Oral Oncology 147 (2023) 106587

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Pembrolizumab versus methotrexate, docetaxel, or cetuximab in recurrent or metastatic head and neck squamous cell carcinoma (KEYNOTE-040): Subgroup analysis by pattern of disease recurrence

K.J. Harrington [a,*], E.E.W. Cohen [b], D. Soulières [c], J. Dinis [d], L. Licitra [e], M.-J. Ahn [f], A. Soria [g], J.-P. Machiels [h], N. Mach [i], R. Mehra [j], B. Burtness [k], R.F. Swaby [l,1], J. Lin [l], J. Ge [l], N. Lerman [l], C. Le Tourneau [m]

[a] 105 Cotswold Road, Division of Radiotherapy and Imaging, The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, London SM2 5NG, United Kingdom
[b] 3855 Health Sciences Dr, Department of Medical Oncology, Moores Cancer Center, UC San Diego Health, La Jolla, CA 92093, United States
[c] 1560, rue Sherbrooke estx, Department of Hematology and Oncology, Centre Hospitalier de l'Université de Montréal, Montreal, QC H2L 4MN, Canada
[d] R Dr. Antonio Bernardino de Almeida Medicina Oncologica Unidade de Investigacao Clinica, Department of Medical Oncology, Instituto Português de Oncologia do Porto Francisco Gentil, 4200-072 Porto, Portugal
[e] Via Giacomo Venezian, 1, Department of Head and Neck Cancer, Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, 20133 Milan, Italy
[f] 81 Irwon-Ro Gangnam, Department of Hematology & Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 06351, South Korea
[g] Ctra. de Colmenar Viejo km. 9,100, Department of Medical Oncology, Hospital Universitario Ramón y Cajal, 28034 Madrid, Spain
[h] Avenue Hippocrate 10, Department of Medical Oncology, Institut Roi Albert II, Cliniques Universitaires Saint-Luc and Institut de Recherche Clinique et Expérimentale, Université Catholique de Louvain (UCLouvain), 1200 Brussels, Belgium
[i] Rue Gabrielle-Perret-Gentil 4, Clinical Research Unit, Department of Oncology, Hôpitaux Universitaires de Genève, 1205 Geneva, Switzerland
[j] 22 South Greene Street, Department of Head and Neck Medical Oncology, Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD 21201, United States
[k] 25 York Street PO Box 208028, Yale Cancer Center and Department of Medicine, Yale University School of Medicine, New Haven, CT 06510, United States
[l] 90 E Scott Ave, Merck & Co., Inc., Rahway, NJ 07065, United States
[m] 26 rue d'Ulm, Department of Drug Development and Innovation (D3i), Institut Curie, Paris-Saclay University, 75005 Paris, France

ARTICLE INFO

Keywords:
Head and neck squamous cell carcinoma
Pembrolizumab
Recurrent
Metastatic

ABSTRACT

Background: In the phase 3 KEYNOTE-040 study, pembrolizumab prolonged OS versus chemotherapy in previously treated recurrent or metastatic (R/M) HNSCC. We present a post hoc subgroup analysis by disease recurrence pattern: recurrent-only, recurrent and metastatic (recurrent-metastatic), and metastatic-only HNSCC.
Materials and Methods: Patients had HNSCC that progressed during or after platinum-containing treatment for R/M disease or had recurrence or progression within 3–6 months of previous platinum-containing definitive therapy for locally advanced disease. Patients were randomly assigned (1:1) to pembrolizumab 200 mg Q3W or investigator's choice of standards of care (SOC): methotrexate, docetaxel, or cetuximab. Outcomes included OS, PFS, ORR, and DOR. The data cutoff was May 15, 2017.
Results: There were 125 patients (pembrolizumab, 53; SOC, 72) in the recurrent-only subgroup, 204 in the recurrent-metastatic subgroup (pembrolizumab, 108; SOC, 96), and 166 in the metastatic-only subgroup (pembrolizumab, 86; SOC, 80). The hazard ratio (95% CI) for death for pembrolizumab versus SOC was 0.83 (0.55–1.25) in the recurrent-only, 0.78 (0.58–1.06) in the recurrent-metastatic, and 0.74 (0.52–1.05) in the metastatic-only subgroups. PFS was similar between treatment arms in all subgroups. ORR was 22.6% for pembrolizumab versus 16.7% for SOC in the recurrent-only, 10.2% versus 6.3% in the recurrent-metastatic, and 15.1% versus 8.8% in the metastatic-only subgroups. DOR was numerically longer with pembrolizumab in all subgroups.

* Corresponding author at: Division of Radiotherapy and Imaging, The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, 15 Cotswold Road, London SM2 5NG, United Kingdom.
E-mail addresses: Kevin.Harrington@icr.ac.uk (K.J. Harrington), ecohen@ucsd.edu (E.E.W. Cohen), denis.soulieres.chum@ssss.gouv.qc.ca (D. Soulières), jdinis@ipoporto.min-saude.pt (J. Dinis).
[1] Present address: Carisma Therapeutics Inc, 3675 Market St., Ste. 200, Philadelphia, PA 19104, United States.

https://doi.org/10.1016/j.oraloncology.2023.106587
Received 25 April 2023; Received in revised form 29 September 2023; Accepted 6 October 2023
Available online 3 November 2023

Conclusion: Pembrolizumab provided numerically longer OS and durable responses in all subgroups compared with SOC, suggesting that patients with previously treated R/M HNSCC benefit from pembrolizumab regardless of recurrence pattern.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is a major cause of cancer-associated illness and death. In 2020, there were approximately 750,000 new cases of lip, oral cavity, oropharynx, hypopharynx, and larynx cancer diagnosed worldwide, accounting for over 360,000 deaths [1]. Although early-stage (stage I/II) HNSCC is treatable with surgery or radiotherapy, more than 60 % of patients present with stage III or IV disease [2]. These patients have an increased risk of developing recurrent or metastatic disease, for which the prognosis is poor [2]. Historically, the median overall survival (OS) for patients with recurrent or metastatic HNSCC was less than 1 year [3], with disease control impeded by treatment resistance and the infiltrative and multifocal nature of recurrent HNSCC [4].

