Received: 6 October 2023 | Revised: 1 January 2024 | Accepted: 11 January 2024

DOI: 10.1002/ijc.34963

RESEARCH ARTICLE

Cancer Therapy and Prevention

IJC INTERNATIONAL JOURNAL of CANCER | UICC

The use of pembrolizumab monotherapy for the management of head and neck squamous cell carcinoma (HNSCC) in the UK

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Abstract

Pembrolizumab has received approval in the UK as first-line monotherapy for recurrent and/or metastatic HNSCC (R/M HNSCC) following the results of the KEYNOTE-048 trial, which demonstrated a longer overall survival (OS) in comparison to the EXTREME chemotherapy regimen in patients with a combined positive score (CPS) ≥1. In this article, we provide retrospective real-world data on the role of pembrolizumab monotherapy as first-line systemic therapy for HNSCC across 18 centers in the UK from March 20, 2020 to May 31, 2021. 211 patients were included, and in the efficacy analysis, the objective response rate (ORR) was 24.7%, the median progression-free survival (PFS) was 4.8 months (95% confidence interval [CI]: 3.6–6.1), and the median OS was 10.8 months (95% CI 9.0–12.5). Pembrolizumab monotherapy was well tolerated, with 18 patients having to stop treatment owing to immune-related adverse events (irAEs). 53 patients proceeded to second-line treatment with

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The data from the three Scottish centers (Edinburgh, Glasgow, and Aberdeen), are also included in a separate real-world retrospective data on the use of pembrolizumab monotherapy and its combination with chemotherapy for patients with HNSCC in Scotland, led by the coauthor Dr. Christina Wilson. However, the Scottish retrospective data includes a different data collection period (with overlap to the data in this manuscript), additional two Scottish centers (not included here) as well as the data of the combination of pembrolizumab with chemotherapy (not approved in England).

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Funding information
This study received no external funding

a median PFS2 of 10.2 months (95% CI: 8.8–11.5). Moreover, patients with documented irAEs had a statistically significant longer median PFS (11.3 vs. 3.3 months; log-rank p value = <.001) and median OS (18.8 vs. 8.9 months; log-rank p value <.001). The efficacy and safety of pembrolizumab first-line monotherapy for HNSCC has been validated using real-world data.

KEYWORDS
head and neck squamous cell carcinoma, immune-related adverse events, immunotherapy, pembrolizumab, real-world data, recurrent/metastatic HNSCC, systemic treatment

What's new?

Pembrolizumab monotherapy is approved for use as first-line palliative systemic treatment for head and neck squamous cell carcinoma (HNSCC). The approval of pembrolizumab was based on data from the KEYNOTE-048 trial, which enforced strict inclusion criteria. Here, the authors analyzed real-world data on first-line monotherapy with pembrolizumab for HNSCC at 18 centers in the UK, with attention to efficacy and safety. Analyses show that pembrolizumab was well tolerated, with relatively few patients experiencing immune-related adverse events. Overall, survival was lower in the study cohort, compared with patients in the KEYNOTE-048 trial, likely owing to differences in patient condition.

1 | INTRODUCTION

Squamous cell cancer accounts for 90% of cancer cases in the head and neck region.[1] Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer worldwide, with ~450,000 deaths reported owing to the disease in 2018.[2] Despite improvements in the treatment of HNSCC, one in three patients will present with recurrent and/or metastatic HNSCC (R/M HNSCC) and have a poor prognosis.[3] Moreover, the incidence of HNSCC is estimated to be 30% higher by 2030 and is expected to be 1.08 million new cases annually.[4]

Until recently, the EXTREME regimen was the established first-line systemic treatment for patients with R/M HNSCC, which included platinum-based chemotherapy (fluorouracil with carboplatin or cisplatin) and cetuximab, an epidermal growth factor monoclonal antibody.[5] The combination of cetuximab with platinum-based chemotherapy led to improved median PFS (5.6 vs. 3.3 months) and median OS (10.1 vs. 7.4 months).[5]

The increasing understanding of the way that tumor cells evade the immune system has driven the expansion of targeted drugs to boost the immune system against tumors.[6] In 2014, the anti-PD1 monoclonal antibodies nivolumab and pembrolizumab (both IgG4) were the first PD1-targeted immunotherapies to receive approval from the FDA for refractory and unresectable melanoma.[7–9] Following the successful results of additional randomized controlled trials (RCTs), the use of PD1 inhibitors was expanded to various solid cancer sites, including urothelial cancer, renal cancer, lung cancer, gastric/gastroesophageal junction cancer, and head and neck cancer.[6,10–13]

Nivolumab was the first immunotherapy to receive approval for the management of HNSCC based on the results of Checkmate-141, an RCT including 361 patients with R/M HNSCC and comparing the investigator's choice of standard of care treatment (cetuximab, methotrexate, and docetaxel) with nivolumab.[14] The efficacy analysis showed that treatment with nivolumab extended OS to 7.5 months in comparison to 5.1 months in patients treated with standard of care treatment. However, the trial did not report any survival benefit in median PFS (2.3 months standard of care vs. 2 months nivolumab group), and there was a poor objective response rate (ORR) (5.8% standard of care vs 13.3% nivolumab group). Our previously published retrospective cohort study evaluating the clinical outcomes of treatment with nivolumab across four cancer centers in England showed PFS (3.9 months) and OS (6.5 months) similar to those observed in the Checkmate-141 trial. Moreover, nivolumab was well tolerated, as only 15% experienced an immune-related adverse event (irAE).[15]

In addition, following the outcomes of the KEYNOTE-048 trial, pembrolizumab has been approved as first-line systemic treatment in R/M HNSCC. The clinical trial showed that treatment with pembrolizumab prolonged OS versus the EXTREME chemotherapy regimen in patients with R/M HNSCC and CPS ≥1 (HR = 0.78; p = .0086) and ≥20 (HR = 0.61; p = .0007). Moreover, the combination of pembrolizumab with cisplatin and 5-fluorouracil (5-FU) chemotherapy reached a superior OS in comparison to the EXTREME chemotherapy regimen in the PD-L1 CPS ≥20, CPS ≥1, and total populations with equivalent safety.[16]

To the best of our knowledge, our study is the first multinational real-world data analysis of the use of pembrolizumab monotherapy as first-line systemic treatment for R/M HNSCC in the UK. RCTs have

strict eligibility criteria and potentially select a nonrepresentative segment of the total population. Thus, analysis of real-world data can usefully define the applicability of a new treatment, such as pembrolizumab, to routine clinical practice.

