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Title

Association between immune-related adverse events and clinical outcomes for head and neck squamous cell carcinoma treated with first-line palliative pembrolizumab monotherapy or in combination with chemotherapy: a national, multi-centre, real-world, retrospective cohort study

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Abstract

Objectives

To provide real-world performance data and identify clinical factors associated with survival outcomes for patients receiving first-line pembrolizumab-containing treatment for head and neck squamous cell carcinoma (HNSCC) in the palliative setting.

Materials and Methods

We analysed the electronic records of patients who initiated pembrolizumab-containing treatment between 01/03/2020–30/09/2021. Outcomes included overall survival (OS), progression-free survival (PFS), duration of response (DOR), disease control rate (DCR). Data were compared with the KEYNOTE-048 study and clinical factors were evaluated for association with survival.

Results

Our cohort included 91 patients (median follow-up 10.8 months). For patients receiving monotherapy (n=76), 12-month and 24-month OS was 45% and 27%, respectively, 12-month PFS was 22%, median DOR was 13.3 months, and DCR was 56.6%. For patients receiving pembrolizumab-chemotherapy (n=15), 12-month OS was 60%, 12-month PFS was 20%, median DOR was 7.3 months and DCR was 60.0%.

Experiencing ≥1 irAE (versus no irAEs), of any grade, was associated with favourable OS and PFS for patients receiving monotherapy in both univariable log-rank analysis (median OS 17.4 months versus 8.6 months, respectively, P=0.0033; median PFS 10.9 months versus 3.0 months, respectively, P<0.0001) and multivariable analysis (Cox proportional hazards regression: OS HR: 0.31, P=0.0009; PFS HR: 0.17, P<0.0001).

Conclusion

Our real-world data, first from a European population, support the KEYNOTE-048 study findings. Additionally, our data is first to show irAEs are associated with better outcomes in this patient group, adding to the growing body of evidence showing irAEs are generally a positive marker of PD-L1 inhibitor response.

Introduction

Palliative treatments are central to the management of head and neck squamous cell cancers (HNSCC) due to the predominance of advanced disease at diagnosis and the high levels of recurrence and comorbidities.[1,2] Within Scotland, only 56% of all patients diagnosed

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survive beyond 5 years after diagnosis, with this survival rate remaining relatively unchanged for the past two decades.[3]

The advent of immune checkpoint inhibitors over the last decade has represented a paradigm shift in cancer care and offers hope for improving these stubbornly static survival outcomes. In particular, the programmed death-1 (PD-1)-mediated inhibition of CD8+ T cell anti-tumour activity has been identified as a critical axis for tumour immune surveillance escape.[4] The recent KEYNOTE-048 Phase 3 randomised controlled trial (RCT) demonstrated the efficacy of pembrolizumab as a first-line treatment for recurrent and metastatic (R/M) HNSCC with international guidelines now recommending pembrolizumab, with or without chemotherapy, as the standard of care first-line treatment for R/M HNSCC with a PD-L1 combined positive score (CPS) ≥1.[2,5-7] In Scotland, pembrolizumab received short-term approval for use without PD-L1 CPS testing as an alternative to immunosuppressing cytotoxic chemotherapy during the COVID-19 pandemic.[8] Since September 2020, it has had full Scottish Medical Consortium approval, with or without chemotherapy, in the first-line palliative setting, for patients with HNSCC where PD-L1 assessment confirms CPS ≥1.[9]

Whilst strict inclusion and exclusion criteria used within RCTs allow for minimally biased evidence, the populations of such studies differ from real-world patient populations, with a tendency to be younger and fitter.[10] Real-world studies are valuable in assessing the efficacy and toxicity of new treatments in routine clinical practice whilst also allowing the analysis of factors influencing treatment response.[11,12] For example, immune-related adverse events (irAEs) are predictive of better outcomes for patients receiving PD-L1 inhibitors in several disease settings including in the second-line palliative setting with Nivolumab in HNSCC.[13-15] Such real-world studies are lacking for first-line palliative pembrolizumab-containing regimens for HNSCC.

To address this gap in the literature, we conducted a national, multi-centre, retrospective cohort study with two aims: to provide real-world performance data and to explore factors predicting clinical outcomes using univariable and multivariable analyses.

Patients and methods

Study Design and Participants

We conducted a retrospective cohort study using electronic records for patients treated at five tertiary cancer care centres covering the entire Scottish population of 5.3 million people. The study collected anonymised health service clinical practice data and was approved by

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NHS Information Governance. REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines were followed when reporting this study.[16]

Patients were identified by searching the local Chemotherapy Electronic Prescribing and Administration Systems (CEPAS) at each centre. Linked records were identified in the local radiotherapy records, electronic clinical records and national radiology records using unique National Health Service Scotland patient identifier numbers (Figure 1). A standardised data collection form was used for all centres and anonymised data collated at a single site for analysis.

Eligible patients had initiated pembrolizumab-containing treatment between 1st March 2020 to 30th September 2021 as first-line palliative therapy for HNSCC. Patients received either pembrolizumab monotherapy (200 mg 3-weekly or 400 mg intravenously [IV] 6-weekly) or pembrolizumab-chemotherapy (pembrolizumab 200 mg IV Day 1, cisplatin 75–100mg/m² or carboplatin AUC 5mg/mL/min IV Day 1, and 5-Fluorouracil 750–1000mg/m² IV Day 1–4) every 21 days for up to 6 cycles followed by pembrolizumab maintenance monotherapy as described. Patients continued treatment for a maximum of two years, until disease progression or unacceptable toxicity. Patients were excluded from this analysis if they received pembrolizumab as part of a clinical study.

