16

BIOMARKERS PREDICTING BENEFIT OF CHECKPOINT INHIBITION IN ADVANCED MERKEL CELL CARCINOMA - A SYSTEMATIC REVIEW

Hannah Björn Andtback[1], Lisa Villabona[2]

[1] *MD, Karolinska Institutet, Stockholm, Sweden*
[2] *MD, PhD, Karolinska University Hospital, Stockholm, Sweden*

Corresponding Author: Hannah Björn Andtback hannah.bjorn.andtback@ki.se

---

Background: Merkel Cell Carcinoma (MCC) is a rare skin cancer with poor prognosis (1). Its pathogenesis is UV-driven or linked to infection with Merkel Cell Polyomavirus (MCPyV)(1). Advanced MCC show 40-50% responses to PD-(L)1 immune checkpoint inhibition (ICI) but reliable biomarkers are lacking, and the potential for side effects is significant (2). Biomarkers of interest in other solid cancers include CD8+ T cells in tumor and periphery, PD-L1-status, MSI-status, and tumor mutational burden (TMB) among others (3). The objective of this systematic review is to provide an updated summary of current predictors of ICI benefit in MCC.

Methods: A literature search was conducted in June 2024 using MEDLINE and EMBASE, focusing on humans with MCC and synonyms for ICI. No time-period was excluded, both English- and non-English articles, clinical trials and case reports were assessed. Articles were reviewed by title, abstract, or full text in a blinded fashion by two independent reviewers. Articles that did not report treatment outcomes related to biomarkers for ICI were excluded.

Results: The search yielded 2,418 results and after review, 20 were selected for this abstract, that met the criteria: tissue or blood-based biomarkers and ICI efficacy in advanced MCC. ***T cell related biomarkers in tissue*:** high intratumoral CD8+ T-cell density was associated with favorable response in one study (4) but showed no correlation with response in others (5, 6). MCPyV-specific infiltrating CD8+ T-cells were also not predictive of outcomes (6). Two studies examined CD8+ phenotype, finding that high T-cell receptor diversity and low clonality were observed in responders (7), and that effector CD8+ T-cells in proximity to tumor cells, along with T-cells exhibiting a memory phenotype, were favorable (8). ***TMB:*** High TMB predicted benefit in one study (9) but failed to do so in others (10, 11). However, specific mutations in ARID2 and NTRK1 were beneficial in one study (11). ***TAMS*:** A subset of tumor associated macrophages was

associated with treatment resistance in one study (12). ***PD-(L)1***: While PD-L1 expression did not consistently predict response, two studies found a trend for it to be numerically higher in responders (13, 14). Responders also had higher PD-1 expression in one study (9), but other studies found no correlation (7, 10, 15). ***MCPyV status****:* MCPyV status was not significantly correlated with response in any of the studies (7-9, 11, 16-18). However, MCPyV negative patients had a trend towards improved response in two studies (18, 19). ***MHC/LOH***: A trend towards improved response was seen in patients with loss of heterozygocity (LOH) in MHC locus and lower MHC class I expression (13) and HLA-downregulation was seen in a secondary resistant tumor in one study(6).***Blood-based biomarkers: CD8 T cells in blood*** have shown some promising results, with a higher frequency of MCPyV-specific CD8+ T-cells at baseline predicting ICI response in one study (20). High tumor-specific T-cells in addition to high CD39+CLA+CD8+ bulk showed higher response even in MCPyV-negative tumors (21). Furthermore, co-expression of PD-1 and TIGIT on circulating T-cells was associated with response in one study (22) and in another study a broad T cell recognition of T-Antigens and T cell frequencies were predictive (23). ***Other blood tests*** that have been investigated are Neuron specific enolase (NSE)-, LDH- and platelet levels. While LDH-levels have shown to be predictive for response in melanoma patients (24), one study of MCC patients found no association between LDH levels—*whether normal or elevated*—and response (25). Neutrophil to lymphocyte ratio, which has shown some promise in melanoma patients, did not predict response in two studies but trended towards response in one (14, 15). NSE in blood during treatment were significantly lowered for responders, however baseline levels were not predictive (26) in one study. In another study the unspecific platelet count pre-treatment was significantly correlated to response (27).

Conclusions: Intratumoral density of CD8+ T-cells, PD-L1 expression and TMB have been shown to correlate with response to ICI in several cancers, but individually none of them universally predict benefit in MCC. This systematic review highlights promising blood-based circulating T-cell biomarkers that correlate with treatment response, as well as tissue-based biomarkers with varying predictive potential. While the diversity of investigated biomarkers is encouraging from an immune mechanism standpoint, the complexity exceeds our current understanding. A personalized approach integrating molecular biomarkers with clinical factors is in our view essential for optimizing ICI-treatment in MCC.

