CO108

Systematic literature review and meta-analysis of the real-world effectiveness and safety of avelumab in patients with locally advanced or metastatic Merkel cell carcinoma

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CONCLUSIONS

- The real-world evidence (RWE) identified in this systematic literature review (SLR) and meta-analysis demonstrates the effectiveness and acceptable safety profile of avelumab treatment in patients with Merkel cell carcinoma (MCC) outside of clinical trials, particularly for stage III vs stage IV disease and first-line (1L) treatment vs subsequent lines
- These data confirm the findings of the JAVELIN Merkel 200 trial and support the broader use of avelumab in patients with advanced MCC
- No RWE studies of pembrolizumab or retifanlimab were identified
- Although additional primary research is warranted, results from this study highlight the value of RWE in expanding treatment options

PLAIN LANGUAGE SUMMARY

- Real-world studies provide information about how well drugs work outside of clinical trials
- Avelumab is a recommended treatment for people with advanced Merkel cell cancer
- In this study, researchers looked at real-world studies of people with advanced Merkel cell cancer who were treated with avelumab. They wanted to see if avelumab treatment worked well outside of clinical trials and how many people had side effects
- Researchers analyzed data from 10 different real-world studies. They found that people treated with avelumab in these studies had similar benefits to people treated in a clinical trial
- Side effects in real-world studies vs a clinical trial could not be compared in detail because the people treated were too different. However, no major differences in side effects were seen
- Overall, these findings provide more evidence showing that avelumab treatment is effective for a wide variety of people with advanced Merkel cell cancer

BACKGROUND

- MCC is an aggressive tumor type that has an increasing incidence; 5-year survival rates range from 41% to 77%[1,2]
- Immunotherapy agents, such as avelumab, pembrolizumab, and retifanlimab, have become a cornerstone of 1L treatment for MCC[1,3]; however, other treatment options for patients with advanced MCC remain limited
- Avelumab received regulatory approval for metastatic MCC based on the efficacy and safety results from the pivotal JAVELIN Merkel 200 trial
  - In part A, which enrolled patients with disease progression after prior chemotherapy, median progression-free survival (PFS) was 2.7 months (95%CI, 1.4-6.9) and median overall survival (OS) was 12.6 months (95% CI, 7.5-17.1), reported after a median follow-up of 16.4 and 65.1 months, respectively[4,5]
  - In part B, which enrolled patients with no prior systemic treatment for metastatic MCC, median PFS was 4.1 months (95% CI, 1.4-6.1) and median OS was 20.3 months (95% CI, 12.4-42.0), reported after a median follow-up of 21.1 and 54.3 months, respectively[6,7]
- Despite methodological limitations, RWE studies can supplement clinical trial data and provide a better understanding of patient populations and broader insights into treatment effectiveness and safety in a clinical practice setting
- This research aimed to assess the real-world benefits of avelumab or other immunotherapies in patients with advanced MCC through an SLR and meta-analysis

METHODS

SLR

- Embase and MEDLINE were searched for relevant real-world studies published from 1 January 2017 to 11 December 2023 that reported effectiveness and safety data for adults with advanced (stage III or IV) MCC who received avelumab or other immunotherapies as 1L or second-line or later (2L+) treatment
- A manual search was conducted for abstracts from key conferences from 2017 to 2023
- Study selection was guided by the population, intervention, comparators, outcomes, and study design criteria
- Outcomes of interest included OS, PFS, and objective response rate (ORR); safety data were also examined
- Literature screening was conducted based on title, abstract, and full text by 2 independent reviewers, with discrepancies resolved by a third, more senior, reviewer
- Data were extracted into a template by 1 reviewer with a second reviewer validating all data entries
- The methodological quality of eligible studies was evaluated using the Newcastle-Ottawa Scale risk-of-bias tool[8]; conference abstracts were not assessed for quality given the limited information provided