Patient characteristics collected were age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking history and any relevant comorbidities. Disease characteristics collected were primary tumour subsite, pathology (including p16 status for oropharyngeal primary tumours and cancers of unknown primary, and PD-L1 CPS), and treatment history. Follow-up data collected included irAEs, additional treatments received during and after pembrolizumab treatment, radiological response, and the date and cause of death. Adverse reactions were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.

Statistical Analysis

Overall survival (OS), progression-free survival (PFS) and duration of response (DOR) were estimated using Kaplan-Meier analysis. OS was defined as the time from cycle 1 of pembrolizumab to the date of death from any cause. PFS was defined as the time from cycle 1 of pembrolizumab to the date of radiological progression, decline in performance requiring treatment cessation or death from any cause, whichever came first. Patients were censored for all survival analyses if still alive at the end of the follow-up period or if lost to follow-up. DOR was defined, as per KEYNOTE-048 analysis,[5] as the length of time from radiological

response to progression, decline in performance requiring treatment cessation or death for patients with radiological response at any time whilst receiving pembrolizumab-containing treatment. Log-rank test was used for survival curve comparative analysis.

The responsible treating clinician defined radiological response, using both clinical and radiological evaluations. Where the treating clinical teams stated the disease as responding to treatment, we categorised this as “response”. Where it was stated there was a mixed response or only some of the disease locations were responding, we categorised this as “mixed response”. Where the treating clinical teams stated the disease was stable or there was no change from the last cross-sectional imaging reports, we categorised this as “stable disease”. Where it was stated that the disease was progressing or no follow-up cross-sectional imaging was performed due to deterioration PS or death, we categorised this as “progressive disease”. Best radiological response during treatment with pembrolizumab was reported.

For disease control rate (DCR) analysis, DCR was defined as the proportion of patients with a best radiological response categorised as response, mixed response or stable disease. Fisher's exact test was used to analyse differences in DCR.

Cox proportional hazards regression was used for univariable and multivariable analyses. For the multivariable analysis, confounding factors were selected for inclusion if associated with differential overall survival in KEYNOTE-048 and potentially with irAEs.[5,17] All statistical analysis was performed using GraphPad PRISM v9.5.1.

Results

Patient characteristics

Of our 91-patient cohort, two (2.2%) patients were lost to follow-up. Median follow-up was 10.8 months (range 0.6–25.3 months), 10.7 months (range 1.0–25.3 months) and 11.7 months (range 0.6–18.6 months) for the whole cohort, patients treated with pembrolizumab monotherapy, and patients treated with pembrolizumab-chemotherapy, respectively.

Baseline characteristics are shown in Table 1. PD-L1 CPS was not measured in 21 (27.6%) patients receiving pembrolizumab monotherapy during the short-term COVID-19 pandemic-related approval period when this was not required. Two patients with nasopharyngeal tumour were included, both were EBV negative/p16 positive HNSCC. Whilst patients with EBV-driven nasopharyngeal cancer represent a distinct disease entity, the patients included

in our cohort were felt to represent a mucosal SCC, in keeping with those found at other sub-sites.

Efficacy

For patients receiving pembrolizumab monotherapy, 12-month and 24-month OS was 45% and 27%, respectively (Figure 1a), and median OS was 11.4 months. PFS was 22% and 14% at 12 months and 24 months, respectively (Figure 1c), and median PFS was 6.4 months. Median DOR was 13.3 months (Figure 1e) with a DCR of 56.6% (35.5% response, 11.8% mixed response and 9.2% stable disease) (Figure 1g).

For patients receiving pembrolizumab-chemotherapy, 12-month OS was 60% (Figure 1b). PFS was 20% at 12 months and median PFS was 4.5 months (Figure 1d). Median DOR was 7.3 months with a DCR of 60.0% (53.3% response, 6.7% mixed response and 0.0% stable disease, Figure 1h). Median OS, and 24-month OS and PFS had not yet been reached for these patients.

irAEs

The irAE profile is shown in Table 2. For those receiving pembrolizumab monotherapy, 28 patients (36.8%) experienced an irAE of any grade (total irAEs = 50). Six patients (7.9%) experienced an irAE graded ≥3 (total grade ≥3 irAEs = 7). The most frequent types of irAE experienced were hypothyroidism (14.5%), fatigue (11.8%) and diarrhoea (10.5%) (Table 2).

For those receiving pembrolizumab-chemotherapy, 6 patients (40.0%) experienced an irAE of any grade (total number of irAEs = 10). Two patients (13.3%) experienced an irAE graded ≥3 (total number of grade ≥3 irAEs = 2). The most frequent irAEs experienced were fatigue (20.0%) and rash (13.3%).

irAEs are associated with better outcomes

Kaplan-Meier and Log-rank analysis showed a significantly better OS (median OS 17.4 versus 8.6 months, respectively, P = 0.0033) and PFS (median PFS 10.9 versus 3.0 months, respectively, P <0.0001) for patients receiving pembrolizumab alone who had experienced ≥1 irAE of any grade compared with those who experienced no irAEs (Figure 2a and 2c). Similar but non-significant trends were observed for patients receiving pembrolizumab-chemotherapy (Figure 2).

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Best radiological response stratified by experiencing ≥1 irAE is shown in Figures 2e and 2f. For patients receiving pembrolizumab monotherapy, DCR was significantly greater (P <0.0001) at 89.3% for those who experienced ≥1 irAE of any grade (64.3% response, 17.9% mixed response and 7.1% stable disease) versus 37.5% for those who experience no irAEs (18.8% response, 8.3% mixed response and 10.4% stable disease).

