transformed MCC management, published data remain limited. This comprehensive review evaluates current evidence on immunotherapy in MCC. Methods: Peer-reviewed articles published between 2000 and 2024 were manually searched in four databases: Scopus, ScienceDirect, PubMed and MEDLINE, using the keywords "Merkel cell carcinoma" AND "immunotherapy". The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology was employed. Results: Immunotherapy can be given in different settings: (A) *Neoadjuvant*: The CheckMate 358 trial reported a 54.5% response rate among 33 radiologically evaluable patients treated with nivolumab, each showing over 30% tumor reduction. (B) *Adjuvant*: (1) The ADMEC-O phase II trial demonstrated improved disease-free survival with adjuvant nivolumab. (2) The ADAM phase III trial evaluates adjuvant avelumab in node-positive patients post-surgery/radiation, with common side effects including nausea, fatigue, and itching. (3) STAMP, a phase III trial, investigates pembrolizumab in stage I–III MCC. Both ADAM and STAMP have completed accrual, pending results. (C) *Primary therapy*: KEYNOTE-017 and JAVELIN trials reported a 60% overall response rate and ~40% 3-year progression-free survival with first-line pembrolizumab or avelumab. Both agents also show promise as salvage therapies. Conclusion: Immunotherapy demonstrates encouraging outcomes in MCC across various treatment stages. Continued research is essential to optimize timing, integrate with multimodal therapies, and address resistance mechanisms such as intra-tumoral STING activation and tumor-associated macrophages.

 doi:10.20944/preprints202507.2063.v1

Keywords: Merkel cell carcinoma; skin cancer; immunotherapy; systematic review; PRISMA review; systemic therapy; cell-free DNA; database; recommendations; clinical trials

1. Introduction

Merkel cell carcinoma (MCC) is a rare but highly aggressive neuroendocrine skin cancer, often associated with Merkel cell polyomavirus (MCPyV) or ultraviolet-induced mutations [1]. Despite its low incidence, MCC carries a disproportionately high mortality rate, with five-year survival estimates ranging from 30%–60% depending on stage and treatment modality.

Historically, treatment options were limited to surgery and radiation, with chemotherapy offering modest and short-lived benefits [2]. However, the emergence of immune checkpoint inhibitors (ICIs) has dramatically reshaped the therapeutic landscape..

Following the American Food and Drug Administration (FDA) approval in 2017, ICIs are now employed in both routine clinical practice and ongoing clinical trials [3,4]. The first ICI approved for MCC was avelumab (Bavencio), which received accelerated approval in March 2017. This milestone marked the first FDA-sanctioned treatment specifically for metastatic MCC [5,6].

Programmed Death-Ligand 1 (PD-L1) is a protein that plays a key role in regulating immune responses. PD-L1 binds to its receptor PD-1 on T cells, effectively putting the brakes on the immune system and allowing some cancer cells to evade detection [7]. Immunotherapy, particularly agents targeting the PD-1/PD-L1 axis, has demonstrated durable responses in advanced MCC, prompting investigations into its role across the disease continuum—from neoadjuvant and adjuvant settings to primary and salvage therapy [8]. Yet, despite promising clinical outcomes, published data remain limited, and questions persist regarding optimal timing, integration with other treatment modalitiies, patient selection and mechanisms of resistance [9].

This comprehensive review aims to synthesize current evidence scattered across the literature on immunotherapy in MCC, with a focus on key clinical trials, treatment strategies, and future directions. This work is unique for several reasons: (1) We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology, which, to our knowledge, has not previously been applied to MCC in the published literature. (2) As clinicians with direct experience managing this rare cancer, we provide expert recommendations to improve current treatment patterns. Our team compiled a robust database of 949 patients, including 303 who presented to our respective cancer centers in Canada, France, and Australia between March 1982 and February 2015 [10]. The remaining patients were drawn from individual patient data extracted from published case reports and series. (3) The most updated literature in 2025 and all major landmark studies are summarized to provide the best comprehensive bedside information for healthcare providers on MCC.

2. Methods

A comprehensive search was conducted across four databases: Scopus, ScienceDirect, PubMed, and MEDLINE (an acronym for Medical Literature Analysis and Retrieval System Online). The keywords “Merkel cell carcinoma” AND “immunotherapy” were used to identify peer-reviewed articles published between January 2000 and March 2024. Inclusion criteria encompassed clinical trials, observational studies, and meta-analyses evaluating immunotherapy in MCC. Exclusion criteria included non-English publications, case reports and studies lacking immunotherapy-specific outcomes. The data were extracted and evaluated by the first two coauthors (P.T. and O.A). Any disagreements were discussed with the intervention of a third researcher. The PRISMA methodology was employed. Data extraction focused on study design, patient population, treatment regimen, response rates, progression-free survival (PFS), overall survival (OS), and reported adverse events. Studies were categorized by treatment setting: neoadjuvant, adjuvant, and primary therapy.

 doi:10.20944/preprints202507.2063.v1

3. Results

The search and study selection process is summarized in the PRISMA flow diagram (Figure 1). A total of 350 records were identified from the databases: Scopus (N=120), PubMed, MEDLINE (N=140), and ScienceDirect (N=90). After removing 70 duplicate entries, 280 records remained for screening. Following a title and abstract review, 180 records were excluded based on irrelevance to the study objectives or failure to meet inclusion criteria. Then the full texts of 100 articles were assessed for eligibility. Of these, 80 were excluded due to reasons such as lacking clinical data, insufficient information on immunotherapy intervention, or inappropriate study design. Finally, twenty articles satisfied all requirements and are summarized in this review.