Author / Year	**No pts**	**ORR**	**MCPyV**	**PD-L1**	**PD 1**	**TMB**	**CD8**		**CD 3**	**NLR**	**NSE**	**TAMs**	**MHC**	**HLA/LOH**
							Tissue	**Blood**						

Church et al 2022	1	n/a	-	-	-	-	o	-	-	-	-	-	-	-
D'Angelo et al 2020	88	33%	-	o	-	o	o	-	-	-	-	-	o	o
Giraldo et al 2018	26	65%*	-	x	+	-	x	-	-	-	-	-	-	-
Hansen et al 2024	26	71%	-	-	-	-	-	o	-	-	-	-	-	-
Incorvaia et al 2023	26/32	53,10%	-	-	-	-	-	-	-	-	-	-	-	-
Kacew et al 2020	37/45	43%	-	-	-	o	-	-	-	-	-	-	-	-
Kim et al 2022	50	52-72%	x	x	-	-	-	-	-	-	-	-	-	-
Knepper et al 2020	36	44%	x	-	+	x	-	-	-	-	-	-	-	-
Levy et al 2020	21	57%	o	-	-	-	-	-	-	-	-	-	-	-
Lien et al 2024	6	50%*	-	-	-	-	-	-	-	-	-	-	-	-
Nghiem et al 2021	50	58%	-	o	-	-	-	-	-	o	-	-	-	-
Pulliam et al 2024	27	-	-	-	-	-	-	x	+	-	-	-	-	+
Ruy et al 2024	24	-	-	-	-	-	-	-	+	-	-	-	-	-
Simon et al 2020	15	67%*	-	-	-	-	-	-	-	-	-	-	-	-
Spassova et al 2020	18	39%	x	x	-	-	+	-	-	-	-	-	-	-
Spassova et al 2021	21/114	47%	x	x	-	-	+	-	-	x	-	-	-	-
Tabachnick-	9/54	69%*	-	-	-	-	+	-	-	-	-	+	-	-

Cherny et al 2024														
Torchio et al 2021	1	n/a	-	o	o	-	-	-	o	-	-	-	o	-
Veenendaal et al 2020	23	65%*	-	-	-	-	-	-	-	-	x	-	-	-
Weppler et al 2020	23	61%	o	-	-	-	-	-	o	-	-		-	-

+ = significant
- = not reported
x = not significant
o = trend
*** = calculated in review**
n/a = not applicable

References

1. Silk AW, Barker CA, Bhatia S, Bollin KB, Chandra S, Eroglu Z, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of nonmelanoma skin cancer. J Immunother Cancer. 2022;10(7).
2. Fojnica A, Ljuca K, Akhtar S, Gatalica Z, Vranic S. An Updated Review of the Biomarkers of Response to Immune Checkpoint Inhibitors in Merkel Cell Carcinoma: Merkel Cell Carcinoma and Immunotherapy. Cancers (Basel). 2023;15(20).
3. Li N, Hou X, Huang S, Tai R, Lei L, Li S, et al. Biomarkers related to immune checkpoint inhibitors therapy. Biomed Pharmacother. 2022;147:112470.

4. D'Angelo SP, Bhatia S, Brohl AS, Hamid O, Mehnert JM, Terheyden P, et al. 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. 2020;8(1):05.
5. Giraldo NA, Nguyen P, Engle EL, Kaunitz GJ, Cottrell TR, Berry S, et al. Multidimensional, quantitative assessment of PD-1/PD-L1 expression in patients with Merkel cell carcinoma and association with response to pembrolizumab. J Immunother Cancer. 2018;6(1):99.
6. Pulliam T, Jani S, Jing L, Ryu H, Jojic A, Shasha C, et al. Circulating cancer-specific CD8 T cell frequency is associated with response to PD-1 blockade in Merkel cell carcinoma. Cell Rep Med. 2024;5(2):101412.
7. Spassova I, Ugurel S, Terheyden P, Sucker A, Hassel JC, Ritter C, et al. Predominance of Central Memory T Cells with High T-Cell Receptor Repertoire Diversity is Associated with Response to PD-1/PD-L1 Inhibition in Merkel Cell Carcinoma. Clin Cancer Res. 2020;26(9):2257-67.
8. Spassova I, Ugurel S, Kubat L, Zimmer L, Terheyden P, Mohr A, et al. Clinical and molecular characteristics associated with response to therapeutic PD-1/PD-L1 inhibition in advanced Merkel cell carcinoma. Journal for Immunotherapy of Cancer. 2022;10(1):01.
9. Knepper TC, Montesion M, Russell JS, Sokol ES, Frampton GM, Miller VA, et al. The Genomic Landscape of Merkel Cell Carcinoma and Clinicogenomic Biomarkers of Response to Immune Checkpoint Inhibitor Therapy. Clin Cancer Res. 2019;25(19):5961-71.
10. Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. N Engl J Med. 2016;374(26):2542-52.
11. Kacew AJ, Dharaneeswaran H, Starrett GJ, Thakuria M, LeBoeuf NR, Silk AW, et al. Predictors of immunotherapy benefit in Merkel cell carcinoma. Oncotarget. 2020;11(47):4401-10.
12. Tabachnick-Cherny S, Pulliam T, Rodriguez HJ, Fan X, Hippe DS, Jones DC, et al. Characterization of Immunosuppressive Myeloid Cells in Merkel Cell Carcinoma: Correlation with Resistance to PD-1 Pathway Blockade. Clin Cancer Res. 2024;30(6):1189-99.
13. D'Angelo SP, Lebbé C, Mortier L, Brohl AS, Fazio N, Grob JJ, et al. 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. J Immunother Cancer. 2021;9(7).
14. Nghiem P, Bhatia S, Lipson EJ, Sharfman WH, Kudchadkar RR, Brohl AS, et al. Three-year survival, correlates and salvage therapies in patients receiving first-line pembrolizumab for advanced Merkel cell carcinoma. J Immunother Cancer. 2021;9(4).
15. Spassova I, Ugurel S, Kubat L, Zimmer L, Terheyden P, Mohr A, et al. Clinical and molecular characteristics associated with response to therapeutic PD-1/PD-L1 inhibition in advanced Merkel cell carcinoma. J Immunother Cancer. 2022;10(1).