2 | MATERIALS AND METHODS

This is a retrospective data analysis of HNSCC patients receiving pembrolizumab monotherapy as their first-line treatment across 18 centers in the UK from March 20, 2020 to May 31, 2021. Pembrolizumab monotherapy received NHS England COVID-19 interim approval on March 20, 2020,[17] followed by cancer drug fund (CDF) approval on November 25, 2020,[18] for its use as first-line treatment in R/M HNSCC in adults whose tumors express PD-L1 with a CPS ≥1. On September 7, 2020, the Scottish Medicines Consortium approved pembrolizumab under the NHS Scotland Patient Access Scheme as monotherapy or in combination with 5-FU and platinum chemotherapy for the first-line treatment of metastatic or unresectable HNSCC in adults with a CPS ≥1.[19] Patients were included in the analysis if they had received pembrolizumab as monotherapy. Patients were excluded if they had received pembrolizumab treatment as part of a trial.

We collected data from patients across 18 participating centers representing a broad geographical spread across England and Scotland (Table S1). The patient and tumor characteristics data collected included baseline patient characteristics, details of primary treatment, treatment response, irAEs, and survival data. All information presented was gathered retrospectively from the patients' electronic records.

2.1 | Baseline characteristics

The baseline characteristics collected included sex, age, performance status, history of autoimmune disease (including the use of oral steroids prior to pembrolizumab commencement), alcohol, and smoking (pack-years) history. The tumor characteristics collected included primary site of disease, staging at original diagnosis, p16 status if applicable, PD-L1 status, date of original diagnosis and details of recurrence if applicable. PD-L1 testing was considered positive if the score was ≥1 in a sample with a minimum of 100 cancer cells using the 22C3 PharmDx assay (Dako platform). The CPS was calculated as the number of PD-L1-positive cells (tumor cells, macrophages, and lymphocytes)/total number of tumor cells × 100. Both the seventh and/or eighth editions of the tumor, nodes, and metastasis (TNM) classification system were used for clinical staging.

2.2 | Treatment characteristics and treatment outcomes

Information on treatment characteristics was collected, including details of primary treatment (including intent of treatment), immunotherapy commencement date, duration of treatment and treatment outcomes. Best treatment response was collected from the electronic records based on radiologists' assessments (no blinded independent central review). PFS was calculated as the time from the date of immunotherapy commencement until disease progression or death from any cause. OS was calculated as the time from the date of immunotherapy commencement until death from any cause. Patients were censored to the last follow-up date if there was no event for PFS and OS. PFS2 was calculated as indicated in Table S2. The National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was used to grade irAEs.

2.3 | Statistical analysis

The Statistical Package for the Social Sciences version 28 was used for statistical analysis. The distributions of duration of response, PFS, and PFS2 were estimated using the Kaplan–Meier method. The between-group differences were calculated using a log-rank test, and a p value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient, tumor, and treatment characteristics

From March 2020 to May 2021, 211 patients received pembrolizumab monotherapy as first-line treatment for HNSCC. Tables 1–3 shows the baseline patient and tumor characteristics. In summary, the median age of the patients (calculated from the day of pembrolizumab commencement) was 66.0 (range: 39–88.1) years, 73.0% of patients were male, and >65% of patients had a history of smoking or alcohol consumption. Four patients were receiving baseline steroids prior to pembrolizumab commencement, although the doses for the steroids were not collected (one for asthma, one for pain and hypotonia, and two for autoimmune disease). Ninety-seven percent of patients (206/211) had a performance status of 0–1. The histological diagnosis for all patients was squamous cell carcinoma (SCC), except for a patient who was diagnosed with sarcomatoid carcinoma with heterologous rhabdomyoblastic differentiation who was treated as SCC following discussion at the local sarcoma multidisciplinary meeting. The main primary tumor sites of disease included oral cavity ($n = 55$; 26.1%), oropharynx ($n = 90$ [51/90 were p16-positive]; 42.7%), and larynx/hypopharynx ($n = 49$; 23.2%), and most patients had stage 4 disease at diagnosis based on TNM7 ($n = 157$; 74.4%). Although pembrolizumab is only approved for use in R/M HNSCC expressing PD-L1 with a CPS of 1 or more, 2 patients (0.9%) had a CPS score <1, and 17 patients (8.1%) did not have a CPS recorded.

We classified patients into three groups according to their presentation prior to immunotherapy commencement: cohort 1 patients presented with recurrent disease (135; 64%), cohort 2 patients presented with de novo metastatic disease (28; 13.3%), and cohort 3 patients presented with locally advanced disease not suitable for radical treatment, that is, owing to comorbidities (47; 22.3%). One

TABLE 1 Baseline patient characteristics.