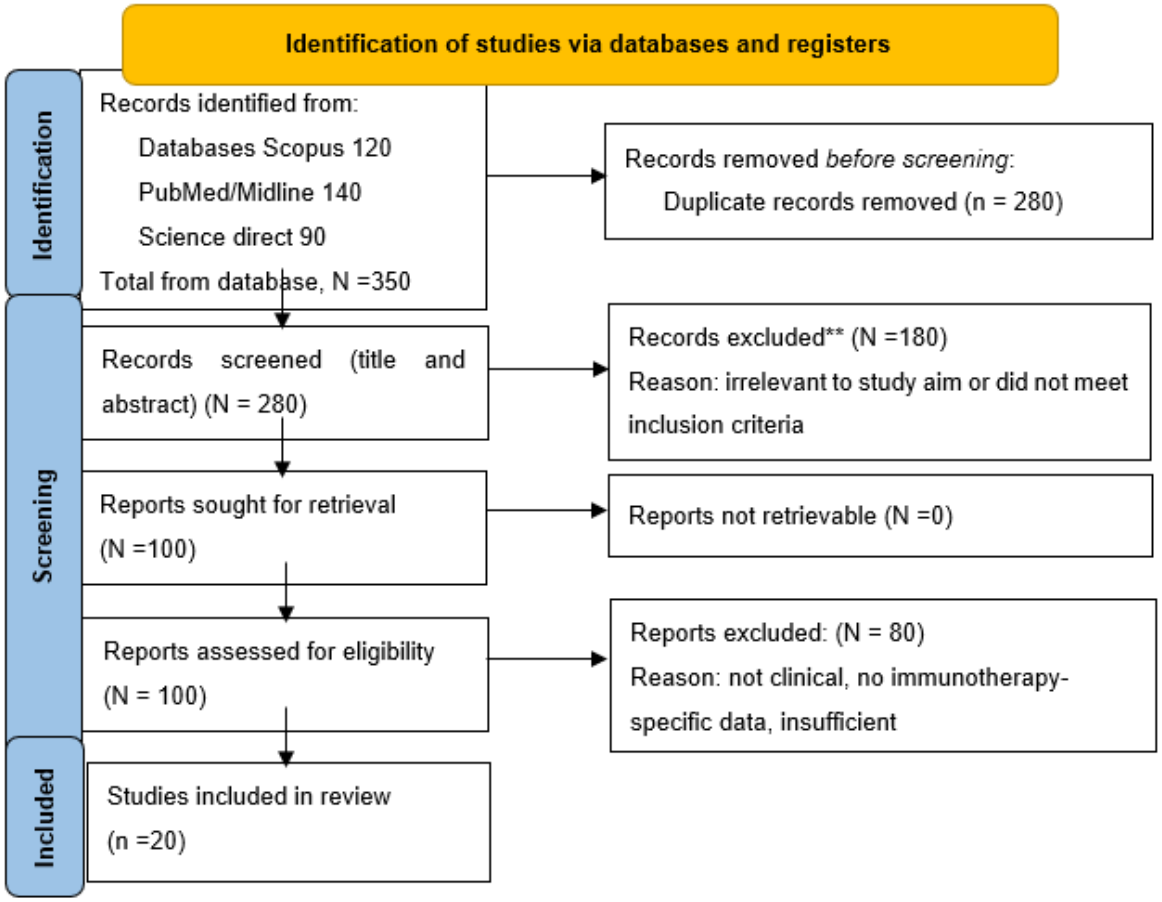

Figure 1. Flow diagram of comprehensive review with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology.

3.1. Neoadjuvant Immunotherapy

The rationale for short-course preoperative immuno-oncology (IO) therapy is that it may induce significant tumor regression, allowing for less extensive surgical resection and improving long-term outcomes. Moreover, neoadjuvant therapy can prime the immune system by exposing it to intact tumor antigens, thereby enhancing systemic anti-tumor immunity. It also serves as an early in vivo test of therapeutic sensitivity for individual patients. If the pathological response is suboptimal, alternative adjuvant treatments can be selected postoperatively.

The CheckMate 358 trial represents a landmark study in the neoadjuvant setting [11]. This phase I/II trial evaluated nivolumab, a PD-1 inhibitor, in patients with resectable MCC. Among 33 radiologically evaluable patients, 54.5% achieved tumor reductions exceeding 30%, with pathologic complete responses (pCR) observed in nearly half. In particular, neoadjuvant nivolumab was well tolerated, with no delays in planned surgery and minimal grade 3–4 adverse events.

 doi:10.20944/preprints202507.2063.v1

3.2. Adjuvant Immunotherapy

The ADMEC-O phase II trial investigated adjuvant nivolumab versus observation in patients with completely resected MCC [12]. Conducted across 20 academic centers in Germany and the Netherlands, the study enrolled 179 patients, randomized in a 2:1 ratio to receive nivolumab or observation. Nivolumab or OPDIVO® (480 mg) was administered intravenously every 4 weeks for up to 1 year (ie, a maximum of 13 doses). At 12 months, disease-free survival (DFS) was 85% in the nivolumab group versus 77% in the control group. Although the difference did not reach statistical significance, the trend favored immunotherapy. *However*, 42% of patients receiving nivolumab experienced grade 3–4 adverse events, including rash and endocrine dysfunction. These findings emphasize the need for careful patient selection and monitoring, especially in the adjuvant setting where patients may be asymptomatic.

The ADAM phase III trial evaluates adjuvant avelumab, a PD-L1 inhibitor, in node-positive MCC patients following surgery and radiation [13,14]. This study, also known as the MCC trial, is a multicenter, randomized, double-blinded, placebo-controlled trial involving patients with nodal metastases from MCC. Participants receive avelumab 10mg/kg intravenously over 1 hour every 15 days during Induction Phase 1 (days 0–120), every 30 days during Induction Phase 2 (days 121–240), and every 120 days during the Maintenance Phase, for up to a total of 720 days (approximately 2 years), provided there is no disease progression or unacceptable toxicity [15]. The trial has completed accrual. Preliminary data suggest improved DFS, with common side effects including nausea, fatigue, and pruritus. The trial aims to clarify whether adjuvant IO can reduce recurrence risk in high-risk patients.

The Surgically Treated Adjuvant Merkel cell carcinoma with Pembrolizumab (STAMP) trial of the Dana-Farber Cancer Institute, another phase III study, has also completed accrual [16]. It assesses the use of pembrolizumab in patients with stage I–III MCC after complete resection (Table 1). It is one of the largest and most comprehensive efforts to define the role of adjuvant immunotherapy in early-stage MCC, potentially expanding its role beyond advanced MCC. The STAMP trial (NCT03712605) is led by U.S. institutions and coordinated by the ECOG-ACRIN Cancer Research Group [17], it includes a broad network of participating centers across the United States, but does not list international sites. While results are pending, preliminary data suggest favorable tolerability and immune activation.

Table 1. Summary of the Surgically Treated Adjuvant Merkel cell carcinoma with Pembrolizumab (STAMP) study (NCT03712605).

Study start: January 2019
Primary completion: completed accrual
Study completion finish: 2026-2027 not publicly announced yet
Key Study Details

- *Primary Objective: Compare recurrence-free survival (RFS) and overall survival (OS) between pembrolizumab and standard observation.*
- *Design: phase III, randomized, placebo-controlled study*
- *Status: Closed to accrual; currently in follow-up phase*
- *Intervention: Arm A (Intervention): Pembrolizumab 200 mg intravenously every 21 days for up to 17 cycles (~1 year), with optional radiation therapy. Arm B (Control): Standard-of-care observation, with follow-up every 3 months for 1 year, then every 6 months for 5 years.*
- *Eligibility: Adults (≥18 years) with stage I–IIIb MCC. Must have undergone complete surgical resection within 16 weeks prior to randomization. Sentinel lymph node biopsy required for stage I patients. Accepts patients with unknown primary tumors if regional disease is present*
- *Secondary Objectives: Assess distant metastasis-free survival (DMFS), evaluate adverse events, analyze the impact of radiation therapy on outcomes*

Location and Sponsor: American centers. National Cancer Institute (NCI).

 doi:10.20944/preprints202507.2063.v1

The I-MAT (NCT04291885), a randomised, placebo-controlled, phase II trial of adjuvant Avelumab in patients with stage I-III Merkel cell carcinoma aiming to explore the efficacy of avelumab as adjuvant immunotherapy to prevent recurrence (Table 2) [18,19]. Its comparison with STAMP trial is listed in Table 3 for clarity.

Table 2. Summary of I-MAT (NCT04291885) study in Merkel cell carcinoma.

Study start: 2020-10-26
Primary completion: 2027-04-01
Study completion finish: 2028-04-01
Key Study Details

- *Primary Goal: to evaluate whether avelumab, an anti–PD-L1 immunotherapy, can improve recurrence-free survival (RFS) following definitive local treatment.*
- *Design: Quadruple-masked, parallel assignment*
- *Intervention: Avelumab 800 mg IV every 2 weeks for 6 months* vs. *placebo*
- *Participants: 122 enrolled*
- *Eligibility: Adults (≥18 years) with histologically confirmed stage I–III MCC (* clinical stage I; * pathological stage I with positive lymphovascular invasion (LVSI) only; * clinical or pathological stage II and III. No distant metastases on PET/CT*
- *Primary Endpoint: RFS at 24 months*
- *Secondary Endpoints: Overall survival, disease-specific survival, loco-regional failure-free survival, distant metastasis-free survival, treatment toxicity, and patient-reported quality of life (FACT-M)*

Locations: Multiple sites in Australia and New Zealand, including major centers like the Peter MacCallum Cancer Centre and Royal Adelaide Hospital.