Before the availability of immune checkpoint inhibitors, platinum-based regimens with or without cetuximab were the standard of care (SOC) for patients with recurrent or metastatic HNSCC that was not amenable to locoregional treatment [5,6]. More recently, programmed death 1 (PD-1) inhibitors pembrolizumab and nivolumab have demonstrated clinically meaningful antitumor activity and manageable safety in phase 3 trials in both first- and second-line settings for patients with recurrent and/or metastatic HNSCC [7–11]. The findings of these trials have changed the treatment paradigm. Both nivolumab and pembrolizumab are recommended as second-line treatment options after progression on platinum-based therapy for patients with immune checkpoint inhibitor–naive HNSCC [6,12]. Based on results from the phase 3 KEYNOTE-048 study [8], pembrolizumab is also now approved in the first-line setting for patients with metastatic or unresectable recurrent HNSCC as monotherapy for patients with programmed death ligand 1 (PD-L1)–positive disease (combined positive score [CPS] $\geq$ 1 [13]) and, in combination with platinum and 5-FU, in either all patients or in those with PD-L1–positive disease (CPS $\geq$ 1), depending on jurisdiction [14,15].

The phase 3 KEYNOTE-040 study was conducted to compare pembrolizumab with investigator's choice of methotrexate, docetaxel, or cetuximab in patients with platinum-refractory recurrent or metastatic HNSCC [7]. These agents were considered SOC at the time the study was designed and conducted. Median OS in KEYNOTE-040 was 8.4 months for pembrolizumab versus 6.9 months for investigator's choice of SOC treatment (hazard ratio [HR], 0.80; 95 % confidence interval [CI], 0.65–0.98; nominal $P = 0.0161$), which was considered a clinically meaningful survival benefit [7].

While the prognostic impact of having a primary diagnosis of early- versus advanced-stage HNSCC is well characterized [16–19], outcomes for patients with relapsed disease by pattern of recurrence remain to be elucidated in the context of PD-1 blockade. This post hoc subgroup analysis of KEYNOTE-040 was conducted to evaluate the efficacy of pembrolizumab versus SOC therapy in patients with previously treated, recurrent and/or metastatic HNSCC by pattern of recurrence. We primarily considered the following subgroups: patients with recurrent-only disease limited to above the neck and/or periclavicular area, patients with both recurrent and metastatic (recurrent-metastatic) disease, and patients with metastatic-only disease.

Methods

Study design and patients

KEYNOTE-040 was an open-label, randomized, phase 3 study in patients with recurrent and/or metastatic HNSCC whose disease progressed during or after platinum-based therapy (NCT02252042). The study design has been published [7]. The key inclusion criteria were age $\geq$ 18 years; histologically or cytologically confirmed recurrent or metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx that was incurable by local therapies; disease progression during or after platinum-containing treatment for recurrent or metastatic disease or recurrence or progression within 3–6 months of definitive platinum-containing multimodal therapy; $\leq$ 2 lines of prior therapy for recurrent or metastatic HNSCC; known HPV p16 status for oropharyngeal cancer; known PD-L1 expression status; $\geq$ 1 measurable lesion per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) [20]; and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Eligible patients were randomly assigned (1:1) to receive intravenous (IV) pembrolizumab 200 mg every 3 weeks or investigator's choice of methotrexate 40 mg/m^2 IV once weekly that could be increased to a maximum of 60 mg/m^2 in the absence of toxicity, docetaxel 75 mg/m^2 IV once every 3 weeks, or cetuximab 400-mg/m^2 IV loading dose and subsequent 250 mg/m^2 weekly. Randomization was stratified by ECOG performance status (0 versus 1), p16 status in patients with oropharyngeal cancer (positive versus negative), and PD-L1 status (tumor proportion score $\geq$ 50 % versus $<$ 50 %).

Assessments

This post hoc analysis assessed efficacy of pembrolizumab versus SOC for the same end points as the protocol-specified analysis in the intention-to-treat (ITT) population. These were OS, progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR). Response was assessed per RECIST v1.1 by blinded independent central review, with or without confirmation. PD-L1 expression was assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA, USA).

Statistical analyses

Efficacy was assessed in the ITT population of all patients randomly allocated to study treatment. Disease status subgroups were defined based on investigator's designation and data entry of the category as captured through electronic case reporting forms. The recurrent-only disease subgroup included patients with locoregional recurrence limited to above the neck and/or periclavicular area and included patients with locally persistent disease (disease that progressed within 6 months of initial definitive treatment or never responded to it). The recurrent-metastatic disease subgroup included patients who had both locoregional recurrence and distant metastases. The metastatic-only subgroup included patients with distant metastases only (no locoregional recurrence). Efficacy was also assessed in a wider subgroup of patients who had recurrent disease with or without distant metastases, which included all patients in the recurrent-only and recurrent-metastatic subgroups. Results for these analyses are provided in the supplemental material. Additionally, OS was evaluated by baseline sum of diameter of target lesions.