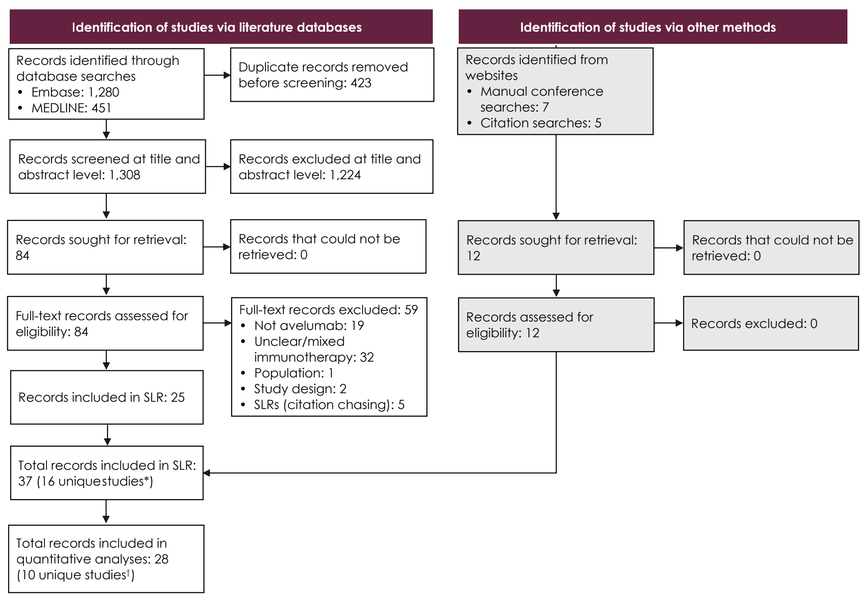
Meta-analysis

- A fixed-effect and random-effects meta-analysis was conducted using R (meta package, version 6.5-0) to assess 12-month OS and PFS rates (ie, landmark data) and response outcomes
- No established meta-analysis method exists to pool median survival time or other types of nonparametric survival data; therefore, landmark data were analyzed as binomial outcomes (ie, proportions)
- 12-month OS and PFS rates were extracted directly from publications if reported or derived from Kaplan-Meier curves
- Analyses were stratified by disease stage (III or IV) and treatment line (1L or 2L+)
- Outcomes were synthesized as proportions using a generalized linear mixed model
  - The event count from the total sample was directly modeled with binomial likelihoods, and the logit link function was used to transform latent true proportions to a linear scale
- Event rates and Clopper-Pearson CIs were calculated for individual studies
- Levels of heterogeneity were computed as follows: I^2 of approximately 25% = low, 50% = medium, and 75% = high
- In the event of no statistical heterogeneity (I^2=0%), the fixed effect and random effects model returned the same pooled estimates and CIs

RESULTS

- 16 unique studies were identified in the SLR (**Figure 1**)[9-24]
  - 11 studies evaluated avelumab monotherapy[10,12-14,16,17,19,20,22-24] and 5 studies evaluated avelumab in combination with other treatments[9,11,15,18,21]
- 3 studies evaluating nivolumab + ipilimumab in patients with avelumab-refractory disease were eligible for inclusion[25-27]; however, study populations differed significantly from those of other studies identified; therefore, only studies of avelumab were included
  - No RWE studies of pembrolizumab or retifanlimab were identified
- Because of significant differences in patient populations and treatment characteristics, only 10 studies of avelumab monotherapy were included in the meta-/quantitative analysis, of which 8 were included in the base-case and/or sensitivity analysis[10-17] and 2 were included in the sensitivity analysis only
- Meta-analysis results for 12-month OS rate, 12-month PFS rate, and ORR by disease stage and treatment line are shown in **Table 1** and **Figures 2-4**
  - Results from the JAVELIN Merkel 200 trial are also shown in **Table 1** for comparison
- 3 studies reported adverse events
  - Across treatment lines and disease stages, rates of all-grade (28%-81%)[23] and grade ≥3 (9%-57%)[16,23] adverse events were lower than rates reported in the JAVELIN Merkel 200 trial (60%-100%)[6,28]
  - Because of insufficient data, no meta-analysis of safety outcomes could be conducted