Table 3. Comparison of the STAMP and I-MAT trials—two landmark studies evaluating adjuvant immunotherapy in early stages of Merkel cell carcinoma (MCC):.

Feature	***STAMP Trial (NCT03712605)***	***I-MAT Trial (NCT04291885)***
Sponsor	*ECOG-ACRIN / National Cancer Institute (USA)*	*Melanoma and Skin Cancer Trials (Australia/New Zealand)*
Start Year	*2019*	*2020*
Status	*Closed to accrual; in follow-up phase*	*Active, not recruiting*
Participants	*~280 patients*	*122 patients*
Eligibility	*Stage I–III MCC, completely resected*	*Stage I–III MCC, no distant metastases*
Intervention	*Pembrolizumab 200 mg IV every 21 days × 17 cycles (~1 year)*	*Avelumab 800 mg IV every 2 weeks × 6 months*
Control Arm	*Standard-of-care observation*	*Placebo*
Primary Endpoint	*Recurrence-free survival (RFS) and overall survival (OS)*	*Recurrence-free survival (RFS)*
Secondary Endpoints	*DMFS, toxicity, QoL, impact of radiation*	*OS, disease-specific survival, toxicity, QoL*
Geographic Scope	*United States only*	*Australia and New Zealand*
Radiation Therapy	*Optional, per standard of care*	*Allowed, based on clinical indication*
Follow-up Duration	*5 years*	*2 years*

 doi:10.20944/preprints202507.2063.v1

3.3. Primary Therapy and Salvage Use

As some patients with MCC are inoperable due to their performance status or disease stage is too advanced to be resected, use of immunotherapy has developed over the years and gained adequate experience to conduct large clinical trials [20,21].

The KEYNOTE-017 trial evaluated pembrolizumab as first-line therapy in advanced MCC [22]. Among treatment-naïve patients, the overall response rate (ORR) was 56%, with complete responses in 24%. At three years, progression-free survival (PFS) was approximately 40%, and overall survival (OS) exceeded 60%. These outcomes compare favorably to historical chemotherapy data, which typically yield short-lived responses and high toxicity.

The JAVELIN trial assessed avelumab in patients with metastatic MCC who had progressed after chemotherapy [23,24]. The ORR was 33%, with durable responses in a subset of patients. Avelumab was well tolerated, with manageable immune-related adverse events. Importantly, responses were observed in both virus-positive and virus-negative tumors, suggesting broad applicability. The latest update was in 2024 [25].

Both pembrolizumab and avelumab have demonstrated efficacy as salvage therapies in patients who relapse after initial treatment [26]. Retreatment or switching agents may be considered, although data are limited. Standard strategies nowadays include chemotherapy, radiotherapy, surgery and combination immunotherapy. Emerging strategies are intralesional STING agonists [], and therapeutic vaccines [], to overcome resistance. Extracted summary is shown in table 4.*

Table 4. Summary of immunotherapy studies in Merkel cell carcinoma.

References	Setting	Intervention	Outcome/results	Keypoints
Neoadjuvant				
Topalian SL (2020) [27]	Neoadjuvant	Nivolumab	50%-60%pCR in resectable MCC. Significant tumor downsizing	Neoadjuvant IO can achieve high rates of pCR, potentially simplify surgery and improve outcomes in localized disease
Bhatia S (2020) [28]	Neoadjuvant (cohort A)	Intratumoral 1L 12 plasmids DNA via electroporation (tavo-EP)	Objective response in injected and non-injected tumors. Demonstrates initial safety/efficacy in early-stage MCC	Intratumoral IO is a promising approach for inducing local and systemic anti-tumor responses, relevant for neoadjuvant strategies
Adjuvant				
Topalian SL (2023) [29]	Adjuvant	Nivolumab vs. observation	Improved DFS after complete resection of MCC, reduces recurrence.	Significantly improves DFS in resected MCC, establishing a new SOC for high-risk patients
Becker JC (2023) [12]	Adjuvant	Nivolumab vs. observation	Improved DFS after complete resection of MCC. OS results not immature yet	Support further adjuvant trials which are clinically feasible
Primary & salvage therapy in advMCC				
D'Angelo SP (2021)[30]	Primary/ salvage	Avelumab	Updated OS data >5 years: durable responses, with many long-term responders	Avelumab: long term survival benefits in mMCC, including previously treated patients
Nghiem PT (2016)[31]	Primary/ salvage	Pembrolizumab	56% ORR with durable responses. First evidence for PD-1 blockade in advMCC	Pembrolizumab is highly effective in advMCC, as new treatment option

 doi:10.20944/preprints202507.2063.v1

Gaiser MR (2018)[32]	Primary/ salvage	Avelumab (review)	~ 33% ORR in refractory disease, >60% in treatment-naïve cases; avelumab is safe	Avelumab is cornerstone of metastatic MCC treatment; effective in both 1L and refractory settings
D'Angelo SP (2021)[33]	Primary	Avelumab (1L)	4-year FU: sustained responses & long-term OS survival in 1L treatment of mMCC	Avelumab as 1L therapy: durable responses and prolonged survival
Kaufman HL (2018)[34]	Salvage	Avelumab (previously treated)	Updated efficacy results after ≥1 year FU up confirmed durable responses in chemo-refractory patients	Avelumab offers durable responses for progression after prior chemotherapy
Shirley M (2018)[35]	Primary/ salvage	Avelumab	Avelumab approval, efficacy & safety profile in metMCC	Reaffirms its role as the first approved IO drug for MCC, effective across treatment lines
D'Angelo SP (2020)[36]	Salvage	Avelumab (previously treated)	Long-term data and biomarker analyses: durable responses and insights into response predictors	Data supports avelumab benefits, with potential for bio marker-guided therapy in salvage settings
D'Angelo SP (2018)[37]	Primary	Avelumab (1L)	Interim analysis: ~ 62% ORR and manageable safety profile in 1L setting.	Avelumab is an effective and safe 1L option for metMCC
Nghiem P (2019)[38]	Primary	Pembrolizumab (1L)	Durable tumor regression, improved OS as 1L therapy in advMCC	Pembrolizumab offers durable benefits as 1L treatment for adv MCC.
D'Angelo SP (2021)[39]	Primary	Avelumab (1L)	Primary and biomarker analyses of 1L avelumab, showing high ORR/DOR	Detailed insight into 1L avelumab efficacy and potential biomarkers for responses
D'Angelo SP (2025)[40]	Salvage (progress post IO)	Management strategies post-PD-L1 progression	Discuss clinical outcomes and management for disease progression after initial IO	Crucial for understanding next steps and "salvage use" after primary IO failure
Mo J (2025)[41]	Same as above	Same as above	Same as above	Same as above
General/contextual reviews				
Topalian SL (2012)[42]	IO in general	Anti-PD-1 antibody (general cancer)	Early phase 1 study on safety/activity	Foundational paper on initial clinical application
Topalian SL (2025)[43]	IO in general	ICI overview	Outlines its general principle & mechanisms	Provides a broad understanding
Lebbé C, et al. (2015)[44]	General MCC treatment	European consensus guideline	Covers diagnosis, treatment, and evolving role of systemic therapy	Includes the integration of IO into overall treatment regimen
Aquino de Moraes F (2024)[45]	Same as above	ICI systemic review & metaanalysis	Efficacy & safety of ICI	Confirms the overll efficacy and safety of ICI

1L: first line, 2L: second line, advMCC: advanced MCC, DFS: disease-free survival, DNA: deoxyribonucleic acid, DOR, duration of response, FU: follow-up, ICI: immune checkpoint inhibitor, IO: immunotherapy, MCC: Merkel

 doi:10.20944/preprints202507.2063.v1

cell carcinoma, metMCC: metastatic MCC, ORR: objective response rate, OS: overall survival, pCR: pathological complete response, SOC: standard of care, EP: electroporation.