Similarly, for patients receiving pembrolizumab-chemotherapy, DCR was significantly greater (P = 0.0278) at 100.0% for those who experienced ≥1 irAE of any grade (83.3% response, 16.7% mixed response and 0.0% stable disease) versus 33.3% for those who experience no irAEs (33.3% response, 0.0% mixed response and 0.0% stable disease).

Identifying other clinical factors associated with OS and PFS

To investigate other clinical factors for association with differential OS or PFS in patients receiving pembrolizumab monotherapy, we performed univariable Cox proportional hazards regression (Table 3). ECOG PS = 2 and p16 positive nasopharyngeal primary site were significantly associated with worse OS with p16 positive nasopharyngeal primary site also associated with worse PFS (Table 3).

Our cohort included a substantial proportion of patients with newly-diagnosed, non-metastatic tumours (27 patients [35.5%] of those receiving pembrolizumab monotherapy), a group with low representation in the KEYNOTE-048 study, 3 patients (1%).[5] When comparing OS and PFS for this group versus patients with locoregional recurrence or metastatic disease, using univariable Cox proportional hazards regression, we found similar survival outcomes (Table 3).

Multivariable survival analysis

Since potential risk factors for irAEs have been associated with differential outcomes in the KEYNOTE-048 study subgroup analysis,[5,17] we controlled for these possible confounding covariables using multivariable analysis (Table 3). When accounting for age, ECOG PS, disease status treated (metastatic; locoregional recurrence; newly diagnosed, non-metastatic), p16 status and PD-L1 CPS, experiencing ≥1 irAE remained highly significantly associated with both OS (HR: 0.31 [95% confidence interval: 0.15–0.60], P = 0.0009) and PFS (HR: 0.17 [95% confidence interval: 0.08–0.33], P <0.0001).

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Discussion

Our national retrospective cohort study reports the real-world performance of pembrolizumab monotherapy and pembrolizumab-chemotherapy as first-line palliative treatment for patients with HNSCC in a European-based population and adds to the limited worldwide real-world data for this treatment. Within our cohort, we found 12-month and 24-month OS was 45% and 27%, respectively, for patients who had received pembrolizumab monotherapy, with a median OS of 11.4 months. This is reassuringly comparable to the KEYNOTE-048 study where 12-month and 24-month OS (the primary endpoint) was 49% and 27%, respectively, with a median OS of 11.6 months for patients receiving the same treatment (Table 4).[5] For patients in our cohort who had received pembrolizumab-chemotherapy, 12-month OS was 60%, with 24-month and median OS yet to be reached. Again, this was broadly similar to the KEYNOTE-048 study where 12-month OS was 53% for patients receiving combination treatment (Table 4). Similarly, 12-month PFS for patients receiving pembrolizumab monotherapy or pembrolizumab-chemotherapy was also comparable to the same endpoints in the KEYNOTE-048 study (Table 4). Three other studies have reported the real-world OS for patients receiving pembrolizumab with or without chemotherapy as first-line palliative treatment for HNSCC (two Japanese and one USA population study). All reported similar results to our cohort.[18-20] One study, of a Japanese cohort, reported 12-month OS was 51.9% and 58.8% for patients receiving pembrolizumab monotherapy and pembrolizumab-chemotherapy, respectively.[19] The second Japanese study did not stratify analyses by treatment type and reported a 12-month OS of 64.5% for all patients receiving any form of pembrolizumab treatment.[18] The third study, of a USA cohort, reported a median OS of 8.8 months and found no significant difference between their observational and reconstructed survival data from the KEYNOTE-048 study.[20] Overall, our data suggest the efficacy of pembrolizumab reported in the KEYNOTE-048 study is reflected in our real-world European population, and is similar to other real-world studies in different geographical populations.

Immune-related adverse events of any grade were experienced by 36.8% of patients who had received pembrolizumab monotherapy and 40.0% of patients who received pembrolizumab-chemotherapy within our cohort, whilst around 8.8% patients receiving any treatment experienced an irAE graded 3 or more. The most frequently recorded irAE for patients receiving pembrolizumab monotherapy within our cohort (hypothyroidism (14.5%), fatigue (11.8%) and diarrhoea (10.5%) were generally similar to the KEYNOTE-048 study population (14%, 28% and 15%, respectively), though fatigue was notably less frequent in our cohort. The only notable higher frequency irAE in our cohort was hepatitis (7.9% in our cohort versus 1% in the KEYNOTE-048 study). For patients receiving pembrolizumab-chemotherapy in our cohort, fatigue (20.0%) and rash (13.3%) were most frequent and were

also broadly similar to the reported rates in the KEYNOTE-048 study (34% and 11%, respectively), though fatigue again was less frequently reported in our cohort. The rigorous monitoring and careful documentation of adverse events in clinical trials, compared with day-to-day clinical practice, may well explain the differences between our data and the KEYNOTE-048 study, and thus toxicity comparisons must be interpreted with caution.

Across multiple tumour types, it has become apparent that experiencing irAEs when receiving PD-1/PD-L1 targeting immune checkpoint inhibitors is associated with better clinical outcomes.[13,15,21-24] We report that patients who had received pembrolizumab monotherapy and who experienced ≥1 irAE had a favourable median OS of 17.4 months versus 8.6 months for those who experienced no irAEs. Similarly, we found this same patient group who experienced ≥1 irAE had a favourable median PFS of 10.9 months versus 3.0 months for those who experienced no irAEs. Using multivariable analysis, we found that, even when controlling for possible confounding factors, a significant association of experiencing ≥1 irAE with favourable OS and PFS was maintained suggesting an independent association. Our data suggest a trend toward an association between irAEs and better survival outcomes in the patients receiving pembrolizumab-chemotherapy, similar to patients receiving pembrolizumab monotherapy, however, this was not statistically significant. Given our data show a strong association between higher DCR and experiencing ≥1 irAE for the pembrolizumab-chemotherapy group, a survival benefit would be expected. The small sample size within our cohort, particularly of evaluable patients at 24 months, may explain why our survival analysis did not meet statistical significance. Thus, further follow-up of a larger cohort will be helpful to further clarify any associations within this group.