Number of patients	211
Age median (range)	66.0 (39–88.1)
Sex (%)	
Male	154 (73.0)
Female	57 (27.0)
Smoking status (%)	
Never	56 (26.5)
Ex-smoker	91 (43.1)
Current smoker	55 (26.1)
Not recorded	9 (4.3)
Alcohol intake (%)	
Current (heavy[a])	27 (12.8)
Current (not heavy[b])	76 (36.0)
Ex (heavy)	27 (12.8)
Ex (not heavy)	15 (7.1)
Never	42 (19.9)
Not recorded	24 (11.4)
Oral steroid use prior to pembrolizumab (%)	4 (1.9)
ECOG Performance status (%)	
0	37 (17.5)
1	169 (80.1)
2	4 (1.9)
Missing	1 (0.5)

Note: Data are median (range) or *n* (%).
Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]Heavy: >21 units/week.
[b]Not heavy: <21 units/week.

TABLE 2 Baseline tumor characteristics.

Site of primary tumor (%)	
Oral cavity	55 (26.1)
Oropharynx	90 (42.7)
p16/HPV status[a]	
Positive	51 (56.7)
Negative	38 (42.3)
Unknown	1 (1.1)
Larynx/Hypopharynx	49 (23.2)
Paranasal sinuses	5 (2.4)
Unknown primary	9 (4.3)
Nasopharynx	2 (0.9)
Synchronous	1 (0.5)
Staging TNM at time of diagnosis (AJCC7) (%)	
1	13 (6.2)
2	14 (6.6)
3	27 (12.8)
4	157
4a	106 (50.2)
4b	25 (11.8)
4c	25 (11.8)
Not subclassified stage 4	1 (0.5)

Note: Data are *n* (%).
Abbreviations: AJCC7, American Joint Committee on Cancer Staging System 7th edition; TNM, tumor, nodes, and metastasis.
[a]P16/HPV: p16 was determined by immunohistochemistry; human papilloma virus (HPV) was detected by polymerase chain reaction.

patient with stage 4a (p16+) oropharyngeal cancer declined radical treatment and thus received pembrolizumab as first-line treatment (Table 3).

In the group of patients treated with curative intent at presentation, 85 received primary radiotherapy (RT) (+/− chemotherapy), 47 received primary surgery (+/− postoperative [chemo] RT) and 3 received induction chemotherapy as their first treatment. In the group of patients treated with palliative intent at presentation (Cohorts 2 and 3), 30 received palliative RT, and 46 received palliative pembrolizumab as their first therapy.

3.2 | Efficacy

The overall response rate (ORR) for all patients was 24.7% ($n = 52$); 40 patients had partial response (PR), and 12 patients had complete response (CR) to treatment (Table 4). Following further classification based on CPS, 29/84 (34.5%) patients with a CPS ≥20 were responders (CR or PR), and 19/108 (17.6%) patients with a CPS 1–19 were responders (Pearson χ^2 $p = .02$; patients with CPS <1 and no recorded CPS were excluded from this subanalysis) (Figure 1A). ORR was similar between the three groups classified according to presentation: recurrent disease (24.4%), de novo metastatic disease (28.6%), and locally advanced disease nonamenable to curative treatment (23.4%) (Figure 1B). Patients with p16 negative disease had a lower response rate compared with patients with p16 positive disease, however the difference was not statistically significant (21.4 vs. 29.1%; Pearson χ^2 $p = .60$; Figure S1A,D). Moreover, there was a similar trend for patients with a smoking history compared with patients with no smoking history (22.1 vs. 28.1%; Pearson χ^2 $p = .121$; Figure S2A). Patients' response to treatment across the different tumor sites is shown in Figure S2B.

3.3 | Duration of treatment and reason for stopping

The median duration of treatment was 4.0 months (95% CI 2.9–5.1 months). In total, 145 patients (68.7%) discontinued treatment owing to disease progression or death (Table 4). The treatment was generally well tolerated; however, 18 patients (8.5%) discontinued treatment owing to irAEs, and 16 patients (7.6%) discontinued when considered unfit for further treatment. Seven patients (3.3%) completed 24 months of treatment, and 20 patients (9.5%) were receiving ongoing treatment at the time of analysis.

TABLE 3 Tumor characteristics and presentation.

PD-L1 status (CPS)[a] (%)	
Not available	17 (8.1)
<1	2 (0.9)
≥1	192 (91.0)
≥1–19	108 (51.2)
≥20	84 (39.8)
Presentation (%)	
Recurrence (Cohort 1)	135 (64.0)
Locoregional	72 (34.1)
Distant and locoregional	14 (6.6)
Distant	48 (22.7)
Not available	1 (0.5)
De-novo metastatic (Cohort 2)	28 (13.3)
Locally advanced disease nonamenable to curative treatment (Cohort 3)	47 (22.3)
Locally advanced disease amenable to curative treatment—patient choice[b]	1 (0.5)

Note: Data are *n* (%).
Abbreviations: CPS, combined positive score; PD-L1, programmed cell death ligand 1.
[a]PD-L1 testing was done using 22C3 PharmDx assay (Dako platform) and was defined as positive if scored ≥1 in a minimum of 100 tumor cells (CPS score). CPS is calculated as the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages)/total number of tumor cells × 100.
[b]Stage 4a (p16+) oropharyngeal cancer declined radical treatment.

TABLE 4 Pembrolizumab treatment response and reasons for stopping treatment.

Characteristics	Patients (*n* = 211)
Best response to treatment (%)	
Progressive disease	107 (50.7%)
Complete response/partial response	52 (24.65%)
Stable disease	52 (24.65%)
Reason for stopping treatment (%)	
Progressive disease	120 (56.9%)
Death	25 (11.8%)
Toxicity	18 (8.5%)
Ongoing treatment	20 (9.5%)
Not fit for treatment	16 (7.6%)
Completed 2 years of pembrolizumab	7 (3.3%)
Patient choice	3 (1.4%)
Not available	2 (0.9%)

Note: Data are *n* (%).