3.4. Mechanisms of Resistance

encouraging outcomes, immunotherapy resistance remains a significant challenge. Treatment resistance was defined by the Society of Immunotherapy for Cancer consensus recommendations [46]:

* *Primary resistance* (upfront progressive or stable disease with subsequent progression, having received at least 6 weeks and up to 6 months of anti-PD-(L)1 therapy).

* *Secondary resistance* - upfront partial or complete response with subsequent progressive disease, or stable disease for > 6 months prior to progression disease, after at least 6 months of anti-PD-(L)1 therapy, with progression occurring ≤12 weeks of anti-PD-(L)1 therapy cessation.

* *Late progression* - if patient had upfront complete/partial response or stable disease for > 6 months prior to progression, with progression occurring > 12 weeks following anti-PD-(L)1 therapy discontinuation.

Several mechanisms have been proposed for drug resistance:

(1) Intra-tumoral STING activation: While STING agonists can enhance immune responses, chronic activation may lead to immune exhaustion or paradoxical suppression [*]. The STING protein was found to be absent in MCC cells themselves, but present in the surrounding immune and stromal cells within the tumor microenvironment [47]. This suggests that STING activators may exert their effects indirectly in MCC, by signaling through these non-tumor cells, rather than acting directly on cancer cells [*]. This observation also suggests that resistance may not be due to chronic activation within cancer cells, but rather to a direct lack of STING expression in the target cells, or that its effect is dose-dependent, as high doses can lead to reduced efficacy or even cause "adverse effects." [48].

(2) Tumor-associated macrophages (TAMs) can create an immunosuppressive microenvironment, inhibiting T-cell infiltration and function [49], as noted by Professor Ann Silk, a leading expert in Merkel cell carcinoma (MCC).

(3) Loss of major histocompatibility complex (MHC) class I expression: Downregulation of antigen presentation impairs recognition by cytotoxic T cells [50,51].

(4) T-cell exhaustion: Chronic antigen exposure may lead to dysfunctional T cells, characterized by upregulation of inhibitory receptors (e.g., TIM-3, LAG-3) [52,53].

(5) Immunosuppressive cytokines: Elevated levels of IL-10 and TGF-β may dampen anti-tumor immunity [54,55].

Understanding these pathways is critical for developing next-generation therapies, including combination checkpoint blockade, adoptive T-cell transfer [39 adjust#later]*, and personalized vaccines [56,57].

3.5. What Measures Will Have the Greatest Impact on Improving Outcomes in MCC?

Merkel cell carcinoma (MCC) shares clinical and biological characteristics with other aggressive skin cancers, notably melanoma. Immunotherapies such as nivolumab and pembrolizumab have demonstrated effectiveness across multiple stages of MCC presentation, leading to improved outcomes in some patients. Despite these advances, optimizing long-term prognosis still requires a multifaceted strategy.

Immunotherapy has significantly transformed the care of patients with MCC [58]. To date, our expert team proposes several actionable recommendations to improve MCC outcomes. First, increasing awareness among both healthcare professionals and the public is essential. MCC's rarity and aggressive nature often delay recognition; timely education campaigns can promote earlier detection and intervention. Second, minimizing delays in diagnosis and ensuring swift referral to specialists is critical for initiating appropriate treatment before disease progression.

Third, stratifying patients into good- and poor-risk categories allows for personalized treatment planning based on tumor biology and clinical aggressiveness. Additionally, clinicians must carefully

 doi:10.20944/preprints202507.2063.v1

evaluate patients' comorbid conditions to minimize both treatment-related toxicities and financial burdens—a concept now recognized as "financial toxicity."

Regular follow-up is indispensable to monitor treatment response and detect recurrence. Emerging technologies such as circulating tumor DNA (ctDNA) assays, MCC polyomavirus viral titers, and advanced imaging modalities offer promising tools for early identification of disease relapse.

Cost-effectiveness must also guide the selection of diagnostic tests used for staging, surveillance, and re-staging at recurrence. Rational test utilization balances clinical benefit with resource stewardship. Finally, enhancing patients' quality of life during and after treatment is vital. This includes minimizing adverse effects, supporting functional outcomes, and providing counseling that addresses psychological, sexual, and social well-being, as in the subsection below.

Taken together, this comprehensive approach aligns with a patient-centered paradigm and holds the greatest promise for improving both survival and quality of life in those affected by MCC.

3.6. Future Direction in Research in MCC: Combination Treatments, Biomarkers, Liquid Biopsy

The future of MCC treatment should involve multimodal integration, with immunotherapy combined with other modalities to improve outcomes and to minimize toxicity. Here's how the landscape is evolving:

3.6.1. Adoptive T- Cell Transfer

Adoptive T-cell transfer (ATT) represents a promising approach, particularly in cases of MCC associated with the Merkel polyomavirus (MPV). For example, a single-patient clinical trial demonstrated that combining HLA-I-enhancing agents with MHC-specific T-cell therapy resulted in tumor regression and delayed the onset of distant metastases [59]. However, challenges remain, such as low MHC class I expression on tumor cells, which can limit the efficacy of the transferred T cells [60]. Future trials aim to address these challenges to increase the effectiveness of this approach [61].

3.6.2. Therapeutic Vaccines:

Therapeutic vaccines aim to stimulate a strong and specific immune response against cancer cells. They are a promising approach, especially in the context of resistance to current IO [62]. Various types of vaccines are being explored for MCC [63].

- Peptide-based vaccines: These vaccines consist of short peptide sequences of tumor antigens and require strong adjuvants to enhance the immune response. They are taken up by dendritic cells, which present them to T cells.
- mRNA vaccines: These vaccines use synthetic mRNA at the desired antigen concentration and are typically in a lipid-based compound. They have a good safety profile and the ability to rapidly stimulate the immune system.
- Vaccines based on oncolytic viruses: These vaccines aim to directly infect and destroy cancer cells, leading to the release of tumor antigens and stimulating an immune response. Examples include modified herpes simplex virus (RP1) [64,65] and oncolytic adenovirus (MEM-288) [66].
- Plasmid/viral vector vaccines: These use a virus to deliver genetic material that elicits an antigen, leading to an immune response. They can improve targeting of treatments to tumor sites and avoid excessive immune activation.
- Exosome-based vaccines: These use extracellular vesicles carrying membrane proteins to increase the immune response and can stimulate T cells similarly to dendritic cells.

Many of these vaccines are being combined with ICIs in ongoing studies to enhance immune responses and counteract resistance. However, enhancing immune responses through combination therapy may increase the risk of serious adverse events, such as those seen with nivolumab and ipilimumab (such as immune hypophysitis, thyroiditis, colitis, and hepatitis).

 doi:10.20944/preprints202507.2063.v1

Cytokine release syndrome is also a possibility [67,68]. However, directing the immune response specifically to cancer cells via vaccination may reduce some of the toxicities of ICIs.

3.6.3. Combining Different Treatment Modalities

Radiotherapy has a synergistic effect as it may increase tumor antigen presentation, making cancer cells more recognizable to the immune system [69]. In addition, shrinkage of the tumor will allow systemic therapeutic agents to reach cancer cells. By using different modalities can also decrease side effects if individual component of the combined therapy can be reduced in intensity, in terms of drug/radiotherapy dose or radiotherapy treatment volume. Careful design of clinical trials is needed as toxicities could increase with combined treatment. Current efforts such as the NCT03304639 study which is testing pembrolizumab with stereotactic body radiation therapy (SBRT) to improve PFS [70].