To our knowledge, the independent association between irAEs and better outcomes has not been reported in patients receiving pembrolizumab as first-line palliative treatment for HNSCC before. Another real-world study, in a Japanese population, has reported an association between experiencing any adverse event, not restricted to irAEs, with better OS for patients receiving pembrolizumab monotherapy in univariable analysis.[19] The same study also found no association between adverse events and OS and a negative associated with PFS for those receiving pembrolizumab-chemotherapy. The inclusion of adverse effects usually attributable to the chemotherapy component, such as neutropenia, may explain this finding in this study. In contrast, analysis of real-world data in a different Japanese cohort found no association between irAEs and OS.[18] The study cohort was smaller (N=32) than our own, and thus potentially underpowered, and combined patients receiving pembrolizumab monotherapy (n=16) and those receiving pembrolizumab-chemotherapy (n=16), potentially increasing noise in the data such that the association could not be detected.

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Our study also found that experiencing ≥1 irAE is associated with markedly higher radiological response rate and DCR for patients receiving both pembrolizumab monotherapy and pembrolizumab-chemotherapy. This association has been described previously in patients receiving nivolumab for HNSCC.[13,21] We believe this is the first report of this association for patients receiving pembrolizumab as first-line palliative treatment for HNSCC. Interestingly, analyses conducted in patients receiving nivolumab for the treatment of non-small cell lung cancer has concluded that irAEs experienced within 6 weeks of treatment initiation are predictive of better DCR, PFS and OS, suggesting irAEs are an early predictive marker of response.[14,23] Our data did not record the timing of irAEs and thus further analyses are warranted to ascertain if this temporal relationship is also true for patients receiving first-line pembrolizumab for HNSCC in the palliative setting.

Our cohort contained a substantial number (n=33) of patients with disease status of newly diagnosed, non-metastatic HNSCC (Table 1). This group made up a low proportion of the KEYNOTE-048 study population (n=7), thus we provide novel performance data in this subgroup.[5] Despite the substantially larger proportion of this subgroup in our cohort, our efficacy endpoints were comparable to the KEYNOTE-48 study. Indeed, our univariable analysis for patients receiving pembrolizumab monotherapy found no significant association between disease status and OS or PFS (Table 3). Our multivariable model found metastatic disease was significantly associated with worse PFS as compared with newly diagnosed, non-metastatic disease (Table 2), however, this analysis was not designed with the appropriate cofactors to specifically test this independent association. Overall, our analysis suggests pembrolizumab performs effectively in treatment naïve patients with newly diagnosed, non-metastatic disease, a group with minimal representation within the KEYNOTE-048 study. Thus, our study highlights that the principles of first-line palliative management for this patient subgroup is equivalent to those applied to the management of recurrent and metastatic disease.

A patient subgroup not represented in the KEYNOTE-048 study but present in our cohort were those with a PS of 2. The patients in our cohort had acutely deteriorated to PS2 due to disease factors, rather than chronic comorbidities. Thus, treatment with pembrolizumab was deemed to be appropriate despite poorer PS.

Our univariable analysis found this PS was associated with poorer OS, in keeping with previous studies investigating patients with HNSCC receiving immune checkpoint inhibitors.[25,26] Given only 5 patients in our cohort had this PS, further studies with a more substantial representation of this patient group are needed and are currently underway.[27]

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Patient characteristics in our study differed between those receiving pembrolizumab monotherapy and pembrolizumab-chemotherapy. A higher response rate, and better early survival performance has been reported in the KEYNOTE-048 study for patients receiving the latter treatment.[5] Based on this, patients in daily clinical practice analysed in our study were selected for pembrolizumab-chemotherapy if there was rapidly growing and/or highly symptomatic disease and if they were able to tolerate the potential increased toxicity of the combination regimen. Due to this selection bias, we analysed patients who received pembrolizumab-chemotherapy as a separate population to those who received pembrolizumab monotherapy. Nonetheless, a higher rate of radiological response was seen in patients receiving pembrolizumab-chemotherapy compared with pembrolizumab monotherapy (Figure 2) primarily due to a lower proportion of mixed responses or stable disease. This qualified observation is in keeping with the findings of the KEYNOTE-048 study and supportive of the rationale behind the choice to offer combination treatment for select patient populations.

A strength of our study was the analogous measurement of survival between our cohort and the KEYNOTE-048 study, providing comparable data in a real-world population. The KEYNOTE-048 protocol specified pembrolizumab treatment needed to be started the same day or within 5 days of randomisation, the starting point for survival measurements.[5] We calculated our survival measures from the date of treatment initiation, thus aligning our measures closely. Despite the retrospective nature of our study, our outcomes are in keeping with those from the KEYNOTE-048 study and suggest our data is likely to be robust generally. A limitation of our study was that radiology did not explicitly use response criteria evaluation in solid tumours (RECIST) when reporting and so radiological response classification was determined by comparison of the radiology reported evaluations and the clinical evaluation of the treating clinician retrospectively.[28] further limitation of our study was the modest sample size. However, our numbers are similar to the larger of the previously published Japanese cohorts, but with European data and longer follow up, therefore, offering new insights to the real-world performance of pembrolizumab in the longer term.