3.4 | Survival outcomes

The median PFS and OS were 4.8 months (95% CI, 3.6–6.1) and 10.8 months (95% CI, 9.0–12.5), respectively. Moreover, the estimated PFS rate at 6 months was 45.0% and at 12 months was 26.2%.

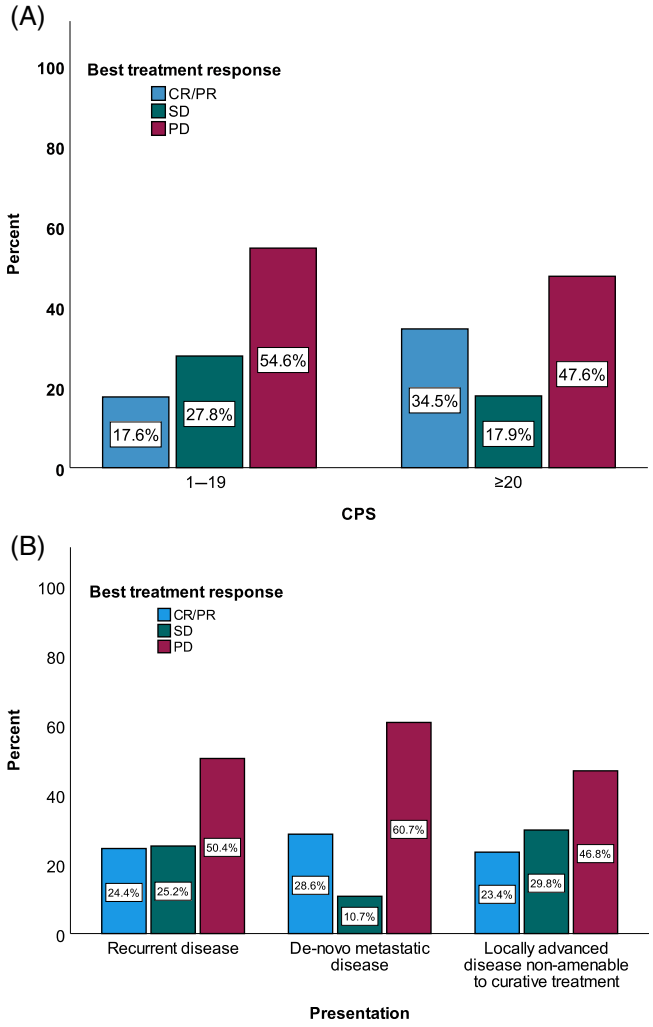

FIGURE 1 Best treatment response. (A) Best treatment response according to CPS. (B) Best treatment response according to patient presentation. For CPS sub-analysis patients with CPS <1 and not recorded CPS were excluded. CPS, combined positive score; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The estimated OS rate at 12 months was 45.2% and at 24 months was 25.3%; Figure 2A,E.

In addition, in the subgroup analysis of survival outcomes based on CPS, there was no statistically significant difference in the median PFS and OS between the groups of patients with CPS 1–19 and ≥20. The median PFS for the CPS 1–19 group was 4.1 months (95% CI, 2.9–5.4) and for CPS ≥20 was 6.3 months (95% CI, 4.2–8.4) (log-rank *p* value = .27); Figure 2B. The median OS for the CPS 1–19 group was 11.3 months (95% CI, 8.3–14.3) and for CPS ≥20 was 10.1 months (95% CI, 8.0–12.3) (log-rank *p* value .42); Figure 2F.

Moreover, additional analysis based on reported toxicity showed a statistically significantly longer median PFS and OS in the group with a documented irAE compared with the group of patients with no documented irAE (PFS 11.3 months [95% CI, 6.7–16.0] vs. 3.3 months [95% CI, 2.3–4.2], log-rank *p* value = <.001; OS