Adjuvant radiation may consolidate local control while immunotherapy targets systemic disease. Research should also focus on selecting the proper patients for postoperative radiotherapy with careful considerations on dose and volume.

Regarding chemo-immunotherapy combinations, many experts express concern about the immunosuppressive effects of chemotherapy and the diminished responses to immuno-oncology agents following prior chemotherapy. However, chemotherapy can reduce tumor burden and may act synergistically with immunotherapy by enhancing cytotoxic effects. Ongoing trials include the MERCURY (NCT05594290) evaluating retifanlimab with cisplatin and etoposide before surgery [71].

Lutetium-177 dotatate (a radiolabeled peptide) is tested in combination with avelumab or pembrolizumab in trials such as GoTHAM and iPRRT [72,73]. The combined treatment may confer targeted cytotoxicity while activating immune responses.

3.6.2. Biomarkers

Viral titers and ctDNA are used to monitor recurrence and guide treatment intensity in some well-off countries, such as the United States [74]. Recent data suggest that baseline levels of ctDNA may serve as early predictors of immunotherapy response, while longitudinal monitoring enables real-time assessment of minimal residual disease and recurrence. In a recent study, ctDNA positivity preceded radiographic relapse by several weeks, supporting its role as a dynamic biomarker in MCC surveillance [75].

PD-L1 status and MCPyV may help predict response to checkpoint inhibitors; however, access remains limited—even in Canada, where a significant proportion of the national budget is allocated to health care. There are long waiting lists for new consultations with medical oncologists, and subsequent biomarker testing on tissue specimens often involves turnaround times of several weeks. Although reflex ordering has been discussed, it has yet to be implemented in many smaller or rural hospitals across Canada.

3.6.4. Improving Quality of Life During and After Treatment

The following reflects expert opinions on minimizing complications and improving quality of life for patients with MCC. Infusion reactions to immunotherapy or chemotherapy are relatively common, and pre-medication protocols could be optimized through further research.

Rehabilitation is crucial to address both physical and psychosexual impacts of aggressive treatments like surgery and radiation. Maxillofacial prostheses (e.g., nose, ear) may be used following facial resection to restore aesthetic form and function, significantly boosting patient confidence. Lymphedema can be prevented through lymphovenous anastomosis and managed with physiotherapy, including exercise with or without compression garments. Physiotherapy also plays a critical role in addressing facial nerve damage and improving facial symmetry and expression.

Rehabilitation extends to psychological well-being, addressing body image concerns, anxiety, and relationship distress through psychosexual counseling and behavioral therapies [76,77]. Pelvic

 doi:10.20944/preprints202507.2063.v1

radiotherapy frequently results in long-term sexual dysfunction. Women may experience vaginal dryness, pain, and stenosis, while men may develop erectile dysfunction or reduced libido. Pelvic floor physiotherapy can be transformative for painful intercourse and overall pelvic health. Other effective rehabilitative strategies for female patients include vaginal lubricants, estrogen creams, and vaginal dilators to prevent vaginal obliteration or stenosis. Oncologists should provide these dilators and reinforce their use during follow-up visits. Successful implementation requires a multidisciplinary approach involving nurses and social workers as well.

For men, treatments for erectile issues are available. To improve post-treatment health, various modern rehabilitations are available. For example, erectile impotence can be treated by oral phosphodiesterase type-5 inhibitors as first-line treatment [78] or , Eroxon gel [79]. The latter is available over the counter and contains ethanol, propylene glycol and glycerine/glycerol. It works within 10 minutes, with few side effects apart from local skin reactions [80,81]. Other treatments are lifestyle interventions, psychological counseling and Kegel exercises. More invasive treatments include self-injections and penile implants (a surgical procedure available in most large Canadian cities).

Last but not the least, since patients with MCC often experience recurrence and poor outcomes, effective communication skills among healthcare workers are essential [82,83]. Ongoing medical and nursing education remains critically important [0,85]. Caring for cancer patients is both an art and a science.

In summary, a proactive multidisciplinary approach and open communication among health care team members and the patients are essential for optimizing patients' quality of life following treatment. The examples presented above relate to situations in the Middle East, the United States, and Canada—regions in which members of this research team received training. It is our hope that these practices can be applied globally, with broad generalizability.

4. Conclusions

Immunotherapy has transformed Merkel cell carcinoma (MCC) management. This comprehensive review summarizes literature from four databases. Immunotherapy is administered either before (CheckMate 358) or after surgery (ADMEC-O, ADAM, STAMP), or solely in advanced disease (KEYNOTE-017 and JAVELIN trials).

The findings in this comprehensive review highlight the need for further clinical research to strengthen the evidence base and guide future therapeutic approaches. Hence, recommendations for improving care of MCC patients and future directions for research have been discussed.

Supplementary Materials:nil.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, P.T. and K.J.; methodology, P.T., K.J. and O.A.; software, O.A.; validation, P.T., O.A.; formal analysis, investigation, resources, data curation and writing – original draft preparation, P.T., O.A.; writing—review and editing, all authors; supervision, P.T.; project administration, P.T., K.J., E.Y. All authors have read and agreed to the published version of the manuscript."

Funding: This research received no external funding.

Acknowledgments: Dr. Muhammad Al-Naeem provided some references. Professor Vimal Prapajati provides funding for junior team members to present different abstracts of MCC at various conferences globally.

Conflicts of Interest: The authors declare no conflicts of interest.

 doi:10.20944/preprints202507.2063.v1

Abbreviations

The following abbreviations are used in this manuscript: *

ctDNA	Circulating tumor DNA
DFS	disease-free survival
DNA	deoxyribonucleic acid
EP	electroporation
ICI	immune checkpoint inhibitor
IO	immunotherapy
MCPyV	Merkel cell polyoma virus
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
PD-L1	Programmed Death-Ligand 1
PFS	Progression free survival
SOC	standard of care
1L	first line
2L	second line

References

1. Tai P, Nghiem PT, Part SY. Pathogenesis, clinical features, and diagnosis of Merkel cell (neuroendocrine) carcinoma. In: UpToDate, Canellos GP, Schnipper L (Ed), UpToDate, Waltham, MA, 2025. https://www.wolterskluwer.com (accessed on 15 July 2025)
2. Singh, N., et al., The evolving treatment landscape of Merkel cell carcinoma. Current treatment options in oncology, 2023. 24(9): p. 1231-1258.
3. Squibb, B.-M., An Investigational Immuno-Therapy Study to Investigate the Safety and Effectiveness of Nivolumab, and Nivolumab Combination Therapy in Virus-Associated Tumors—Full Text View—Clinicaltrials. Gov.[(accessed on 30 January 2021)], 2018.
4. Becker, J.C., et al., Merkel cell carcinoma: integrating epidemiology, immunology, and therapeutic updates. American Journal of Clinical Dermatology, 2024. 25(4): p. 541-557.
5. www.fda.gov (accessed on 15 July 2025)https://www.cancer.gov (accessed on 15 July 2025)
6. Missing ref
7. https://www.mypathologyreport.ca/pathology-dictionary/. (accessed on 15 July 2025)
8. Tanda, E.T., et al., Merkel cell carcinoma: an immunotherapy fairy-tale? Frontiers in Oncology, 2021. 11: p. 739006.
9. de Moraes, F.C.A., et al., Efficacy and safety of PD-1/PD-L1 inhibitors in patients with Merkel Cell Carcinoma: a systematic review and Meta-analysis. BMC cancer, 2024. 24(1): p. 1357.
10. Tai P, Joseph K, Prajapati VH, Thachuthara AJ, Lian J, Assouline A, Yu E, Veness M. Merkel cell carcinoma of the skin: Deducing the pattern of spread from an international aggregated database of 949 patients. Curr Oncol 2025;32:211. DOI: 10.3390/curroncol32040211
11. Topalian SL, Bhatia S, Amin A, Kudchadkar RR, Sharfman WH, Lebbé C, Delord JP, Dunn LA, Shinohara MM, Kulikauskas R, et al. Neoadjuvant Nivolumab for Patients With Resectable Merkel Cell Carcinoma in the CheckMate 358 Trial. J Clin Oncol. 2020 Aug 1;38(22):2476-2487. doi: 10.1200/JCO.20.00201. Epub 2020 Apr 23. PMID: 32324435; PMCID: PMC7392746.
12. Becker JC, Ugurel S, Leiter U, Meier F, Gutzmer R, Haferkamp S, Zimmer L, Livingstone E, Eigentler TK, Hauschild A, et al; DeCOG. Adjuvant immunotherapy with nivolumab versus observation in completely resected Merkel cell carcinoma (ADMEC-O): disease-free survival results from a randomised, open-label, phase 2 trial. Lancet. 2023;402(10404):798-808. doi: 10.1016/S0140-6736(23)00769-9. PMID: 37451295.
13. D'Angelo SP, Russell J, Lebbé C, Chmielowski B, Gambichler T, Grob JJ, Kiecker F, Rabinowits G, Terheyden P, Zwiener I, Bajars M, Hennessy M, Kaufman HL. Efficacy and Safety of First-line Avelumab Treatment in Patients With Stage IV Metastatic Merkel Cell Carcinoma: A Preplanned Interim Analysis of