Conclusion

In conclusion, we performed a national, multi-centre, real-world, retrospective cohort study of patients in Scotland receiving pembrolizumab with or without chemotherapy as a first-line palliative treatment for HNSCC. Our data shows pembrolizumab performs comparably to the pivotal Phase 3 KEYNOTE-048 study, in day-to-day clinical practice, including in patients with newly diagnosed, non-metastatic disease. Finally, we conclude that irAEs are highly

associated with better clinical outcomes in patients receiving pembrolizumab monotherapy, with trend towards an association in patients receiving pembrolizumab-chemotherapy.

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Conflict of Interest Statement

Christina Wilson reports an honoraria from MSD outwith this study. Rafael Moleron reports advisory boards for MSD and Vasodynamics. All remaining authors report no conflicts of interest.

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Figures and tables

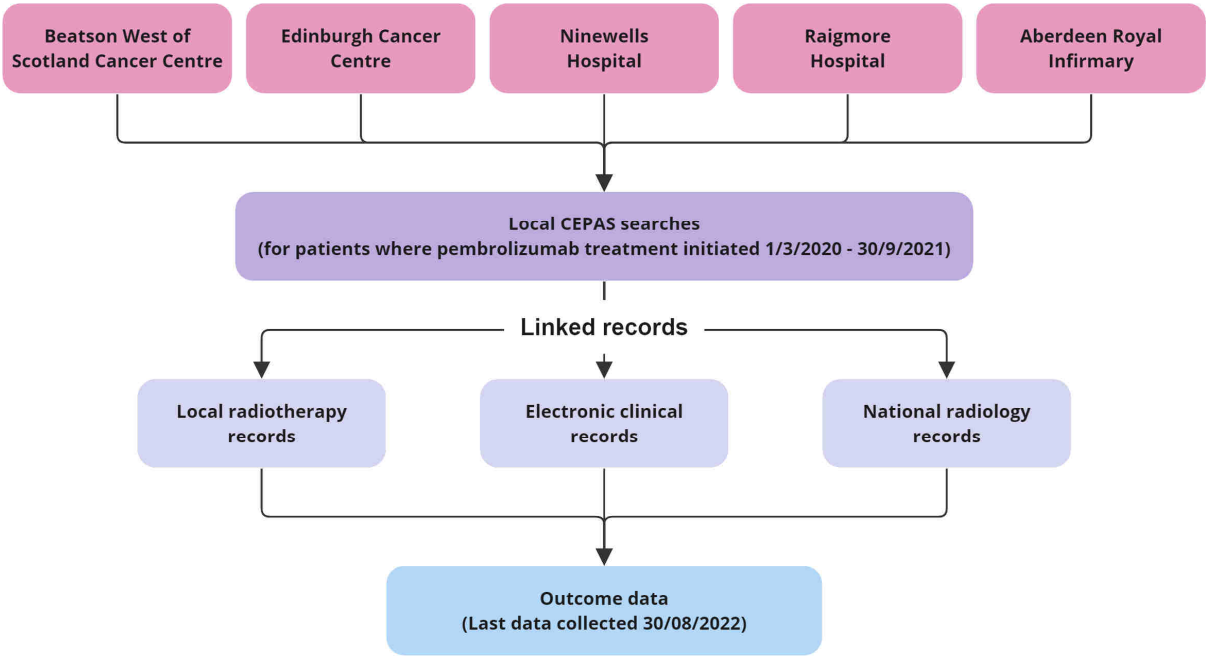

Figure 1. Record linkage flow diagram. Cancer centres involved in the study are shown at the top. CEPAS, Chemotherapy Electronic Prescribing and Administration System.

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	Scottish study		KEYNOTE-048	
	Pembrolizumab monotherapy	Pembrolizumab -chemotherapy	Pembrolizumab monotherapy	Pembrolizumab -chemotherapy
	n = 76	n = 15	n = 301	n = 281
Age, median years (range)				
	66 (38–86)	53 (34–76)	62 (56–68)	61 (55–68)
Age, years, n (%)				
≤50	5 (6.6)	4 (26.7)		
50–70	51 (67.1)	9 (60.0)		
>70	20 (26.3)	2 (13.3)		
Gender, n (%)				
Male	55 (72.4)	8 (53.3)	250 (83)*	224 (80)*
Female	21 (27.6)	7 (46.7)	51 (17)*	57 (20)*
ECOG performance status, n (%)				
0	15 (19.7)	6 (40.0)	118 (39)	110 (39)
1	56 (73.7)	9 (60.0)	183 (61)	171 (61)
2	5 (6.6)	0 (0.0)	0 (0)	
Smoking status, n (%)				
Current or former	67 (88.2)	12 (80.0)	239 (79)	224 (80)
Never	9 (11.8)	3 (20.0)	62 (21)	57 (20)
p16 status, n (%)				
Positive	11 (14.5)	4 (26.7)	63 (21)	60 (21)
Negative	17 (22.4)	2 (13.3)		
Not done/Not applicable	48 (63.2)	9 (60.0)		
PD-L1 CPS, n (%)				
≥1 – <20	38 (50.0)	8 (53.3)	124 (41)	116 (41)
≥20	17 (22.4)	7 (46.7)	133 (44)	126 (45)
Not measured	21 (27.6)	0 (0.0)		
Disease status, n (%)				
Newly diagnosed, non-metastatic	27 (35.5)	6 (40.0)	3 (1)	4 (1)
Locoregional recurrence†	24 (31.6)	7 (46.7)	82 (27)	76 (27)
Metastatic	25 (32.9)	2 (13.3)	216 (72)	201 (72)
Primary tumour site, n (%)				
Oropharynx	26 (34.2)	6 (40.0)	113 (38)	113 (40)
Oral cavity	12 (15.8)	7 (46.7)	82 (27)	82 (29)
Hypopharynx	20 (26.3)	0 (0.0)	38 (13)	44 (16)
Larynx	11 (14.5)	0 (0.0)	74 (25)	46 (16)
Nasopharynx	1 (1.3)	1 (6.7)		
Sinus	3 (3.9)	1 (6.7)		
Unknown primary site	3 (3.9)	0 (0.0)		
Platinum therapy received, n (%)				
Cisplatin	N/A	14 (93.3)		121 (43)
Carboplatin	N/A	1 (6.7)		160 (57)