Figure 1. Literature analysis flow diagram



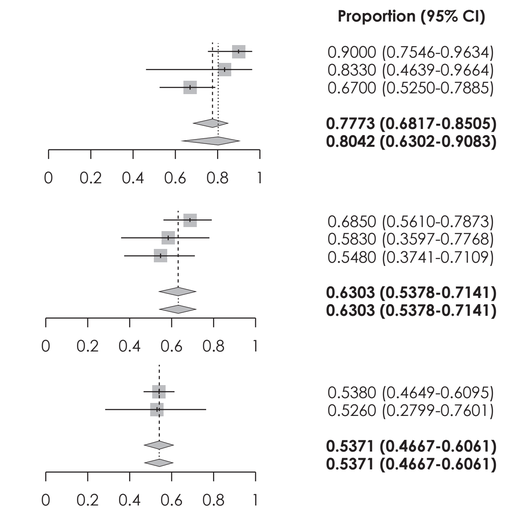
SLR, systematic literature review.
*The SLR also identified 3 studies evaluating nivolumab + ipilimumab in patients with avelumab-refractory disease; however, the study populations differed significantly from other studies where avelumab was included, and these studies were not considered further.
†Only 8 of the 10 studies were suitable for meta-analysis; the other 2 studies were included in sensitivity analyses.

Table 1. Meta-analysis results for OS, PFS, and ORR in RWE studies of avelumab compared with JAVELIN Merkel 200 results

	Fixed-effects pooled proportion (95% CI), % [no. of studies]		
	Stage III, 1L treatment	Stage IV, 1L treatment	Stage IV, 2L+ treatment
12-month OS rate			
Meta-analysis (Figure 2)	77.7 (68.2-85.1) [n=3]	63.0 (53.8-71.4) [n=3]	53.7 (46.7-60.6) [n=2]
JAVELIN Merkel 200	–	60.0 (50.0-68.0)	52.0 (41.0-62.0)
12-month PFS rate			
Meta-analysis (Figure 3)	53.3 (39.0-67.1) [n=2]	39.3 (29.4-50.2) [n=2]	37.4 (29.4-46.2) [n=2]
JAVELIN Merkel 200	–	31.0 (23.0-40.0)	30.0 (21.0-41.0)
ORR			
Meta-analysis (Figure 4)	58.8 (35.2-79.0) [n=2]	54.6 (42.5-66.1) [n=3]	50.7 (45.5-55.9) [n=4]
JAVELIN Merkel 200	–	39.7 (30.7-49.2)	33.0 (23.3-43.8)

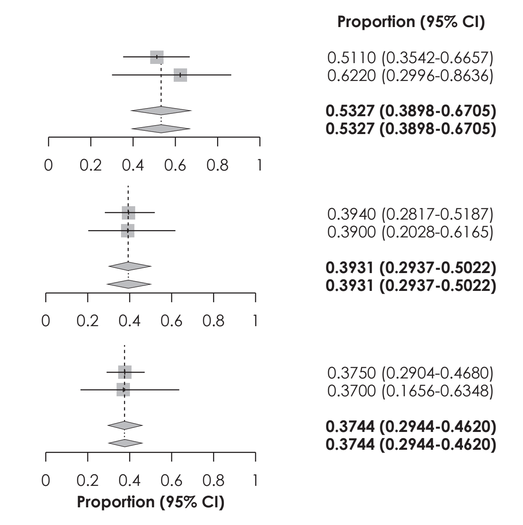
1L, first line; **2L+**, second line or later; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **RWE**, real-world evidence.

Figure 2. Forest plot showing pooled 12-month OS rates with avelumab. (A) Stage III, 1L treatment. (B) Stage IV, 1L treatment. (C) Stage IV, 2L+ treatment



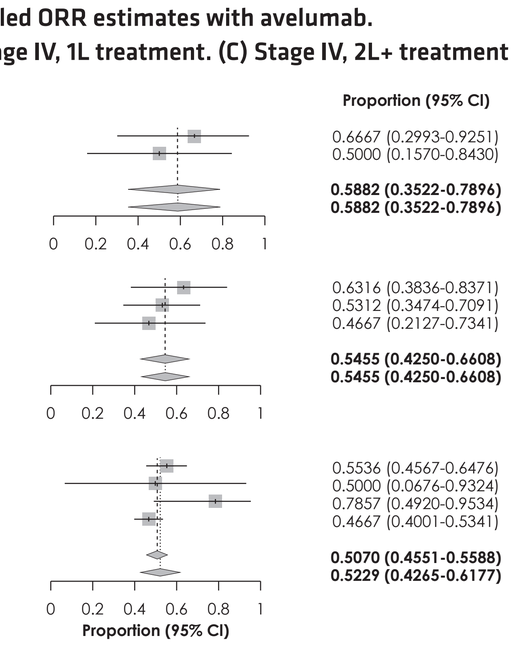
1L, first line; **2L+**, second line or later; **OS**, overall survival.