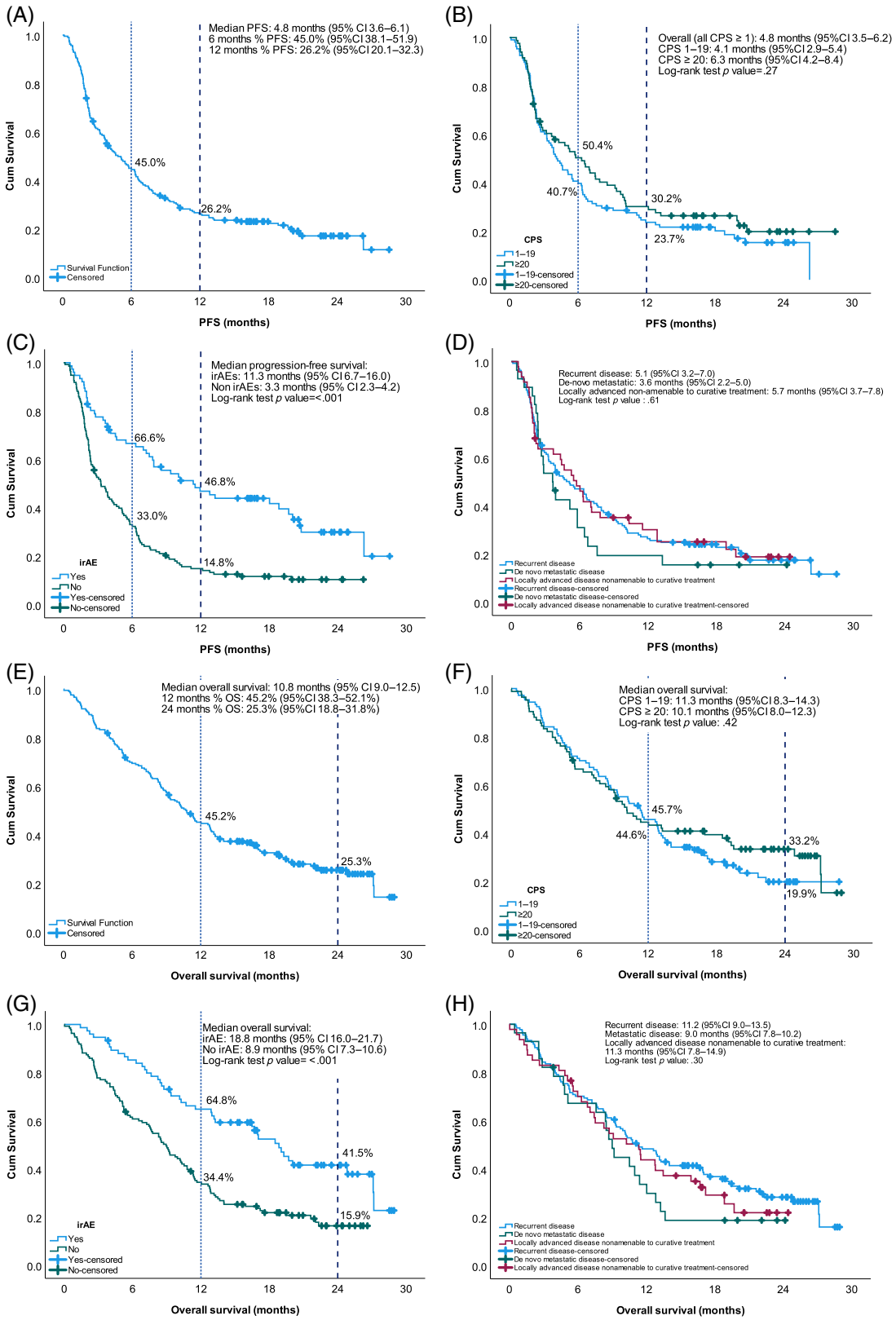

FIGURE 2 Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS). (A) PFS of the whole population. (B) PFS based on CPS score (1–19 vs. ≥20). (C) PFS in patients with or without immune-related adverse events (irAEs). (D) PFS based on patient presentation. (E) OS of the whole population. (F) OS based on CPS score (1–19 vs. ≥20). (G) OS in patients with or without immune-related adverse events (irAEs). (H) OS based on patient presentation. For CPS subanalysis patients with CPS <1 and not recorded CPS were excluded. PFS, progression free survival, calculated as time from pembrolizumab commencement to disease progression or death; OS, overall survival, calculated as time from pembrolizumab commencement to death from any cause; CPS, combined positive score.

18.8 months [95% CI, 16.0–21.7] vs. 8.9 months [95% CI, 7.3–10.6], log-rank p value <.001); Figure 2C,G. The median PFS was lower in the group of patients who presented with de novo metastatic disease (3.6 months; 95% CI, 2.2–5.0) than in the group who presented with recurrent (5.1 months; 95% CI, 3.2–7.0) or locally advanced disease not suitable for radical treatment (5.7 months; 95% CI, 3.7–7.8). Nevertheless, this difference was not statistically significant (Figure 2D). Similarly, the median OS was lower in the group of patients who presented with de novo metastatic disease (9.0 months; 95% CI, 7.8–10.2) than in those who presented with recurrent (11.2 months; 95% CI, 9.0–13.5) or locally advanced disease not suitable for radical treatment (11.3 months; 95% CI, 7.8–14.9). Again, this difference was not statistically significant (Figure 2H). Finally, in a further subgroup analysis based on p16 status, patients with p16-positive disease had statistically significantly longer median OS (14.0 months; 95% CI, 6.3–21.7) than those with p16-negative disease (9.2 months; 95% CI, 6.4–11.9) (Figure S1B–F). Moreover, there was no statistically significant difference in median PFS or OS for patients with or without smoking history, irrespective of pack years (Figure S2C–E).

3.5 | Radiotherapy and immunotherapy

The scheduling of RT and immunotherapy combination treatment remains a hot research topic with several unanswered questions.[20] In this group of patients, 68 received palliative RT: 56 before commencement of immunotherapy (81.5% of patients within 6 months of treatment), 7 after completion of immunotherapy and 5 during immunotherapy. Interestingly, patients who did not receive palliative RT as part of their treatment had a nonstatistically significant higher ORR compared with the group of patients who received palliative RT (RT delivered during or prior to immunotherapy) (28.0% vs. 16.4%; Pearson $\chi^2 = 0.08$; Figure S3A), a statistically significant longer PFS (5.6 vs. 3.6 months; log-rank p value .005; Figure S3B) and similar OS (11.4 vs. 10.1 months; log-rank p value = .12; Figures S3C and S4A–D).

3.6 | Safety and immune-related toxicity

Table 5 gives a summary of irAEs associated with pembrolizumab treatment. In 211 patients included in the analysis, we noted 95 irAEs from 76 patients (1 irAE: 60 patients; 2 irAEs: 13 patients; 3 irAEs: 3 patients). Gastrointestinal adverse effects were the most common by total irAEs ($n = 22$); grade 1 skin ($n = 10$), grade 2 endocrine ($n = 11$), and grade 3 gastrointestinal ($n = 10$) irAEs were the most common according to severity.

3.7 | Progression-free survival 2 (PFS2)

Fifty-three patients proceeded to second-line treatment after pembrolizumab. Thirty-six patients received platinum (carboplatin/cisplatin) chemotherapy plus 5-FU/capecitabine +/− cetuximab, nine patients received platinum plus taxane, one patient received carboplatin + cetuximab, one patient received single-agent platinum chemotherapy, three patients received single-agent taxane chemotherapy, and three patients received a trial drug (Table 6). Eighteen patients had CR or PR to second-line chemotherapy, 8 patients had SD, 22 patients had PD, 2 patients stopped owing to toxicity, and 3 patients had no available documentation. The median PFS2 was 10.2 months (95% CI, 8.8–11.5) (Figure 3A) and it was similar across the CPS subcategories (Figure 3B).