OS, PFS, and DOR were estimated using the Kaplan–Meier method. HRs and 95 % CIs were calculated using a Cox model with a single treatment covariate. No adjustments were made for multiplicity.

Results

A total of 495 patients were randomly assigned to treatment in KEYNOTE-040 (pembrolizumab, 247; SOC, 248). In this analysis, 125 patients were included in the recurrent-only disease subgroup (pembrolizumab, 53; SOC, 72); 204 were included in the recurrent-metastatic subgroup (pembrolizumab, 108; SOC, 96); and 166 patients were included in the metastatic-only subgroup (pembrolizumab, 86; SOC, 80) (supplemental Fig. 1). Baseline demographics were generally balanced between treatment arms and subgroups (Table 1). Exceptions included a higher proportion of patients in the metastatic-only subgroup with an ECOG performance status of 0, HPV-associated disease, and receipt of two prior lines of chemotherapy compared with the other subgroups. Additionally, a larger proportion of pembrolizumab-treated patients in the metastatic-only subgroup had an ECOG performance status of 0 and a PD-L1 CPS of ≥ 1 compared with SOC-treated patients, and a smaller proportion of pembrolizumab-treated patients in the recurrent-metastatic subgroup had a PD-L1 tumor proportion score of 1 % to < 50 % compared with SOC-treated patients. More patients received docetaxel as investigator's choice of SOC rather than methotrexate or cetuximab (Table 1).

Median time from randomization to data cutoff (May 15, 2017) was 20.0 months for pembrolizumab and 17.3 months for SOC in the recurrent-only subgroup, 17.7 versus 19.1 months in the recurrent-metastatic subgroup, and 18.7 versus 17.7 months in the metastatic-only subgroup (supplemental Table 1).