16. Kim S, Wuthrick E, Blakaj D, Eroglu Z, Verschraegen C, Thapa R, et al. Combined nivolumab and ipilimumab with or without stereotactic body radiation therapy for advanced Merkel cell carcinoma: a randomised, open label, phase 2 trial. Lancet. 2022;400(10357):1008-19.
17. Levy S, Aarts MJB, Eskens F, Keymeulen K, Been LB, Grünhagen D, et al. Avelumab for advanced Merkel cell carcinoma in the Netherlands: a real-world cohort. J Immunother Cancer. 2020;8(2).
18. Weppler AM, Pattison A, Bhave P, De Ieso P, Raleigh J, Hatzimihalis A, et al. Clinical, FDG-PET and molecular markers of immune checkpoint inhibitor response in patients with metastatic Merkel cell carcinoma. J Immunother Cancer. 2020;8(2).
19. D'Angelo SP, Bhatia S, Brohl AS, Hamid O, Mehnert JM, Terheyden P, et al. 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. J Immunother Cancer. 2020;8(1).
20. Pulliam T, Jani S, Jing L, Ryu H, Jojic A, Shasha C, et al. Circulating cancer-specific CD8 T cell frequency is associated with response to PD-1 blockade in Merkel cell carcinoma. Cell Rep Med. 2024;5(2):101412.
21. Ryu H, Bi TM, Pulliam TH, Sarkar K, Church CD, Kumar N, et al. Merkel cell polyomavirus-specific and CD39(+)CLA(+) CD8 T cells as blood-based predictive biomarkers for PD-1 blockade in Merkel cell carcinoma. Cell Rep Med. 2024;5(2):101390.
22. Simon S, Voillet V, Vignard V, Wu Z, Dabrowski C, Jouand N, et al. PD-1 and TIGIT coexpression identifies a circulating CD8 T cell subset predictive of response to anti-PD-1 therapy. Journal for Immunotherapy of Cancer. 2020;8(2):11.
23. Hansen UK, Church CD, Carnaz Simoes AM, Frej MS, Bentzen AK, Tvingsholm SA, et al. T antigen-specific CD8+ T cells associate with PD-1 blockade response in virus-positive Merkel cell carcinoma. J Clin Invest. 2024;134(8):30.
24. Petrelli F, Ardito R, Merelli B, Lonati V, Cabiddu M, Seghezzi S, et al. Prognostic and predictive role of elevated lactate dehydrogenase in patients with melanoma treated with immunotherapy and BRAF inhibitors: a systematic review and meta-analysis. Melanoma Res. 2019;29(1):1-12.
25. Levy S, Aarts MJB, Eskens F, Keymeulen K, Been LB, Grunhagen D, et al. Avelumab for advanced Merkel cell carcinoma in the Netherlands: a real-world cohort. Journal for Immunotherapy of Cancer. 2020;8(2):09.
26. van Veenendaal LM, Bertolli E, Korse CM, Klop WMC, Tesselaar MET, van Akkooi ACJ. The Clinical Utility of Neuron-Specific Enolase (NSE) Serum Levels as a Biomarker for Merkel Cell Carcinoma (MCC). Ann Surg Oncol. 2021;28(2):1019-28.

27. Incorvaia L, Dimino A, Algeri L, Brando C, Magrin L, De Luca I, et al. Body mass index and baseline platelet count as predictive factors in Merkel cell carcinoma patients treated with avelumab. Front Oncol. 2023;13:1141500.