Table 1. Baseline demographics in the present study (Scottish study) and the KEYNOTE-048 study.[5]

In the present study, p16 result was only recorded for oropharyngeal and unknown primary site

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tumours. CPS, combined positive score; PD-L1, programmed death-ligand 1. *KEYNOTE-048 study reported sex of participants. †Recurrent disease at primary site and/or regional lymph nodes.

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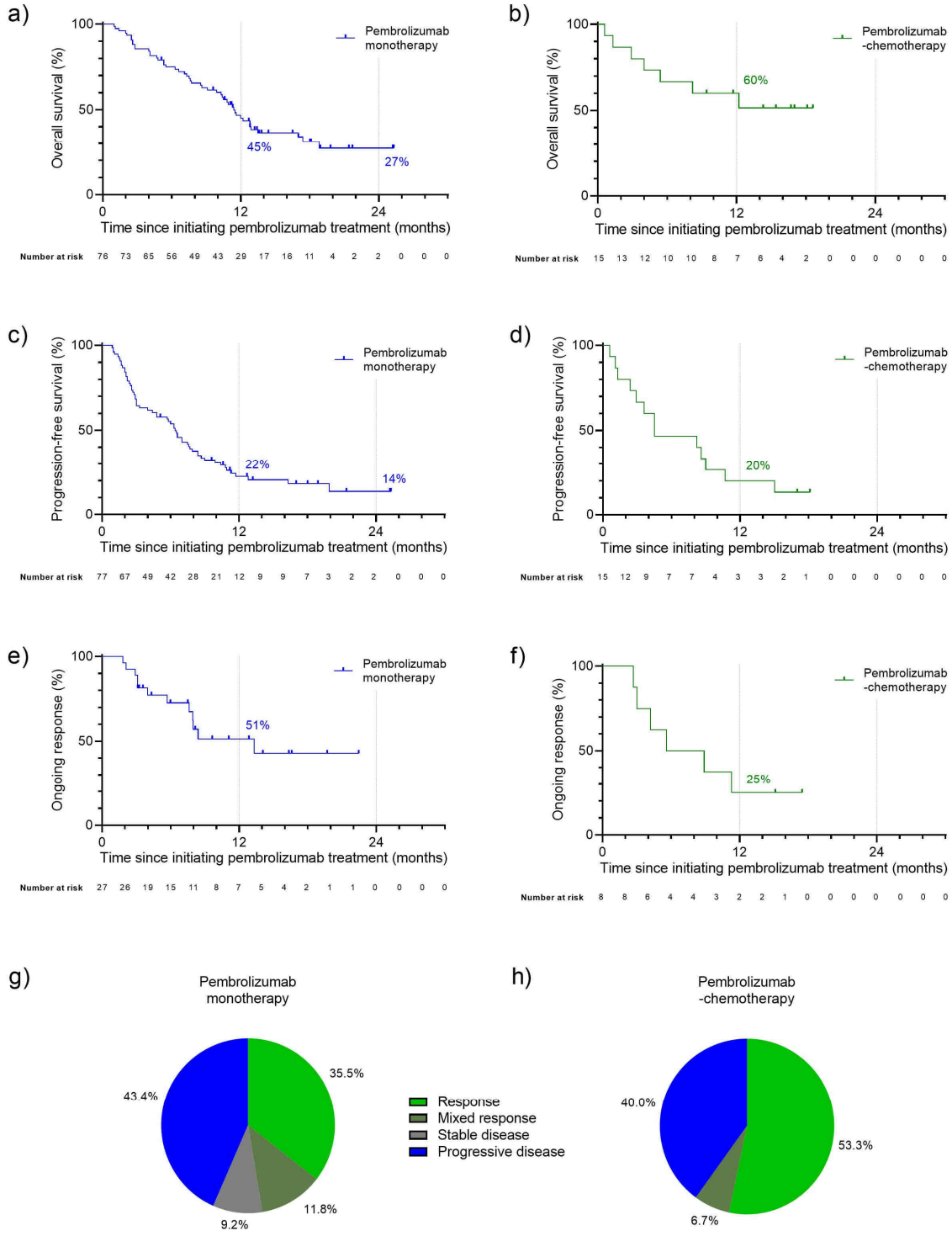

Figure 2. Kaplan-Meier survival curves for overall survival, progression-free and duration of response in patients receiving pembrolizumab monotherapy (a), c) and e), respectively) or with chemotherapy (b), d) and f), respectively). Where reached, percentage survival at 12- and 24-month are shown. Best radiological response during treatment for patients receiving g) pembrolizumab alone or h) with chemotherapy. No patients receiving pembrolizumab-chemotherapy had the best radiological response categorised as stable disease.