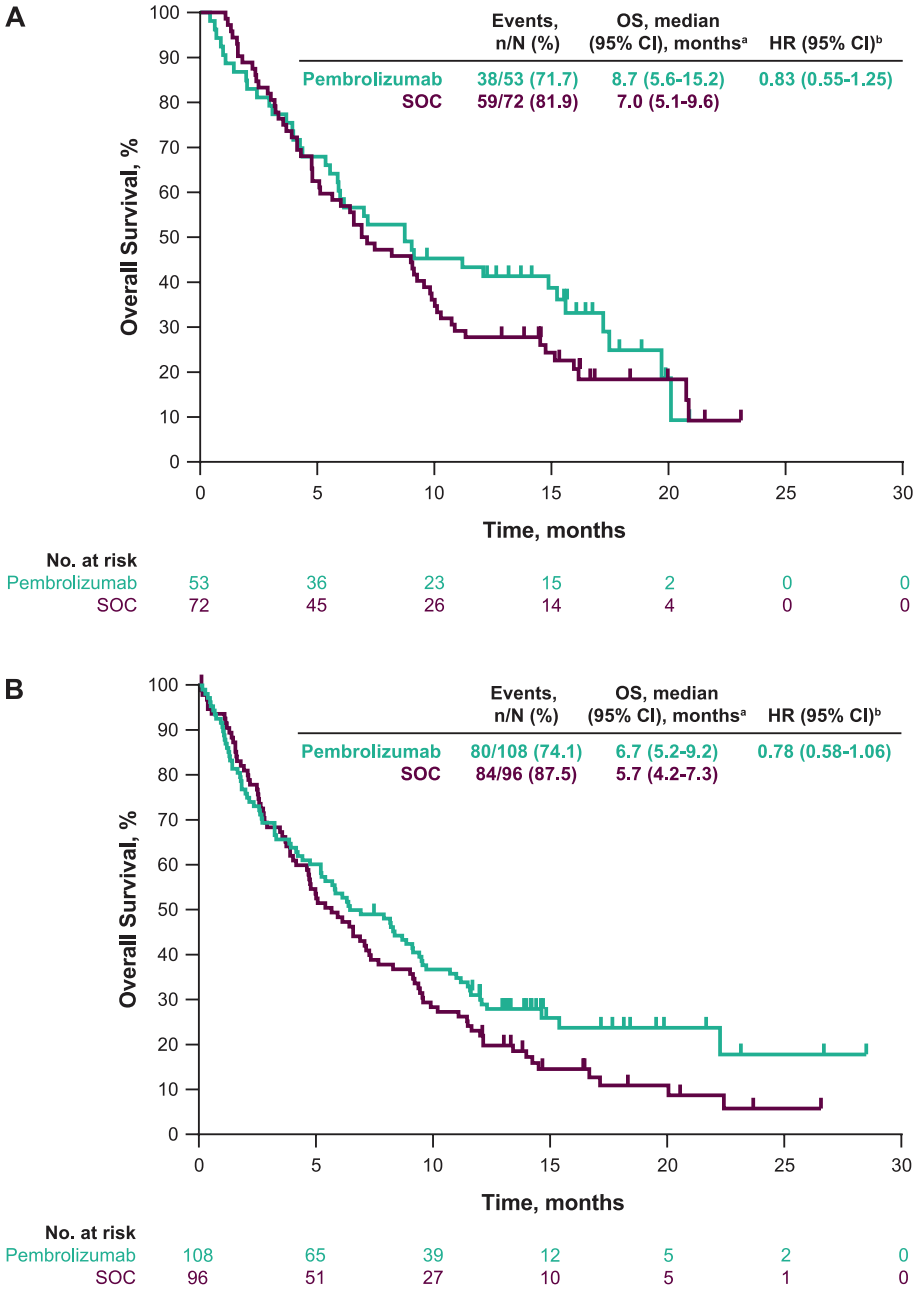

Figure 1. Overall survival in patients with (A) recurrent-only, (B) recurrent-metastatic, and (C) metastatic-only disease. HR, hazard ratio; OS, overall survival; SOC, standard of care. [a]From product-limit (Kaplan–Meier) method for censored data. [b]Based on Cox regression model, with treatment as a single covariate.

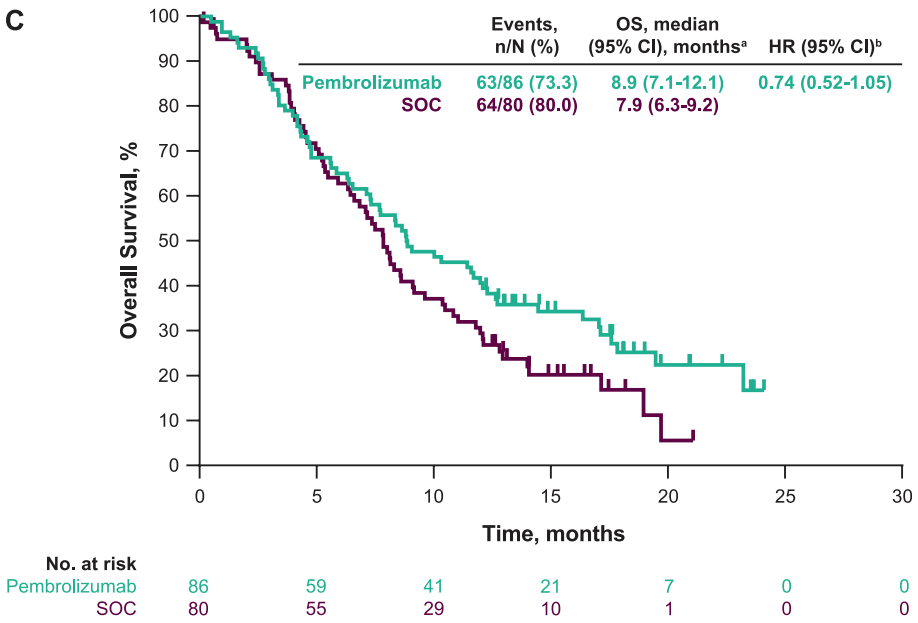

Figure 1. (*continued*).

Table 1
Demographic and disease characteristics at baseline for patients with recurrent-only, recurrent-metastatic, and metastatic-only disease (ITT population).

	Recurrent-only		Recurrent-metastatic		Metastatic-only	
	Pembrolizumab n = 53	SOC n = 72	Pembrolizumab n = 108	SOC n = 96	Pembrolizumab n = 86	SOC n = 80
Age, median (range), years	62.0 (28–78)	60.5 (36–76)	60.0 (19–83)	59.0 (34–78)	59.5 (31–85)	62.0 (44–77)
Sex						
Male	43 (81.1)	57 (79.2)	90 (83.3)	82 (85.4)	74 (86.0)	66 (82.5)
Female	10 (18.9)	15 (20.8)	18 (16.7)	14 (14.6)	12 (14.0)	14 (17.5)
ECOG performance status						
0	11 (20.8)	16 (22.2)	24 (22.2)	27 (28.1)	36 (41.9)	24 (30.0)
1	42 (79.2)	56 (77.8)	84 (77.8)	68 (70.8)	50 (58.1)	56 (70.0)
2	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Current or former smoker	36 (67.9)	51 (70.8)	81 (75.0)	71 (74.0)	62 (72.1)	60 (75.0)
p16 positive in the oropharynx	9 (17.0)	10 (13.9)	25 (23.1)	22 (22.9)	27 (31.4)	26 (32.5)
PD-L1 tumor proportion score[a]						
0 %	17 (32.1)	24 (33.3)	50 (46.3)	37 (38.5)	36 (41.9)	32 (40.0)
1 % to < 50 %	19 (35.8)	25 (34.7)	30 (27.8)	39 (40.6)	30 (34.9)	23 (28.8)
≥ 50 %	16 (30.2)	23 (31.9)	28 (25.9)	19 (19.8)	20 (23.3)	23 (28.8)
Missing	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	2 (2.5)
PD-L1 combined positive score[b]						
< 1	9 (17.0)	16 (22.2)	28 (25.9)	20 (20.8)	13 (15.1)	18 (22.5)
≥ 1	43 (81.1)	56 (77.8)	80 (74.1)	75 (78.1)	73 (84.9)	60 (75.0)
Missing	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	2 (2.5)
Investigator's choice of SOC therapy[c]						
Methotrexate	—	21 (29.2)	—	22 (22.9)	—	22 (27.5)
Docetaxel	—	31 (43.1)	—	49 (51.0)	—	30 (37.5)
Cetuximab	—	20 (27.8)	—	25 (26.0)	—	28 (35.0)
Chemotherapy before enrollment						
Curative intent[d]	8 (15.1)	12 (16.7)	20 (18.5)	16 (16.7)	6 (7.0)	12 (15.0)
First-line	30 (56.6)	48 (66.7)	62 (57.4)	50 (52.1)	49 (57.0)	43 (53.8)
Second-line	13 (24.5)	12 (16.7)	26 (24.1)	29 (30.2)	30 (34.9)	23 (28.8)
Third-line	2 (3.8)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.2)	2 (2.5)
Baseline sum of diameter of target lesion, median (range)[e]	55.5 (15.0–152.0)	55.0 (16.0–825.0)	61.0 (15.0–226.0)	61.0 (16.0–450.0)	55.0 (16.0–276.0)	74.5 (12.0–366.0)

ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PD-L1, programmed death ligand 1; SOC, standard of care.
Data are n (%) unless otherwise stated.
[a] The PD-L1 tumor proportion score was defined as the percentage of tumor cells with membranous PD-L1 expression.
[b] The PD-L1 combined positive score was defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.
[c] Identified before randomization.
[d] Including adjuvant, neoadjuvant, or definitive treatment.
[e] 119 patients in the recurrent-only, 202 in the recurrent-metastatic, and 160 in the metastatic group had evaluable data.

Median OS for pembrolizumab versus SOC was 8.7 months (95 % CI, 5.6–15.2) versus 7.0 months (95 % CI, 5.1–9.6) in the recurrent-only subgroup (HR, 0.83; 95 % CI, 0.55–1.25), 6.7 months (95 % CI, 5.2–9.2) versus 5.7 months (95 % CI, 4.2–7.3) in the recurrent-metastatic subgroup (HR, 0.78; 95 % CI, 0.58–1.06), and 8.9 months (95 % CI, 7.1–12.1) versus 7.9 months (95 % CI, 6.3–9.2) in the metastatic-only subgroup (HR, 0.74; 95 % CI, 0.52–1.05) (Fig. 1). Median PFS for pembrolizumab versus SOC was 3.9 months (95 % CI, 2.2–4.9) versus 3.5 months (95 % CI, 2.2–4.1) in the recurrent-only subgroup (HR, 0.93; 95 % CI, 0.64–1.37), 2.1 months (95 % CI, 2.0–2.1) versus 2.1 months (95 % CI, 2.0–2.6) in the recurrent-metastatic subgroup (HR, 0.95; 95 % CI, 0.71–1.28), and 2.1 months (95 % CI, 2.1–2.2) versus 2.2 (95 % CI, 2.1–3.4) in the metastatic-only subgroup (HR, 0.86; 95 % CI, 0.62–1.19) (Fig. 2).

In the recurrent-only subgroup, ORR was 22.6 % (95 % CI, 12.3–36.2) for pembrolizumab versus 16.7 % (95 % CI, 8.9–27.3) for SOC (Table 2). In the recurrent-metastatic subgroup, ORR was 10.2 % (95 % CI, 5.2–17.5) for pembrolizumab versus 6.3 % (95 % CI, 2.3–13.1) for SOC (Table 2). In the metastatic-only subgroup, the ORR was 15.1 % (95 % CI, 8.3–24.5) for pembrolizumab versus 8.8 % (95 % CI, 3.6–17.2) for SOC (Table 2). Median DOR for pembrolizumab versus SOC was 5.5 months (range, 0.0 + to 13.8 +) versus 4.8 months (range, 0.0 + to 18.8) in the recurrent-only subgroup, not reached (range, 1.4 to 13.7 +) versus 4.3 months (range, 2.3–5.0) in the recurrent-metastatic subgroup, and 6.2 months (range, 1.4–18.4) versus 2.9 months (range, 1.3 to 10.4 +) in the metastatic-only subgroup (Table 2; supplemental Fig. 2). Summary data for percentage change from baseline in the sum of target lesion size are provided in supplemental Table 2.

Data for the wider subgroup of patients with recurrent disease with or without metastatic disease are provided in the supplemental results

