First-line treatment patterns and overall survival in patients diagnosed with metastatic Merkel cell carcinoma in England from 2013 to 2020: results of a nationwide observational cohort study

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Dear Editor, Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumour of the skin with a poor prognosis.[1] In 2017, based on results from the JAVELIN Merkel 200 phase II trial, avelumab, an anti-programmed death-ligand 1 immune checkpoint inhibitor, became the first approved treatment for patients with metastatic MCC (mMCC; stage IV) in the USA and Europe,[2,3] and has been approved in multiple other countries worldwide. Treatment outcomes in patients with mMCC in the UK have not been reported.

This observational, retrospective cohort study was conducted using routine administrative healthcare data collated and managed by NHS England. Details regarding data sources, inclusion criteria and data analysis have been reported previously.[4] In this study, patients in England with an incident primary diagnosis of mMCC between 1 January 2013 and 31 December 2020 were included, and followed until death or study end (May 2022), whichever occurred first.

Of 2622 patients diagnosed with MCC between 2013 and 2020, 667 patients with stage III/IV disease who met study inclusion criteria were identified. Demographics and tumour characteristics of these patients are shown in Table 1, including in subgroups stratified by disease stage at diagnosis and whether first-line avelumab treatment was received. Two-thirds of patients (n=442; 66.3%) presented with stage III (regional) disease and one-third (n=225; 33.7%) presented with stage IV (distant metastatic) disease. Per the Index of Multiple Deprivation, more patients resided in the least income-deprived quintile of England (n=152; 22.8%) than in the most income-deprived quintile (n=100; 15.0%). Median follow-up from diagnosis was 18.0 months [interquartile range (IQR) 6.9–38.6]. Characteristics of patients with stage III and stage IV MCC were similar, although the duration of follow-up was longer in patients with stage III disease [median 22.4 months (IQR 10.3–48.2) vs. 8.3 months (IQR 3.6–26.7)].

Most patients in the study cohort had no evidence of having received systemic anticancer treatment (468 of 667; 70.2%). Among patients who had received systemic anticancer treatment (199 of 667; 29.8%), treatment was more common in those who presented with stage IV (80 of 225; 35.6%) than in those with stage III disease (119 of 442; 26.9%). Avelumab was received as first-line treatment by 78 of 199 systemically treated patients (39.2%), with little difference by disease stage at diagnosis [stage III, 47 of 119 (39.5%) vs. stage IV, 31 of 80 (38.8%)]. Overall, platinum-based chemotherapy was the most common first-line

Table 1 Patient characteristics at diagnosis and overall survival (OS) from first-line (1L) treatment initiation in patients with metastatic Merkel cell carcinoma (mMCC), stratified by tumour stage and receipt of 1L avelumab

		Patients diagnosed with stage III MCC			Patients diagnosed with stage IV MCC		
	All patients diagnosed with mMCC	All patients	Received 1L avelumab	Received non-avelumab 1L	All patients	Received 1L avelumab	Received non-avelumab 1L
Incident cancer diagnosis[a]	667 (100)	442 (100)	47 (10.6)	72 (16.3)	225 (100)	31 (13.8)	49 (21.8)
Age (years), median (IQR)	79.0 (71.0–85.0)	79.0 (71.0–85.0)	78.0 (72.0–81.0)	73.0 (67.8–80.3)	79.0 (70.0–84.0)	75.0 (67.0–82.0)	70.0 (63.0–76.0)
Self-reported gender							
Male	407 (61.0)	263 (59.5)	32 (68.1)	42 (58.3)	144 (64.0)	26 (83.9)	40 (81.6)
Female	260 (39.0)	179 (40.5)	15 (31.9)	30 (41.7)	81 (36.0)	5 (16.1)	9 (18.4)
Immunocompromised[b]	94 (14.1)	65 (14.7)	9 (19.1)	11 (15.3)	29 (12.9)	4 (12.9)	6 (12.2)
CCI, mean (SD)[c]	4.0 (1.8)	3.9 (1.6)	3.5 (1.2)	3.3 (1.4)	4.3 (2.1)	3.6 (1.7)	3.1 (1.8)
Received systemic anticancer treatment	199 (29.8)	–	47 (100)	72 (100)	–	31 (100)	49 (100)
Median OS (months) (95% CI)[d]	12.2 (9.1–16.5)	–	37.8 (12.9–NE)	13.0 (8.3–19.6)	–	19.9 (5.0–NE)	7.2 (5.9–9.1)
OS rates, % (95% CI)[d]							
12 months	51.0 (44.0–57.0)	–	67.0 (51.0–79.0)	52.0 (40.0–63.0)	–	55.0 (36.0–70.0)	31.0 (18.0–44.0)
18 months	42.0 (35.0–49.0)	–	55.8 (39.4–69.4)	40.9 (29.4–52.0)	–	51.6 (33.0–67.4)	24.5 (13.6–37.1)
24 months	37.5 (30.5–44.4)	–	56.0 (39.0–69.0)	35.0 (24.0–46.0)	–	48.0 (29.0–64.0)	–[e]