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	Pembrolizumab alone		Pembrolizumab -chemotherapy	
	n = 76		n = 15	
irAE, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
GI disorders	16 (21.1)	4 (5.3)	1 (6.7)	1 (6.7)
Hepatitis	6 (7.9)	3 (3.9)	0 (0.0)	0 (0.0)
Diarrhoea	8 (10.5)	1 (1.3)	1 (6.7)	1 (6.7)
Oesophagitis	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Mucositis	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	14 (18.4)	2 (2.6)	1 (6.7)	0 (0.0)
Hypothyroidism	11 (14.5)	0 (0.0)	1 (6.7)	0 (0.0)
Hypoadrenalism	2 (2.6)	2 (2.6)	0 (0.0)	0 (0.0)
Hyperthyroidism	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic, n (%)	9 (11.8)	0 (0.0)	3 (20.0)	0 (0.0)
Fatigue	9 (11.8)	0 (0.0)	3 (20.0)	0 (0.0)
Dermatological disorders	5 (6.6)	1 (1.3)	2 (13.3)	1 (6.7)
Rash	3 (3.9)	1 (1.3)	2 (13.3)	1 (6.7)
Pruritus	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Peri-oral rash	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal disorders	4 (5.3)	0 (0.0)	1 (6.7)	0 (0.0)
Arthralgia	4 (5.3)	0 (0.0)	1 (6.7)	0 (0.0)
Respiratory disorders	1 (1.3)	0 (0.0)	1 (6.7)	0 (0.0)
Pneumonitis	1 (1.3)	0 (0.0)	1 (6.7)	0 (0.0)
Renal disorders	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
Nephritis	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
Neurological disorders	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathic pain	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)

Table 2. Immune-related adverse event profile. GI, gastrointestinal; irAE, immune-related adverse event.

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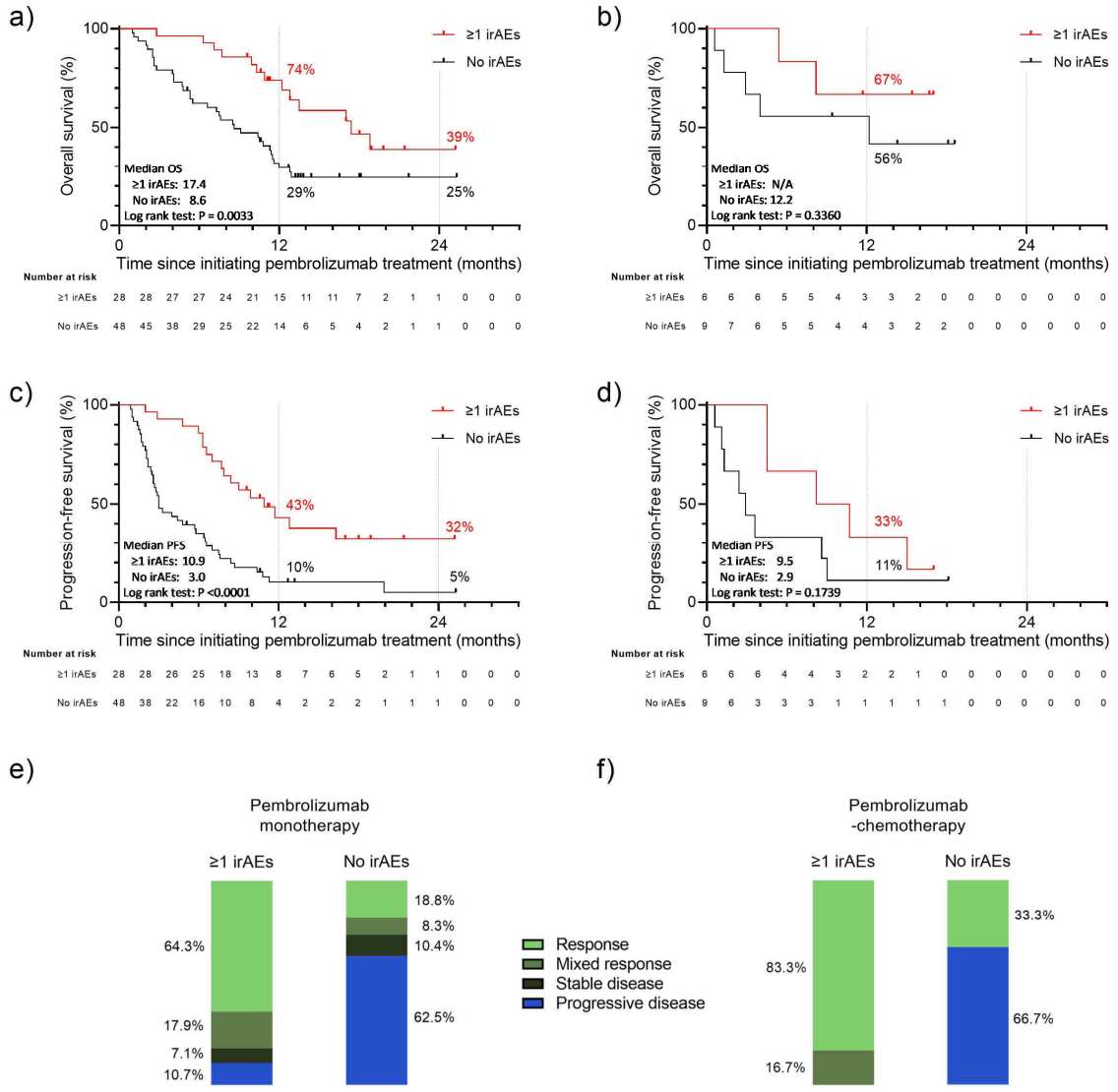

Figure 3. Kaplan-Meier survival curves for a) overall survival and c) progression-free survival in patients receiving pembrolizumab alone, and b) overall survival and d) progression-free survival in patients receiving pembrolizumab with chemotherapy, stratified by the presence or absence of irAEs of any grade. Best radiological response during treatment as judged by the treating clinical team for patients receiving e) pembrolizumab alone and f) pembrolizumab-chemotherapy, who experienced 1 or more irAE of any grade (left bars) or no irAE (right bars). No patients receiving pembrolizumab-chemotherapy had the best radiological response categorised as stable disease. irAEs, immune-related adverse events; N/A, not applicable; OS, overall survival; PFS, progression-free survival.