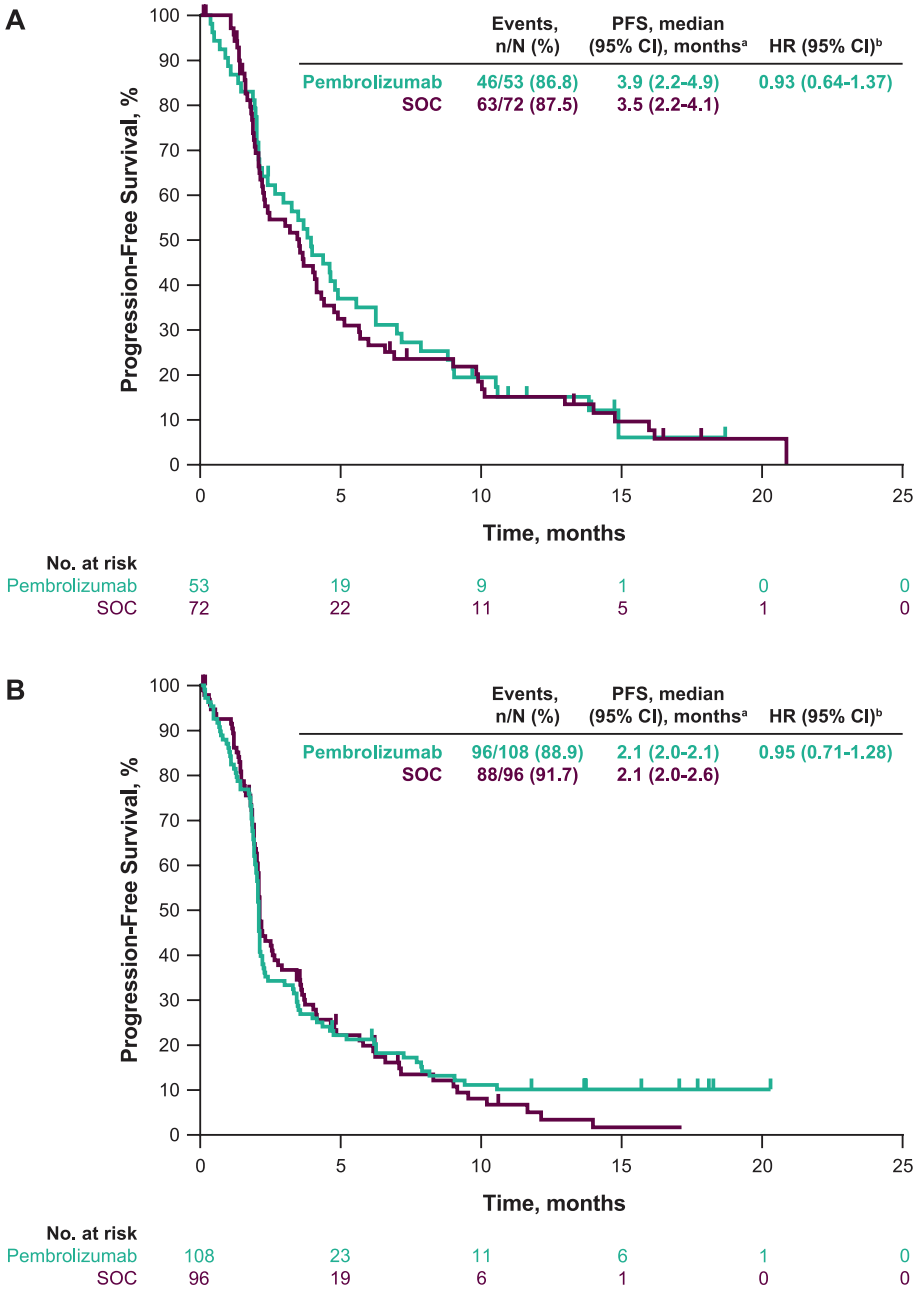

Figure 2. Progression-free survival in patients with (A) recurrent-only, (B) recurrent-metastatic, and (C) metastatic-only disease. HR, hazard ratio; PFS, progression-free survival; SOC, standard of care. [a]From product-limit (Kaplan–Meier) method for censored data. [b]Based on Cox regression model, with treatment as a single covariate.

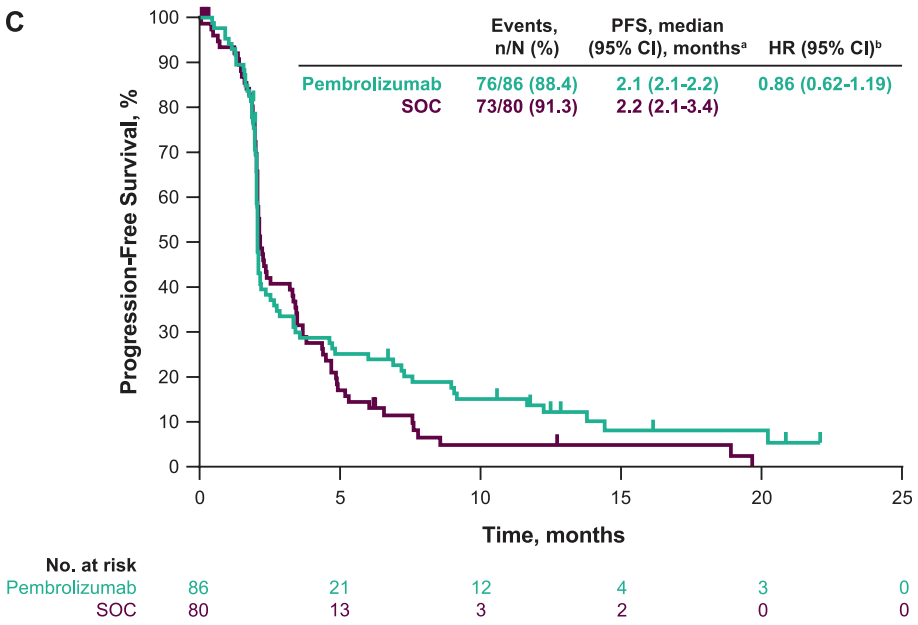

Figure 2. (*continued*).

Table 2
Objective response[a] in patients with recurrent-only, recurrent-metastatic, and metastatic-only disease.