TABLE 5 Immune-related adverse events (irAEs) secondary to pembrolizumab.

Patients with 1 or more immune-related adverse events (irAEs)[a]					
Toxicity	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Not graded**
Hepatitis	6	1	1	4	0
Hyperglycemia/DM	3	0	0	1	2
Pneumonitis	1	0	0	0	1
Fatigue/drop PS	10	3	3	1	3
Gastrointestinal	22	2	9	10	1
Skin	16	10	1	4	1
Endocrine	19	1	11	3	4
Adrenal failure	6	0	4	1	1
Hypothyroidism	13	0	8	1	4
Hyperthyroidism	1	1	0	0	0
Rheumatoid	7	1	3	3	0
Other	11	2	2	5	2

Note: Data are *n*.
Abbreviations: DM, diabetes mellitus; PS, performance status.
[a]irAEs were graded by National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Some patients experienced more than 1 endocrine toxicity; total number of endocrine toxicities different than total number of patients with an endocrine toxicity.

TABLE 6 Second-line treatment regimens and response in patients who proceeded after first-line pembrolizumab.

	Patients (n = 53)
Type of chemotherapy	
Platinum + 5-FU/cape +/− cetuximab	36 (67.9%)
Platinum + taxane	9 (17.0%)
Platinum + cetuximab	1 (1.9%)
Platinum (single agent)	1 (1.9%)
Taxane (single agent)	3 (5.7%)
Trial drug	3 (5.7%)
Best response to treatment (%)	
Progressive disease	22 (41.5%)
Complete response/partial response	18 (34.0%)
Stable disease	8 (15.1%)
Stopped owing to toxicity	2 (3.8%)
Not available	3 (5.7%)

Abbreviations: 5-FU, 5-fluorouracil; Cape, capecitabine.

4 | DISCUSSION

In this project, we established the safety and efficacy of pembrolizumab monotherapy as a first-line systemic treatment for HNSCC using real-world data. In the UK, pembrolizumab monotherapy has been approved as first-line treatment in R/M HNSCC in adults whose tumors expresses PD-L1 with a CPS ≥1. In this real-world retrospective cohort, compared with the CPS ≥1 group of KEYNOTE-048, we showed a higher ORR (24.7% vs. 19.1%), longer PFS (4.8 vs. 3.2 months), similar PFS2 (10.2 vs. 9.0 months) and lower OS (10.8 vs. 12.3 months; Table S3).

In this cohort, we have shown 1.6 months longer PFS (4.8 vs. 3.2 months) compared with the results of KEYNOTE-048 in the total population. A possible explanation for this difference is the timing of assessing response to treatment in a real-world setting compared with a clinical trial. In KEYNOTE-048, the first imaging scan was performed at 9 weeks from the time of randomization; thus, most patients would have had their scan within 2 months of treatment commencement. Moreover, subsequent imaging was performed every 6 weeks. However, in the real-world setting, most centers will proceed to their first scan 3 months post-treatment commencement and subsequent imaging every 2–3 months, with possible delays in reporting and clinician's assessment of the results of the scan. Outside the context of a defined trial protocol, it is also possible that more patients will have received additional treatment beyond progression before formal declaration of a PFS event. Despite longer PFS, we have reported a lower OS compared with the results of KEYNOTE-048 (10.8 vs. 12.3 months). This may be attributed to the fact that the eligibility criteria for the trial population are much stricter, and the population selected reflects a healthier population with a better PS when compared with the real-world treated patients.

The safety of pembrolizumab treatment for this cohort was established, as fewer than 10% of patients stopped treatment owing to

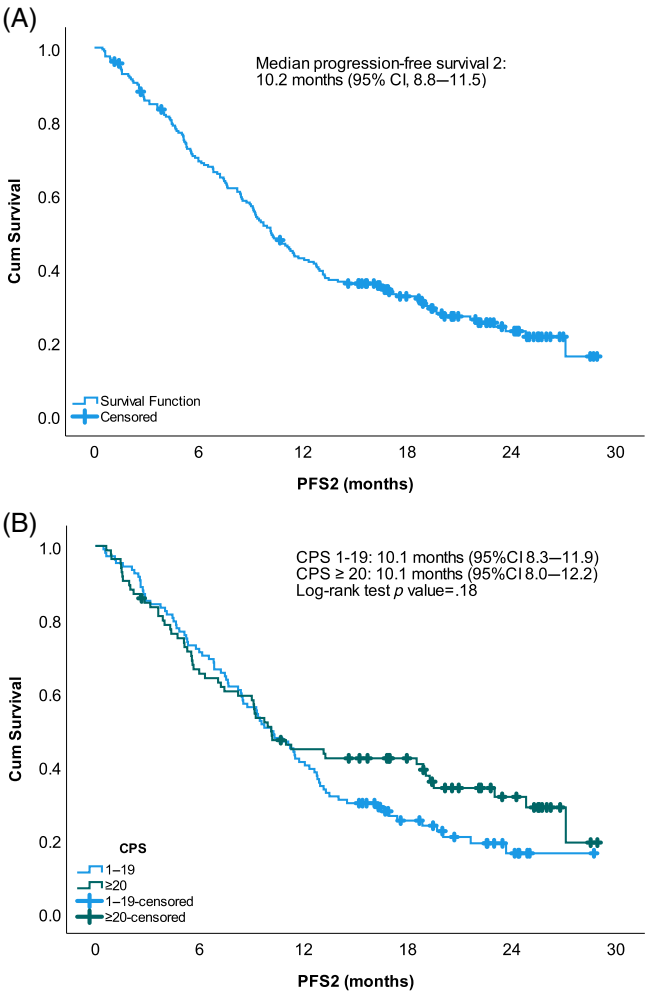

FIGURE 3 Kaplan–Meier estimates of progression-free survival on the next line of therapy (PFS2). (A) PFS2 of the whole population. (B) PFS2 according to CPS score.