 doi:10.20944/preprints202507.2063.v1

a Clinical Trial. JAMA Oncol. 2018 Sep 1;4(9):e180077. doi: 10.1001/jamaoncol.2018.0077. Epub 2018 Sep 13. PMID: 29566106; PMCID: PMC5885245.

14. https://ichgcp.net/clinical-trials-registry/NCT03271372 (Accessed on 15 July, 2025)
15. https://ascopubs.org/doi/10.1200/JCO.2018.36.15_suppl.TPS9605 (Accessed on 14 July, 2025)
16. https://www.dana-farber.org/clinical-trials /19-712 (Accessed on 14 July, 2025)
17. https://ecog-acrin.org/ (Accessed on 14 July, 2025)
18. https://ichgcp.net/clinical-trials-registry/ NCT04291885 (Accessed on 14 July, 2025)
19. https://www.clinrol.com/study/ NCT04291885 (Accessed on 14 July, 2025)
20. Nghiem, P., et al., Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. Journal of Clinical Oncology, 2019. 37(9): p. 693-702.
21. Walker, J.W., et al., Efficacy and safety of avelumab treatment in patients with metastatic Merkel cell carcinoma: experience from a global expanded access program. Journal for immunotherapy of cancer, 2020. 8(1): p. e000313.
22. Bradford D, Demko S, Jin S, Mishra-Kalyani P, Beckles AR, Goldberg KB, Lemery S, Ward A, Keegan P, Pazdur R. FDA Accelerated Approval of Pembrolizumab for Recurrent Locally Advanced or Metastatic Merkel Cell Carcinoma. Oncologist. 2020 Jul;25(7):e1077-e1082. doi: 10.1634/theoncologist.2020-0184. PMID: 32272501; PMCID: PMC7356706.
23. Kaufman, H.L., et al., Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after≥ 1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. Journal for immunotherapy of cancer, 2018. 6: p. 1-7.
24. D'Angelo, S., et al., Avelumab in patients with previously treated metastatic Merkel cell carcinoma (JAVELIN Merkel 200): updated overall survival data after> 5 years of follow-up. ESMO open, 2021. 6(6): p. 100290.
25. D'Angelo, S., et al., First-line avelumab treatment in patients with metastatic Merkel cell carcinoma: 4-year follow-up from part B of the JAVELIN Merkel 200 study. ESMO open, 2024. 9(5): p. 103461.
26. Nghiem, P., et al., Three-year survival, correlates and salvage therapies in patients receiving first-line pembrolizumab for advanced Merkel cell carcinoma. Journal for immunotherapy of cancer, 2021. 9(4): p. e002478.
27. Topalian, S. L., Bhatia, S., Amin, A., Kudchadkar, R. R., Sharfman, W. H., Lebbé, C., Delord, J.-P., Dunn, L. A., Shinohara, M. M., Kulikauskas, R., Chung, C. H., Martens, U. M., Ferris, R. L., Stein, J. E., Engle, E. L., Devriese, L. A., Lao, C. D., Gu, J., Li, B., ... & Nghiem, P. (2020). Neoadjuvant Nivolumab for Patients With Resectable Merkel Cell Carcinoma in the CheckMate 358 Trial. *Journal of Clinical Oncology*, *38*(22), 2471–2481.
28. Bhatia, S., Longino, N. V., Miller, N. J., Kulikauskas, R., Iyer, J. G., Ibrani, D., Blom, A., Byrd, D. R., Parvathaneni, U., Twitty, C. G., Campbell, J. S., Le, M. H., Gargosky, S., Pierce, R. H., Heller, R., Daud, A. I., & Nghiem, P. (2020). Intratumoral Delivery of Plasmid IL12 Via Electroporation Leads to Regression of Injected and Noninjected Tumors in Merkel Cell Carcinoma. *Clinical Cancer Research*, *26*(3), 598–608.
29. Topalian, S. L., Barrows, A., Brohl, A. S., et al. (2023). Adjuvant immunotherapy with nivolumab versus observation in completely resected Merkel cell carcinoma (ADMEC-O): disease-free survival results from a randomised, open-label, phase 2 trial. *Journal for ImmunoTherapy of Cancer*, *11*(8), e007353. https://jitc.bmj.com/content/11/8/e007353
30. D'Angelo, S. P., Lebbé, C., Mortier, L., Brohl, A. S., Fazio, N., Grob, J.-J., Prinzi, N., Hanna, G. J., Hassel, J. C., Kiecker, F., von Heydebreck, A., Güzel, G., & Nghiem, P. (2021). First-line avelumab treatment in patients with metastatic Merkel cell carcinoma: 4-year follow-up from part B of the JAVELIN Merkel 200 study. *ESMO Open*, *6*(6), 100290. https://www.esmoopen.com/article/S2059-7029(21)00290-0/fulltext
31. Nghiem PT, Bhatia S, Lipson EJ, Sharfman WH, Kudchadkar RR, Brohl AS, et al. PD-1 blockade with pembrolizumab in advanced Merkel cell carcinoma. *N Engl J Med*. 2016;374(26):2542–2552.
32. Gaiser, M. R., Bongiorno, M., & Brownell, I. (2018). PD-L1 Inhibition with Avelumab for Metastatic Merkel Cell Carcinoma. *Expert Review of Clinical Pharmacology*, *11*(4), 345–359.