Figure 3. Forest plot showing pooled 12-month PFS rates with avelumab. (A) Stage III, 1L treatment. (B) Stage IV, 1L treatment. (C) Stage IV, 2L+ treatment



1L, first line; **2L+**, second line and later; **PFS**, progression-free survival.

Figure 4. Forest plot showing pooled ORR estimates with avelumab. (A) Stage III, 1L treatment. (B) Stage IV, 1L treatment. (C) Stage IV, 2L+ treatment



1L, first line; **2L+**, second line and later; **ORR**, objective response rate.

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REFERENCES 1. Sergi MC, et al. Biochim Biophys Acta Rev Cancer. 2023;1878(3):188880. **2.** Jacobs D, et al. JAMA Dermatol. 2021;157(1):59-65. **3.** NCCN Clinical Practice Guidelines in Oncology: Merkel Cell Carcinoma. V1.2024. **4.** D'Angelo SP, et al. ESMO Open. 2021;6(6):100290. **5.** Kaufman HL, et al. J Immunother Cancer. 2018;6(1):7. **6.** D'Angelo SP, et al. J Immunother Cancer. 2021;9(7):e002646. **7.** D'Angelo SP, et al. ESMO Open. 2024;9(5):103461. **8.** The Ottawa Hospital Accessed July 9, 2024. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp **9.** Bhatia S, et al. J Immunother Cancer. 2022;10(8):e004904. **10.** Becker J, et al. Ann Oncol. 2023;34(Suppl 2):Abstract 1145P. **11.** Bhanegaonkar A, et al. Oncologist. 2021;26(9):e1633-43. **12.** Blom Fily A, et al. J Clin Oncol. 2023;41(16 Suppl):Abstract 9537. **13.** Fife K, et al. Front Oncol. 2021;11:672021. **14.** Incorvaia L, et al. Front Oncol. 2023;13:1141500. **15.** Knott C, et al. Ann Oncol. 2023;34(Suppl 2):Abstract 1147P. **16.** Levy S, et al. J Immunother Cancer. 2020;8(2):e001076. **17.** Walker JW, et al. J Immunother Cancer. 2020;8(1):e000313. **18.** Hasmat S, et al. J Med Imaging Radiat Oncol. 2021;65(6):760-7. **19.** Averbuch I, et al. Cancer Med. 2023;12(11):12065-70. **20.** Badalamenti G, et al. J Clin Oncol. 2022;40(16 Suppl):Abstract e21525. **21.** Dudzisz-Śledź M, et al. J Clin Oncol. 2021;39(15 Suppl):Abstract e21521. **22.** Miller DM, et al. J Clin Oncol. 2023;41(16 Suppl):Abstract e21514. **23.** Uhara H, et al. J Dermatol. 2024;51(4):475-83. **24.** Zijlker LP, et al. Cancer. 2024;130(3):433-8. **25.** Glutsch V, et al. Cancer Immunol Immunother. 2021;70(7):2087-93. **26.** Haykal T, et al. J Immunother Cancer. 2022;10(Suppl 2):A861 (abstract 827). **27.** Shalhout SZ, et al. J Immunother. 2022;45(7):299-302. **28.** D'Angelo SP, et al. J Immunother Cancer. 2020;8(1):e000674. **DISCLOSURES M. Kearney** is an employee of Merck, which funded this study. **Z. Lan, M. Rutherford,** and **H. Moradian** are employees of Cytel, which received funding from Merck for the work reported. **C. S. Kwon** and **A. Freitag** were employed by Cytel at the time of the study. **ACKNOWLEDGMENTS** This study was sponsored by Merck (CrossRef Funder ID: 10.13039/100009945). Editorial support was provided by Nucleus Global and was funded by Merck.

Poster No. CO108. Presented at ISPOR Europe, 17-20 November 2024; Barcelona, Spain.