	Recurrent-only		Recurrent-metastatic		Metastatic-only	
	Pembrolizumab n = 53	SOC n = 72	Pembrolizumab n = 108	SOC n = 96	Pembrolizumab n = 86	SOC n = 80
Objective response, *n*	12	12	11	6	13	7
ORR (95 % CI), %	22.6 (12.3–36.2)	16.7 (8.9–27.3)	10.2 (5.2–17.5)	6.3 (2.3–13.1)	15.1 (8.3–24.5)	8.8 (3.6–17.2)
Estimated difference in ORR (95 % CI)[b]	6.0 (−7.9 to 20.9)		3.9 (−4.1 to 12.0)		6.4 (−3.8 to 16.7)	
DOR, median (range), months	5.5 (0.0 + to 13.8 +)	4.8 (0.0 + to 18.8)	NR (1.4 to 13.7 +)	4.3 (2.3 to 5.0)	6.2 (1.4 to 18.4)	2.9 (1.3 to 10.4 +)

DOR, duration of response; NR, not reached; ORR, objective response rate; SOC, standard of care.
"+" indicates there was no progressive disease by the time of last disease assessment.
[a] Response was assessed per RECIST v1.1 by blinded independent central review with and without confirmation.
[b] Comparison of ORR between treatment groups was performed using the stratified Miettinen and Nurminen method, with strata weighting by sample size.

(supplemental Tables 1–4; supplemental Figs. 2–4).

When the data were evaluated by baseline sum of diameter of target lesions, 163, 159, and 159 patients were in the lower, middle, and upper tertiles, respectively. For the total populations, median OS was 12.0 (95 % CI, 9.1–14.7), 7.1 (95 % CI, 6.3–8.7), and 5.2 (95 % CI, 4.0–6.4) months for the lower, middle, and upper tertiles of baseline sum of diameter of target lesions (supplemental Fig. 5).

For patients in the lower tertile, median OS for pembrolizumab versus chemotherapy was 12.1 (95 % CI, 7.2–17.1) and 11.3 (95 % CI, 8.0–15.1) months (HR, 0.94 [95 % CI, 0.64–1.38]), respectively (supplemental Fig. 6A). For patients in the middle tertile, median OS for pembrolizumab versus chemotherapy was 7.7 (95 CI, 5.4–9.6) versus 7.1 (95 CI, 6.0–8.6) months (HR, 0.68 [95 % CI, 0.48–0.97]), respectively (supplemental Fig. 6B). For patients in the upper tertile, median OS for pembrolizumab versus chemotherapy was 5.8 (95 % CI, 3.3–8.3) and 4.6 (3.8–6.1) months (HR, 0.82 [95 % CI, 0.59–1.14]), respectively (supplemental Fig. 6C).

Discussion

The current post hoc subgroup analysis of the KEYNOTE-040 trial was conducted to address clinicians' queries about the potential benefit of single-agent pembrolizumab in patients with different patterns of recurrence. The results suggest that there is treatment benefit with pembrolizumab in patients with previously treated recurrent or metastatic HNSCC regardless of recurrence pattern, albeit with relatively small group sizes for each comparison. OS was numerically longer with pembrolizumab versus investigator's choice of methotrexate, docetaxel, or cetuximab in all subgroups, and a higher proportion of patients receiving pembrolizumab versus SOC had an objective response. Responses observed with pembrolizumab were durable, particularly among patients in the recurrent-metastatic and metastatic-only subgroups. The favorable results observed in the recurrent-only subgroup are of particular note because these patients are often symptomatic and at risk of rapid disease progression. There were no differences in PFS between treatment arms in any subgroup. The longest median PFS was seen in the recurrent-only subgroup, which may reflect the difficulty in definitive diagnosis of progression in the previously irradiated and/or operated tissues of the head and neck region. Additionally, evaluating OS by burden of disease (as defined by target lesion sum-of-diameter tertiles) determined that patients with greater disease burden had worse outcomes, suggesting that overall treatment effect might vary with disease burden. However, analysis of OS outcomes with pembrolizumab versus SOC in each sum-of-diameter tertile did not show a clear association between disease burden and benefit from pembrolizumab. As the analysis measured target lesions only, which do not fully account for all aspects of disease burden, the analysis should be considered hypothesis-generating only.

Limited data are available regarding differential outcomes for patients with HNSCC who have locoregional recurrence versus recurrent disease with metastases. Subgroup analysis of OS in the KEYNOTE-048 trial showed that HRs favored pembrolizumab and pembrolizumab-

chemotherapy compared with cetuximab-chemotherapy for patients with metastatic disease but not recurrent-only disease [8]. These findings differ from those of the current analysis, in which a numeric improvement was observed in OS in all subgroups but did not reach statistical significance, with all 95 % CIs overlapping 1.

Analyses of OS by pattern of recurrence or clinical stage have not been conducted in prospective clinical trials investigating nivolumab in advanced HNSCC, but results from two small retrospective analyses have been reported. One analysis of 53 patients with platinum-refractory recurrent or metastatic HNSCC treated with nivolumab showed no difference in PFS or OS between patients with distant metastatic disease versus patients with locoregional disease without distant metastases (AJCC clinical stage IVC versus III, IVA, IVB disease: HR for PFS, 0.98 [95 % CI, 0.42–2.26]; HR for OS, 1.04 [95 % CI, 0.35–3.12]) [21]. In contrast, a recent analysis of 30 patients with recurrent or metastatic HSNCC treated with nivolumab after platinum-based therapy reported that median PFS was longer in patients who had metastatic-only disease compared with patients with both locoregional and metastatic disease (8.8 versus 5.1 months), and that response rate was higher in patients with metastatic lesions than in patients with locoregional disease (41.6 % versus 20 %) [22].

This study has several limitations. Most important, the analysis was post hoc and did not include adjustments for multiplicity. Results should be interpreted with caution. Differences in baseline characteristics, such as ECOG performance status and number of prior lines of therapy may have influenced the results. The metastatic-only subgroup also included a higher proportion of patients with HPV-associated disease than did other subgroups, which is generally considered indicative of better prognosis [23–25]. While this should be noted, subgroup analyses of previous trials investigating PD-1 inhibitors in advanced HNSCC have shown no significant differences in outcome between patients with HPV-associated versus HPV-negative disease [7,8,10], suggesting that this imbalance is unlikely to have impacted outcomes in the current analysis.