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	OS						PFS					
	Univariable analysis			Multivariable analysis			Univariable analysis			Multivariable analysis		
Factor	HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value
≥1 irAE (reference: No)												
Yes	0.39	(0.20–0.73)	**0.0045**	0.31	(0.15–0.60)	**0.0009**	0.32	(0.18–0.56)	**<0.0001**	0.17	(0.08–0.33)	**<0.0001**
Age (reference: ≥65 years)												
<65 years	0.91	(0.48–1.64)	0.7515	1.36	(0.53–3.22)	0.5038	0.89	(0.51–1.50)	0.6610	1.16	(0.50–2.63)	0.7190
Gender (reference: Male)												
Female	1.61	(0.88–2.85)	0.1131				1.62	(0.93–2.76)	0.0791			
ECOG PS at cycle 1 (reference: 1)												
0	0.55	(0.23–1.17)	0.1515	0.46	(0.17–1.10)	0.1002	0.62	(0.30–1.19)	0.1791	0.50	(0.20–1.13)	0.1169
2	3.38	(1.13–8.22)	**0.0141**	3.95	(1.06–13.47)	**0.0311**	1.89	(0.65–4.37)	0.1801	1.91	(0.52–6.31)	0.3026
Smoking status (reference: Current or former)												
Never	1.64	(0.67–3.46)	0.2312				1.27	(0.56–2.54)	0.5265			
p16 status (reference: negative)												
Positive	1.04	(0.32–3.03)	0.9383	0.88	(0.22–3.09)	0.8401	1.04	(0.39–2.59)	0.9324	0.67	(0.19–2.14)	0.5156
Not done/Not applicable	1.84	(0.92–4.10)	0.1037	2.31	(1.03–5.71)	0.0528	1.63	(0.88–3.24)	0.1384	2.34	(1.09–5.43)	**0.0367**
PD-L1 CPS (reference: ≥1 to <20)												
≥20	1.38	(0.66–2.72)	0.3719	1.45	(0.67–3.02)	0.3247	1.65	(0.86–3.06)	0.1167	1.73	(0.87–3.36)	0.1096
Not measured	0.89	(0.44–1.74)	0.7395	0.61	(0.29–1.25)	0.1889	0.80	(0.42–1.47)	0.4862	0.52	(0.25–1.02)	0.0650
Disease status (reference: Newly diagnosed, non-metastatic)												
Locoregional recurrence†	0.60	(0.28–1.24)	0.1790	0.50	(0.22–1.10)	0.0925	0.76	(0.40–1.43)	0.3939	0.61	(0.28–1.26)	0.1896
Metastatic	1.06	(0.55–2.03)	0.8605	1.16	(0.56–2.34)	0.6800	1.46	(0.79–2.68)	0.2252	2.29	(1.11–4.74)	**0.0244**
Primary tumour site (reference: Oropharynx)												
Oral cavity	1.37	(0.54–3.26)	0.4829				1.40	(0.62–2.98)	0.3934			

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Hypopharynx	1.74	(0.82–3.72)	0.1468		1.56	(0.81–3.03)	0.1819	
Larynx	1.68	(0.59–4.27)	0.2924		1.24	(0.51–2.76)	0.6193	
Nasopharynx	19.24	(0.98–127.30)	**0.0083**		18.16	(0.93–118.30)	**0.0093**	
Sinus	3.25	(0.74–10.17)	0.0671		1.58	(0.37–4.68)	0.4653	
Unknown primary site	1.37	(0.21–4.98)	0.6818		0.73	(0.12–2.52)	0.6665	
Primary XRT received (reference: No)								
Yes	1.04	(0.57–1.85)	0.8966		1.07	(0.63–1.78)	0.8104	
Palliative XRT received (reference: No)								
Yes	1.16	(0.61–2.11)	0.6291		1.44	(0.81–2.47)	0.1960	
Time from Dx to pembrolizumab (reference: <12 months)								
≥12 months	0.88	(0.48–1.57)	0.6666		0.83	(0.49–1.40)	0.4961	

Table 3. Univariable analysis of factors potentially associated with OS and PFS for patients receiving pembrolizumab alone. Multivariable analysis adjusting for factors potentially confounding the association between experiencing ≥1 irAE and OS ad PFS. Statistically significant P values are shown in bold and underlined. The most frequent category was chosen as the reference. CI, confidence interval; CPS, combined positive score; Dx, diagnosis; HR, hazard ratio; irAEs, immune-related adverse events; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PS, performance score; XRT, radiotherapy. †Recurrent disease at primary site and/or regional lymph nodes.

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	Scottish study		KEYNOTE-048 study	
Outcome	Pembrolizumab monotherapy	Pembrolizumab -chemotherapy	Pembrolizumab monotherapy	Pembrolizumab -chemotherapy
OS - median (months)	11.4	Not yet reached	11.6	13.0
OS - 12 months	45%	60%	49%	53%
OS - 24 months	27%	Not yet reached	27%	29%
PFS - 12 months	22%	20%	17%	17%
DOR - median (months)	13.3	7.3	22.6	6.7

Table 4. Summary of efficacy outcomes from our study and the KEYNOTE-048 trial.[5] DOR, duration of response; irAEs, immune-related adverse events; OS, overall survival; PFS, progression-free survival.