All data are presented as *n* (%) unless otherwise indicated. CCI, Charlson Comorbidity Index; CI, confidence interval; IQR, interquartile range; NE, not estimable (based on available follow-up). [a]Patients diagnosed between 1 January 2013 and 31 December 2020. If multiple primary diagnoses were documented in the same patient between 2013 and 2020, the characteristics of the earliest-registered diagnosis are reported. [b]Patients were classified as immunocompromised if they had evidence of an HIV, AIDS, multiple myeloma, chronic lymphocytic leukaemia or hypogammaglobulinaemia diagnosis, or an organ transplant (including allogeneic stem cell transplant), between 6 years and 1 day prior to their mMCC diagnosis. [c]A CCI score was derived in each patient according to evidence of prespecified health conditions documented 3–27 months prior to mMCC diagnosis. [d]Survival was calculated using the Kaplan–Meier estimator. Time at risk was calculated from initiation of 1L treatment to the earliest of death or censoring, with failure defined as all-cause death. [e]Data suppressed due to the at-risk population falling to < 10.

systemic treatment (108 of 199; 54.3%). Among the 121 systemically treated patients (60.8%) who did not receive first-line avelumab, chemotherapy was the most common first-line treatment (*n* = 116; 95.9%). A second-line treatment was received by 49 patients, including avelumab in 44.9% (*n* = 22) and platinum compounds in 34.7% (*n* = 17).

Estimates of overall survival (OS) from initiation of first-line treatment are shown in Table 1. Of the 199 patients who had disease of any stage and received systemic anticancer treatment, 130 (65.3%) died during the study, and median OS was 12.2 months [95% confidence interval (CI) 9.1–16.5]. In patients who presented with stage III MCC, median OS was 37.8 months (95% CI 12.9–not estimable based on available follow-up) with first-line avelumab treatment and 13.0 months (95% CI 8.3–19.6) with other first-line treatments. In patients who presented with stage IV MCC, median OS was 19.9 months (95% CI 5.0–not estimable) with first-line avelumab treatment and 7.2 months (95% CI 5.9–9.1) with other first-line treatments.

The study's time frame covers a period of change in the treatment of mMCC. Of the 30% of patients who received systemic anticancer treatment in this cohort from England, only 39% received first-line avelumab treatment. However, avelumab did not become available in England via the Cancer Drugs Fund until March 2018 and was not available for routine use as a first-line treatment for patients with stage IV MCC until April 2021.[5] Therefore, higher rates of avelumab treatment for patients with mMCC in England would be predicted from 2021 onward. Patients with mMCC who received first-line avelumab treatment had a longer observed OS than patients who received other first-line treatments, albeit with overlapping CIs. Results in patients with stage IV MCC in this cohort are comparable with OS data with avelumab first-line treatment in JAVELIN Merkel 200 [median OS was 20.3 months (95% CI 12.4–42.0); 24-month OS rate was 49% (95% CI 40–58%)].[2]

This study has some limitations. Firstly, the data source lacked prospective patient data such as disease progression and secondly, treatments funded outside the NHS system or prescribed in NHS primary care services were not captured. In addition, information on disease stage was missing for 34% of patients diagnosed with MCC, and no information was available to indicate whether tumours were considered resectable.

In conclusion, despite these limitations, the results from this nationwide cohort study provide important real-world data contributing to the increasing evidence base demonstrating the effectiveness of avelumab first-line treatment for mMCC, and can inform international treatment guidelines. Increased use of avelumab has the potential to improve outcomes in patients diagnosed with this rare but aggressive disease.

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Data availability: Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck's Data Sharing Policy. All requests should be submitted in writing to Merck's data sharing portal (https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html). When Merck has a co-research, codevelopment, or comarketing or copromotion agreement, or when the product has been outlicensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck will endeavour to gain agreement to share data in response to requests.

Ethics statement: Ethical approval was not required for this study. National Disease Registries Directions 2021, Sections 254(1) and 254(6) of the 2012 Health and Social Care Act provide the legal basis for the collection and processing of identifiable patient information by NHS Digital and the National Disease Registration Service. Results presented in this paper are routine anonymized statistical outputs.

Patient consent: Not applicable.

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