irAEs. In this cohort, we had 19 cases of immune-related endocrine toxicity (hypothyroidism 13/211; 6.2%), which is much lower than the rates observed in clinical trials of pembrolizumab treatment in HNSCC including Keynote-012 (hypothyroidism 10%[21]), Keynote-048 (pembrolizumab monotherapy arm, hypothyroidism 18%[16]), Keynote-040 (hypothyroidism 15%[13]). irAEs have been associated with a better response to treatment in various tumor sites, including renal cancer, non-small cell lung cancer and melanoma.[22–24] In HNSCC, published studies have demonstrated that the population of patients with irAEs had improved clinical outcomes, including ORR[25] and 1-year survival rate.[26] Our analysis supports these findings, as both PFS and OS were statistically significantly higher in the group with a documented irAE than in the group with no documented irAE. However, the inclusion of retrospective observational studies and immortal-time bias may limit the significance of this analysis. Pembrolizumab-induced irAEs can be delayed and typically occur between 3 and 4 weeks and up to 1 year following treatment; thus, only patients who live long enough may experience irAEs.[27]

Interestingly, despite showing a significant survival improvement, pembrolizumab monotherapy has not shown any benefit in PFS. A

supplementary analysis of the Keynote-048 cohort showed a longer median PFS on next-line therapy (PFS2) for pembrolizumab monotherapy versus EXTREME chemotherapy regimen in the CPS ≥20 (11.7 vs. 9.4 months) and CPS ≥1 groups (9.4 months vs. 8.9 months).[28] In this cohort, 53 patients continued to receive second-line chemotherapy with a PFS2 similar to that of KEYNOTE-048 at 10.2 months. Despite the limited data investigating response to subsequent treatment options for HNSCC, the existing evidence may indicate that immune checkpoint inhibitors (ICIs) can sensitize tumors to the succeeding therapies.

PD-L1 overexpression on tumor cells has been associated with a better response to anti-PD-1 ICIs in various solid tumors.[29–32] Nevertheless, some patients with PD-L1-negative tumors have a good response to anti-PD-1 treatment, which creates important dilemmas regarding the role of PD-L1 expression as a predictive biomarker. In this cohort, the group of patients with a CPS ≥20 had a statistically significantly higher ORR (34.5% vs. 17.6%) with similar PFS (6.3 vs. 4.2 months; log-rank p value .276) and OS (10.1 vs. 11.3 months; log-rank p value .426) compared with the groups of patients with CPS scores 1–19. In the subgroup analysis of the KEYNOTE-048 population according to CPS score, there was no statistically significant difference in the OS and PFS in the CPS 1–19 population between pembrolizumab monotherapy and chemotherapy with cetuximab.[33] Overall, there is an observed trend toward improved pembrolizumab efficacy with increasing expression of PD-L1.

Keynote-012 is a phase 1b study investigating the use of pembrolizumab in R/M HNSCC patients, and efficacy analysis based on PD-L1 status concluded that patients with PD-L1-positive tumors (CPS ≥1) had an improved response (21% vs. 6%, $p = .023$) and OS (10 vs. 5 months, $p = .008$) compared with patients with PD-L1-negative tumors (CPS <1).[34] Some of the limitations in utilizing PD-L1 expression as a predictive biomarker include sampling error, intratumoral heterogeneity, variability in scoring systems, differences in the monoclonal antibodies and the lack of common standards for the PD-L1 assays used.[35,36] Tumor positive score (TPS) is defined as the number of PD-L1-positive tumor cells/total number of tumor cells ×100 (minimum of 100 viable tumor cells). In Keynote-040, patients with TPS < 50% did not have significant survival differences when compared with standard of care, while patients with TPS ≥ 50% showed an improved response rate, PFS and median OS.[13] In addition, in Keynote-055, a phase 2 study investigating the use of pembrolizumab in R/M HNSCC patients resistant to platinum chemotherapy and cetuximab, the ORR was higher according to PD-L1 positivity (ORR 18% in CPS ≥1% vs. 12% in CPS <1%; CPS analysis to 50% based on raw scores ORR 27% CPS ≥50% vs. 13% CPS <50%). However, this was not reflected in PFS or OS.[37] In Checkmate-141, survival analysis has shown a greater reduction in the risk of death with nivolumab when compared with the standard of care in patients with PD-L1-positive (CPS ≥1%) tumors (HR death: 0.55; 95% CI, 0.36–0.83) compared with patients with PD-L1-negative tumors (HR for death: 0.89; 95% CI, 0.54–1.45).[14] Further research is needed to explore additional potential biomarkers to detect responders in patients with low PD-L1 expression. Some of the exploratory predictive biomarkers include tumor mutational burden,[38–40] T-cell inflamed gene expression profile[40] and tumor-infiltrating lymphocytes.[36,41]

Most patients with HNSCC present with locally advanced disease, and a small proportion of these patients are not eligible to receive curative treatment, mainly owing to patient choice, advanced stage, poor performance status, and comorbidities.[42] The inclusion criteria for KEYNOTE-48 were patients with histologically or cytologically confirmed R/M HNSCC that was considered incurable by local therapies.[16] However, in the current cohort, 47 patients had locally advanced disease nonamenable to curative treatment, and the efficacy analysis showed a similar ORR (23.4% vs. 24.4% vs. 28.6%), PFS (5.7 vs. 5.1 vs. 3.6 months) and OS (11.3 vs. 11.2 vs. 9.0 months) in this group compared with patients with recurrent or de novo metastatic disease. We have reported a higher representation of this unusual patient group, possibly owing to the consequences of the COVID-19 pandemic and the delays in both presentation and clinical diagnosis for patients. Moreover, in a recent publication of the updated results of KEYNOTE-048, hazard ratios generally favored pembrolizumab alone versus cetuximab with chemotherapy except for recurrent disease subgroup.[28] In contrast, both PFS and OS were numerically higher in patients with recurrent disease than in patients with de novo metastatic disease in our cohort.