 doi:10.20944/preprints202507.2063.v1

33. D'Angelo, S. P., Lebbé, C., Mortier, L., Brohl, A. S., Fazio, N., Grob, J.-J., Prinzi, N., Hanna, G. J., Hassel, J. C., Kiecker, F., Georges, S., Ellers-Lenz, B., Shah, P., Güzel, G., & Nghiem, P. (2021). First-line avelumab in a cohort of 116 patients with metastatic Merkel cell carcinoma (JAVELIN Merkel 200): primary and biomarker analyses of a phase II study. *Journal for ImmunoTherapy of Cancer*, *9*(5), e002646. https://jitc.bmj.com/content/9/5/e002646
34. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, 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):1374–1385.
35. Shirley, M. (2018). Avelumab: A Review in Metastatic Merkel Cell Carcinoma. *Targeted Oncology*, *13*(3), 395–406.
36. D'Angelo, S. P., Bhatia, S., Brohl, A. S., Hamid, O., Mehnert, J. M., Terheyden, P., Shih, K. C., Brownell, I., Lebbé, C., Lewis, K. D., Linette, G. P., Milella, M., Georges, S., Shah, P., Ellers-Lenz, B., Bajars, M., Güzel, G., & Nghiem, P. T. (2020). Avelumab in patients with previously treated metastatic Merkel cell carcinoma: long-term data and biomarker analyses from the single-arm phase 2 JAVELIN Merkel 200 trial. *Journal for ImmunoTherapy of Cancer*, *8*(1), e000674. https://jitc.bmj.com/content/8/1/e000674
37. D'Angelo, S. P., Russell, J., Lebbé, C., Chmielowski, B., Gambichler, T., Grob, J.-J., Kiecker, F., Rabinowits, G., Terheyden, P., Zwiener, I., Bajars, M., Hennessy, M., & Kaufman, H. L. (2018). Efficacy and Safety of First-line Avelumab Treatment in Patients With Stage IV Metastatic Merkel Cell Carcinoma: A Preplanned Interim Analysis of a Clinical Trial. *JAMA Oncology*, *4*(9), 1279–1281.
38. Nghiem, P., Bhatia, S., Lipson, E. J., Sharfman, W. H., Kudchadkar, R. R., Brohl, A. S., Friedlander, P. A., Daud, A., Kluger, H. M., Reddy, S. A., Boulmay, B. C., Riker, A. I., Burgess, M. A., Hanks, B. A., Olencki, T., Margolin, K., Lundgren, L. M., Soni, A., Ramchurren, N., ... & Topalian, S. L. (2019). Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy. *Journal of Clinical Oncology*, *37*(8), 693–702.
39. D'Angelo, S. P., Lebbé, C., Mortier, L., Brohl, A. S., Fazio, N., Grob, J.-J., Prinzi, N., Hanna, G. J., Hassel, J. C., Kiecker, F., Georges, S., Ellers-Lenz, B., Shah, P., Güzel, G., & Nghiem, P. (2021). First-line avelumab in a cohort of 116 patients with metastatic Merkel cell carcinoma (JAVELIN Merkel 200): primary and biomarker analyses of a phase II study. *Journal for ImmunoTherapy of Cancer*, *9*(5), e002646. https://jitc.bmj.com/content/9/5/e002646
40. D'Angelo, S. P., Brohl, A. S., Amin, A., et al. (2025). Clinical outcomes and management following progressive disease with anti-PD-(L)1 therapy in patients with advanced Merkel Cell Carcinoma. *ESMO Open*. https://www.esmoopen.com/article/S2059-7029(25)00007-8/fulltext
41. Mo J, Zaremba A, Inderjeeth AJ, El Zeinaty P, Li A, Wicky A, Della Marta N, Marqueste CG, Bohne AS, Matias M, McNamee N, Festino L, Chen C, Ch'ng S, van Akkooi ACJ, Meda LD, Park JJ, Ascierto PA, Hauschild A, Lee JH, Grob JJ, Mangana J, Guminski A, Michielin O, Xu W, Lebbe C, Sandhu S, Zimmer L, Menzies AM, Lo SN, Long GV, Carlino MS, da Silva IP. Clinical outcomes and management following progressive disease with anti-PD-(L)1 therapy in patients with advanced Merkel Cell Carcinoma. Eur J Cancer. 2025 Feb 25;217:115254. doi: 10.1016/j.ejca.2025.115254. Epub 2025 Jan 27. PMID: 39874912.
42. Topalian, S. L., Hodi, F. S., Brahmer, J. R., Gettinger, S. N., Smith, D. C., McDermott, D. F., Powderly, J. D., Carvajal, R. D., Sosman, J. A., Atkins, M. B., Leming, P. D., Spigel, D. R., Antonia, S. J., Horn, L., Daniel, D., Piotrowska, A., Hepburn, K., Tsukamoto, Y., Sznol, J., ... & Pardoll, D. M. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. *N Eng J Med 2012;366*(26), 2443–2454.
43. **Topalian SL, Pardoll DM.** Neoadjuvant anti–PD-1-based immunotherapy: evolving a new standard of care. *J Immunother Cancer*. 2025;13:e010833. doi:10.1136/jitc-2024-010833.
44. Lebbé, C., Becker, J. C., Grob, J.-J., Malvehy, J., del Marmol, V., Pehamberger, H., Peris, K., Saiag, P., Middleton, M. R., Bastholt, L., Testori, A., Stratigos, A., & Garbe, C. (2015). Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline. *European Journal of Cancer*, *51*(16), 2396–2403.
45. Aquino de Moraes, F. C., Kreuz, M., Amaral de Lara, I. C., Macena Lobo, A. d. O., & Rodríguez Burbano, R. M. (2024). Efficacy and safety of PD-1/PD-L1 inhibitors in patients with Merkel Cell Carcinoma: a systematic review and Meta-analysis. *BMC Cancer*, *24*(1), 1357. https://doi.org/10.1186/s12885-024-13129-1