The results of this analysis showed that pembrolizumab provided longer OS and durable responses in patients with previously treated HNSCC, regardless of whether they had recurrent-only disease, recurrent disease with distant metastases, or metastatic disease only. These findings suggest patients with previously treated recurrent or metastatic HNSCC can benefit from pembrolizumab regardless of pattern of recurrence.

Declaration of Competing Interest

KJH reports honoraria from BMS, Merck-Serono, MSD, and Replimune; advisory/consultancy roles with Arch Oncology, AstraZeneca, BMS, Boehringer-Ingelheim, Codiak, Eisai, Inzen, Merck-Serono, MSD, Oncolys, Pfizer, and Replimune; speaker bureau for BMS, Merck-Serono, MSD, and Replimune; and research grant/funding from AstraZeneca, Boehringer-Ingelheim, and Replimune. EEWC reports advisory/consultancy roles with Axelia, Cel Sci, Eisai, Hoopika, ImmunoSensor, Istari, Janssen, Kahr Medical, Mana Therapeutics, Merck, Mirati, MSD, Nectin Tx, Pangea Therapeutics, and Roche; is a member of the board of directors for Psiouxus Therapeutics, and NCCN; has stock/shares with Kinnate Biopharma and Primmune Therapeutics; and has a leadership role with Ayala, Kura, and Kinnate Biopharma DS reports advisory/consultancy roles with Merck and Adlai-Nortye and research grant/funding from Merck, GSK, Adlai-Nortye, and BMS. JD reports advisory/consultancy role with Roche, PharmaMar, BMS, Merck Serono, and MSD; is a principal investigator for studies from Roche, BI, and MSD; and travel expenses from PharmaMar. LL reports research funding from Astrazeneca, BMS, Boehringer Ingelheim, Celgene International, Eisai, Exelixis, Debiopharm International SA, Hoffmann-La Roche ltd, IRX Therapeutics, Medpace, Merck-Serono, MSD, Novartis, Pfizer, Roche, and Buran; and occasional fees for participation as a speaker at conferences/congresses or as a scientific consultant for advisory boards from Astrazeneca, Bayer, MSD, Merck-Serono, AccMed, and Neutron Therapeutics, Inc. MJA reports honoraria from AstraZeneca, Lilly, MSD, Merck, TAKEDA, ONO, Amgen, YUHAN, and Roche; advisory/consultancy roles with AstraZeneca, Lilly, MSD, Merck, TAKEDA, ONO, Amgen, YUHAN, Roche, and Alpha Pharmaceuticals; and research grant/funding from YUHAN. AS reports honoraria from MSD, Merck Serono, Novartis Pharma, Bristol Myers Squibb, Pierre Fabre, and Sanofi; and advisory/consultancy roles with MSD, Merck Serono, Novartis Pharma, Bristol Myers Squibb, Pierre Fabre, and Sanofi. JPM reports advisory/consultancy roles with Pfizer, Roche, AstraZeneca, Bayer, Innate, Merck Serono, Boerhinger, BMS, Novartis, Janssen, Incyte, Cue Biopharma, ALX Oncology, iTEOS, eTheRNA, NEKTAR, F-Star, Seagen, Genmab, Astellas, and Psioxius; leadership roles with the EORTC head and neck group (Chair); travel/accommodation/expenses from Amgen, BMS, Pfizer, MSD, and Gilead; and non-remunerated activities with MSD (Advisory board). NM reports being a co-founder and shareholder MaxiVAX, a personalized cancer immunotherapy biotech, with ongoing Phase IIa in patients with advanced Head & Neck cancer; and being the Chief Medical Officer at MaxiVAX. RM reports advisor/consultancy role for Janssen, AstraZeneca (uncompensated), Coherus and Rakuten Medical; and research funding from Merck. BB reports advisory/consultancy roles with Genentech, Glaxo Smith Kline, Nektar, Debio, Merck KgA, Astra Zeneca,Vaccinex, Exelexis, Cue BioPharma, Fusion, Arvinas, Coherus, ALX Oncology, Hookipa Kura, Astra Zeneca/Medimmune, Nektar, and Roche; and research grant/funding from Cue Biopharma, Merck, Gilead, Exelexis, and Vaccinex. RFS reports employment at the time of the study at Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; current employment at Carisma Therapeutics. JL reports employment at Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and stock ownership in Merck & Co., Inc., Rahway, NJ, USA. JG reports employment at Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and stock ownership in Merck & Co., Inc., Rahway, NJ, USA. NL reports employment at Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and stock ownership in Merck & Co., Inc., Rahway, NJ, USA. CLT reports honoraria from MSD, BMS, Merck Serono, Celgene, Astra Zeneca, Seattle Genetics, Maxivax, Seagen, and Roche; research grant/funding from MSD; and travel/accommodation/expenses from MSD, Merck Serono, Astra Zeneca, and BMS.

Acknowledgments

The authors thank the patients and their families and caregivers and all investigators and site personnel for participating in this trial. Medical writing and/or editorial assistance was provided by Jemimah Walker, PhD, and Doyel Mitra, PhD, CMPP, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2023.106587.

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