The combination of RT with immunotherapy is an actively growing research field, with a rapid increase in the number of clinical trials in several tumor sites.[20] In this cohort, 68 patients received palliative RT, with the majority receiving the treatment in the 6-month window prior to the date of commencing immunotherapy. Interestingly, the group of patients who received palliative RT had a numerically lower ORR (16.4% vs. 28.0%) and a statistically significantly shorter PFS (3.6 vs. 5.6 months) with a similar OS (10.1 vs. 11.4 months) compared with the group that did not receive palliative RT. In HNSCC, two randomized phase III trials assessing the combination effect of immunotherapy with radical chemoradiotherapy failed to meet primary endpoints.[43,44] In addition, in a phase II trial, the addition of stereotactic body RT to nivolumab treatment in metastatic HNSCC showed no improvement in response and no evidence of an abscopal effect.[45] It is suggested that local RT can lead to systemic immunity through an in situ vaccination effect.[46] Moreover, the expansion of antitumor CD8+ T cells within tumor-draining lymph nodes can mediate the antitumor immune response produced by PD-1/PD-L1 inhibitors.[47] A possible suggestion of these negative results is that RT including the draining lymph nodes may cause depletion of the nascent immunoreactive population. In our cohort, there was significant heterogeneity in the patient population in terms of the general condition and fitness and it is also uncertain how the patients were selected for palliative radiotherapy. In addition, there are variabilities in the timing of treatment compared with the commencement of immunotherapy, dose, and fractionation of palliative RT as well as treatment site (distant vs. local disease), which makes it difficult to draw clear conclusions from our observations. The results of the clinical studies and our analysis emphasize the fact that the optimal regimens of RT, in terms of optimal sequencing and dose/fractionation, volume and location of tumor irradiated, need to be further investigated and defined.

The most important limitation of this study is that the data were collected retrospectively. Thus, for the final survival analysis, patients were censored according to the last follow-up, which was variable for each center owing to small differences in the final submission date. In addition, the appearance of irAE is a time-dependent variable that can create an immortal-time bias when analyzed as a fixed covariate.[27] Finally, there is possible underreporting of irAEs in comparison with the reported toxicities of published studies.

In conclusion, we have confirmed the efficacy and safety of pembrolizumab as a first-line monotherapy for R/M HNSCC. However, we have shown a lower OS in this cohort, likely reflecting the differences regarding fitness of patients included in trials compared with the real-world setting. Finally, further research is required to tackle the challenging task of identifying potential predictive biomarkers.

AUTHOR CONTRIBUTIONS

Conceptualization: Anthony Kong, Shreerang Bhide, Ifigenia Vasiliadou. *Methodology*: Ifigenia Vasiliadou, Shreerang Bhide, and Anthony Kong. *Formal analysis*: Ifigenia Vasiliadou. *Resources*: Anthony Kong. *Data curation*: Ifigenia Vasiliadou, Elsa Lee, Isla Leslie, Mahwish Karim, Derek Grose, Christina Wilson, Alekh Thapa, Andrew Hartley, Sarah Partridge, Katharine Medlow, James De Boisanger, Robert Metcalf, Andrew Williamson, Anoop Haridass, David Noble, Karen Mactier, Harriet Walter, Ning Ma, Emma De Winton, Jennifer Cohen, Lindsay Rayner, Konstantinos Geropantas, Olly Donnelly, Petra Jankowska, Jessica Mason, Rafael Moleron, Kirsten Laws, Danny Ulahannan, Chandran Nallathambi, Andriana Michaelidou, Susanna Nallamilli, Sherif Raouf, Kieran Palmer, Saira Khalique, Tracy Karet, and Maya Bienz. *Writing—original draft preparation*: Ifigenia Vasiliadou and Anthony Kong. *Writing—review and editing*: Kevin Harrington, Shreerang Bhide, Chandran Nallathambi, Claire Paterson, and Anthony Kong. *Supervision*: Shreerang Bhide and Anthony Kong. All authors have read and agreed to the published version of the manuscript. The work reported in the article has been performed by the authors, unless clearly specified in the text.

ACKNOWLEDGMENTS

Kevin Harrington and Shreerang Bhide acknowledge funding from the Royal Marsden Hospital/The Institute of Cancer Research NIHR Biomedical Research center.

CONFLICT OF INTEREST STATEMENT

Anthony Kong received grant support from PUMA BioTechnology and AstraZeneca and fees for consulting, advisory and speaker roles from PUMA BioTechnology, Merck, MSD, Bristol-Myers Squibb, and Avvinity Therapeutics. Kevin Harrington received grant support from Boehringer Ingelheim and Replimune, Honoraria: AstraZeneca, BMS, Boehringer Ingelheim, Bergene, Merck-Serono, MSD, Pfizer. Rafael Moleron participated in the advisory boards for MSD and Vasodynamics. Robert Metcalf received honoraria from MSD. Konstantinos Geropantas received honoraria for advisory work with Merck. All other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The anonymized data that support the findings of this study are available from the corresponding author upon reasonable request. Institutional permission will need to be sought to share data with external parties.

ETHICS STATEMENT

An ethical approval and consent to participate form are not required as this is a retrospective study and all data collected are anonymised.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Vasiliadou I, Grose D, Wilson C, et al. The use of pembrolizumab monotherapy for the management of head and neck squamous cell carcinoma (HNSCC) in the UK. *Int J Cancer*. 2024;155(5):883-893. doi:10.1002/ijc.34963