 doi:10.20944/preprints202507.2063.v1

46. Kluger HM, Tawbi HA, Ascierto ML, Bowden M, Callahan MK, Cha E, Chen HX, Drake CG, Feltquate DM, Ferris RL, et al. Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC immunotherapy resistance taskforce. J Immunother Cancer 2020;8(1):e000398. https://doi.org/10.1136/jitc- 2019-000398.
47. Pulliam T, Jani S, Goff PH, Bhakuni R, Tabachnick-Cherny S, Smythe K, et al. Intratumoral STING agonist reverses immune evasion in PD-(L)1-refractory Merkel cell carcinoma: mechanistic insights from detailed biomarker analyses. Journal for ImmunoTherapy of Cancer. 2024 Oct;12(10):e009803.
48. Zhang W, Huang X. Targeting cGAS-STING pathway for reprogramming tumor-associated macrophages to enhance anti-tumor immunotherapy. Biomarker Research. 2025 Mar 12;13(1).
49. Silk AW, Davar D. Tumor-Associated Macrophages in Merkel Cell Carcinoma: Old Balances, New Checks. Clin Cancer Res. 2024 Jan 17:OF1-OF3. doi: 10.1158/1078-0432.CCR-23-3320. Epub ahead of print. PMID: 38230965.
50. Cornel AM, Santegoets SJ, Welters MJ, de Groot AF, van den Berg JH, Kroep JR, et al. MHC class I downregulation in cancer: underlying mechanisms and potential targets for cancer immunotherapy. *Cancers (Basel)*. 2020;12(7):1760.
51. Dhatchinamoorthy K, Colbert JD, Rock KL. Cancer immune evasion through loss of MHC class I antigen presentation. *Front Immunol*. 2021;12:636568.
52. Cianciotti BC, Pannuti A, Lattanzi A, Rampoldi A, Petrelli A, Lucchini G, et al. TIM-3, LAG-3, or 2B4 gene disruptions increase the anti-tumor response of engineered T cells. *Front Immunol*. 2024;15:1315283.
53. Cai L, Xu F, Zhang Z, Lin J, Wang T, Wu D, et al. Targeting LAG-3, TIM-3, and TIGIT for cancer immunotherapy. *J Hematol Oncol*. 2023;16(1):90.
54. Liu J, Wang Y, Zhou Y. The immunosuppressive landscape in the tumor microenvironment. *Immunol Res*. 2024;72(3):287–302.
55. Tie Y, Tan Y, Liu L, Lu Z, Pan X, Zheng H, et al. Immunosuppressive cells in cancer: mechanisms and potential therapeutic targets. *J Hematol Oncol*. 2022;15(1):61. Available from: https://jhoonline.biomedcentral.com/articles/10.1186/s13045-022-01282-8
56. Wang F, Hao Y. Therapeutic vaccine strategies in cancer: advances, challenges, and future directions. *Clin Cancer Bull*. 2025;2(2):63–79.
57. Aljabali AA, Akkawi M, Altaany Z, Keshavarz M, Fares MA, Heshmati E, et al. Neoantigen vaccines: advancing personalized cancer immunotherapy. *Explor Immunol*. 2025;5:130–144.
58. American Cancer Society. Immunotherapy for Merkel Cell Carcinoma (MCC). *Cancer.org*. Revised January 10, 2025. Available from: https://www.cancer.org/cancer/types/merkel-cell-skin-cancer/treating/immunotherapy.html
59. Chapuis AG, Afanasiev OK, Iyer JG, Paulson KG, Upendra Parvathaneni, Joo Ha Hwang, et al. Regression of Metastatic Merkel Cell Carcinoma Following Transfer of Polyomavirus-Specific T Cells and Therapies Capable of Reinducing HLA Class-I. Cancer immunology research. 2013 Nov 4;2(1):27–36.
60. Saeed AF. Tumor-Associated Macrophages: Polarization, Immunoregulation, and Immunotherapy. Cells. 2025 May 19;14(10):741.
61. Garrido F, Aptsiauri N, Doorduijn EM, Garcia Lora AM, van Hall T. The urgent need to recover MHC class I in cancers for effective immunotherapy. Current Opinion in Immunology [Internet]. 2016 Apr;39(39):44–51. Available from: https://www.sciencedirect.com/science/article/pii/S0952791515001739
62. Xiang S, Li S, Xu J. Unravelling T cell exhaustion through co-inhibitory receptors and its transformative role in cancer immunotherapy. Clinical and Translational Medicine. 2025 May 1;15(5).
63. Gambichler T, Schrama D, Käpynen R, Weyer-Fahlbusch SS, Becker JC, Susok L, et al. Current Progress in Vaccines against Merkel Cell Carcinoma: A Narrative Review and Update. Vaccines [Internet]. 2024 May 13 [cited 2024 Jun 11];12(5):533. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11125734/
64. In GK, Cheng PM, Rastegarpour A, et al. RP1 combined with nivolumab in advanced anti–PD-1–failed melanoma (IGNYTE). *J Clin Oncol*. 2025;43(20):e22050.
65. Robilotti E, Zeitouni N, Orloff M. Biosafety of RP1: considerations from a nursing perspective. *Front Mol Biosci*. 2023;10:1178382.

 doi:10.20944/preprints202507.2063.v1

66. Zheng H, Dai W, Antonia SJ, Cantwell MJ, Beg AA. Development of MEM-288, a dual-transgene armed and conditionally replication-enhanced oncolytic adenovirus with potent systemic antitumor immunity. *Cancer Res*. 2020;80(16 Suppl):4578.
67. Porter DL, Maloney DG. Cytokine release syndrome (CRS). *UpToDate*. Updated Apr 2, 2024. Literature review current through Jun 2025. https://www.uptodate.com/contents/cytokine-release-syndrome-crs
68. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. *J Immunother Cancer*. 2018;6:56. https://jitc.bmj.com/content/6/1/56
69. Mc Neil, V. and S.W. Lee, *Advancing Cancer Treatment: A Review of Immune Checkpoint Inhibitors and Combination Strategies*. Cancers, 2025. **17**(9): p. 1408.
70. National Cancer Institute (NCI). A randomized phase II study of anti–PD-1 antibody [MK-3475 (pembrolizumab)] alone versus anti–PD-1 antibody plus stereotactic body radiation therapy in advanced Merkel cell carcinoma. *ClinicalTrials.gov*. Updated April 20, 2025. Available from: https://clinicaltrials.gov/study/NCT03304639
71. Chemo-immunotherapy in patients with resectable Merkel cell carcinoma prior to surgery (MERCURY). *ClinicalTrials.gov*. Updated June 11, 2025. Available from: https://clinicaltrials.gov/study/NCT05594290
72. https://clinicaltrials.gov/study/NCT04261855
73. Everolimus and lutetium Lu 177 dotatate in metastatic midgut neuroendocrine tumors (NET RETREAT/iPRRT). *ClinicalTrials.gov*. Updated July 9, 2025. Available from: https://clinicaltrials.gov/study/NCT05773274
74. Starrett, G.J., et al., Clinical and molecular characterization of virus-positive and virus-negative Merkel cell carcinoma. Genome medicine, 2020. 12: p. 1-22.
75. Akaike T, Thakuria M, Silk AW, et al. Circulating Tumor DNA Assay Detects Merkel Cell Carcinoma Recurrence, Disease Progression, and Minimal Residual Disease: Surveillance and Prognostic Implications. *Journal of Clinical Oncology*. 2024;42(26):3151–3161. Published online July 25, 2024. doi:10.1200/JCO.23.02054 PMID: 39052958
76. Alnaeem, M. M., Al Qadire, M., & Nashwan, A. J. (2025). Unmet needs, burden, and quality of life among family caregivers of patients with advanced hematological malignancy. *Psychology, health & medicine*, 1–16. Advance online publication. https://doi.org/10.1080/13548506.2025.2482954
77. Al-Ghabeesh SH, Al-Kalaldah M, Rayyan A, Al-Rifai A, Al-Halaiqa F. (2019). Psychological distress and quality of life among Jordanian women diagnosed with breast cancer: The role of trait mindfulness. *Eur J Cancer Care*. 2019;e13082. https ://doi.org/10.1111/ecc.13082
78. Fazio L, Brock G. Erectile dysfunction: management update. CMAJ. 2004 Apr 27;170(9):1429-37. doi: 10.1503/cmaj.1020049. PMID: 15111479; PMCID: PMC395819.
79. Clinical data summary for Eroxon® gel. Updated 2025. https://eroxon.com/healthcare-professionals/clinical-data
80. Ralph DJ, et al. Efficacy and safety of MED2005, a topical glyceryl trinitrate formulation, in the treatment of erectile dysfunction: a randomized crossover study. *J Sex Med*. 2018;15(2):167–175.
81. Hellstrom WJG, et al. PD52-07: Efficacy and safety of MED3000, a novel topical therapy for the treatment of erectile dysfunction. *J Urol*. 2024;211(4 Suppl):e1234.
82. Ahmad M., Esmeiran H., Alafafsheh A., Al-Ghabeesh S., Al-Hamdan Z. (2016). Beliefs and preferred communication channels toward patients with cancer in Jordan. World Cancer Research Journal, 3 (3): e753.
83. Rayan, A., Al-Ghabeesh, S., Qarallah, I. (2022). Critical Care Nurses' Attitudes, Roles, and Barriers Regarding Breaking Bad News. SAGE Open Nursing, Volume 8: 1–9 DOI: 10.1177/23779608221089999.

 doi:10.20944/preprints202507.2063.v1

84. Saifan, A., Bashayreh, I., Al-Ghabeesh, S., Batiha, A., Alrimawi, I., Al-Saraireh, M., Al-Momani, M. (2019). Exploring Factors that inhibit effective pain management in cancer patients among healthcare professionals. Central European Journal of Nursing and Midwifery, 10(1), pp. 967-976.
85. Al-Ghabeesh, S. H., Abu-Moghli, F., Salsali, M., Saleh, M. (2012). Exploring sources of knowledge utilized by Jordanian registered nurses. Journal of Evaluation in Clinical Practice, 19 (5): 1-6.