Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study

*Ezra E W Cohen, Denis Soulières, Christophe Le Tourneau, José Dinis, Lisa Licitra, Myung-Ju Ahn, Ainara Soria, Jean-Pascal Machiels, Nicolas Mach, Ranee Mehra, Barbara Burtness, Pingye Zhang, Jonathan Cheng, Ramona F Swaby, Kevin J Harrington, on behalf of the KEYNOTE-040 investigators**

Summary

Background There are few effective treatment options for patients with recurrent or metastatic head-and-neck squamous cell carcinoma. Pembrolizumab showed antitumour activity and manageable toxicity in early-phase trials. We aimed to compare the efficacy and safety of pembrolizumab versus standard-of-care therapy for the treatment of head-and-neck squamous cell carcinoma.

Methods We did a randomised, open-label, phase 3 study at 97 medical centres in 20 countries. Patients with head-and-neck squamous cell carcinoma that progressed during or after platinum-containing treatment for recurrent or metastatic disease (or both), or whose disease recurred or progressed within 3–6 months of previous multimodal therapy containing platinum for locally advanced disease, were randomly assigned (1:1) in blocks of four per stratum with an interactive voice-response and integrated web-response system to receive pembrolizumab 200 mg every 3 weeks intravenously or investigator's choice of standard doses of methotrexate, docetaxel, or cetuximab intravenously (standard-of-care group). The primary endpoint was overall survival in the intention-to-treat population. Safety was analysed in the as-treated population. This trial is registered with ClinicalTrials.gov, number NCT02252042, and is no longer enrolling patients.

Findings Between Dec 24, 2014, and May 13, 2016, 247 patients were randomly allocated to pembrolizumab and 248 were randomly allocated to standard of care. As of May 15, 2017, 181 (73%) of 247 patients in the pembrolizumab group and 207 (83%) of 248 patients in the standard-of-care group had died. Median overall survival in the intention-to-treat population was 8·4 months (95% CI 6·4–9·4) with pembrolizumab and 6·9 months (5·9–8·0) with standard of care (hazard ratio 0·80, 0·65–0·98; nominal p=0·0161). Fewer patients treated with pembrolizumab than with standard of care had grade 3 or worse treatment-related adverse events (33 [13%] of 246 *vs* 85 [36%] of 234). The most common treatment-related adverse event was hypothyroidism with pembrolizumab (in 33 [13%] patients) and fatigue with standard of care (in 43 [18%]). Treatment-related death occurred in four patients treated with pembrolizumab (unspecified cause, large intestine perforation, malignant neoplasm progression, and Stevens-Johnson syndrome) and two patients treated with standard of care (malignant neoplasm progression and pneumonia).

Interpretation The clinically meaningful prolongation of overall survival and favourable safety profile of pembrolizumab in patients with recurrent or metastatic head and neck squamous cell carcinoma support the further evaluation of pembrolizumab as a monotherapy and as part of combination therapy in earlier stages of disease.

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*Investigators listed in the appendix

San Diego Moores Cancer Center, University of California, San Diego, CA, USA (Prof E E W Cohen MD); **Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada** (D Soulières MD); **Department of Drug Development and Innovation, Institut Curie, Paris, France** (Prof C Le Tourneau MD); **INSERM U900 Research Unit, Paris, France** (Prof C Le Tourneau); **Versailles-Saint-Quentin-en-Yvelines University, Paris, France** (Prof C Le Tourneau); **Instituto Português de Oncologia do Porto Francisco Gentil, Porto, Portugal** (J Dinis MD); **Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy** (Prof L Licitra MD); **University of Milan, Milan, Italy** (Prof L Licitra); **Samsung Medical Centre, Seoul, South Korea** (Prof M-J Ahn MD); **Hospital Universitario Ramón y Cajal, Madrid, Spain** (A Soria MD); **Cliniques Universitaires Saint-Luc, Brussels, Belgium** (Prof J-P Machiels MD); **Université Catholique de Louvain, Louvain-la-Neuve, Belgium** (Prof J-P Machiels); **Hôpitaux Universitaires de Genève, Geneva, Switzerland** (N Mach MD); **Fox Chase Cancer Center, Philadelphia, PA, USA (currently affiliated with Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA)** (R Mehra MD); **Yale University School of Medicine and Yale**

Introduction

Despite multimodal therapy including platinum-based chemoradiotherapy, more than 50% of patients with locoregionally advanced squamous cell carcinoma of the head and neck have recurrence or develop metastases (or both) within 3 years of treatment.[1–3] Platinum-based combination chemotherapy regimens and cetuximab are commonly used in the first-line recurrent and metastatic settings.[1,2] The EXTREME regimen, which consists of platinum, fluorouracil, and cetuximab, is approved in many countries for first-line treatment of patients whose disease progressed more than 6 months after receiving a platinum-containing chemoradiotherapy regimen administered with curative intent.[4] Until 2017, treatment options for recurrent and metastatic disease following progression on a platinum-based regimen were limited to single-agent chemotherapy or cetuximab, which yield a median overall survival of 7 months or less.[1,2,5–7]

Inhibitors of the programmed death 1 (PD-1) pathway, which is implicated in tumour immune escape, have emerged as valid treatment options in patients

Cancer Center, New Haven, CT, USA (Prof B Burtness MD); **Merck & Co, Kenilworth, NJ, USA** (P Zhang PhD, J Cheng MD, R F Swaby MD); **The Institute of Cancer Research, London, UK** (Prof K J Harrington PhD); **and The Royal Marsden NHS Foundation Trust, National Institute of Health Research Biomedical Research Centre, London, UK** (Prof K J Harrington)

Correspondence to:
Prof Ezra E W Cohen, San Diego Moores Cancer Center, University of California, San Diego, CA 92093, USA
ecohen@ucsd.edu

Research in context

Evidence before this study

We searched PubMed on April 11, 2018, using the terms "PD-1", "PD-L1", "MK-3475", "lambrolizumab", "pembrolizumab", "Keytruda", "BMS-936558", "nivolumab", "Opdivo", "MPDL3280A", "atezolizumab", "Tecentriq", "MEDI4736", "durvalumab", "Imfinzi", "MSB0010718C", "avelumab", or "Bavencio" and "head and neck cancer". We applied no time limits or language restrictions to the search. We also searched the abstracts for the 2016 and 2017 American Society of Clinical Oncology Annual Meeting and the 2016 and 2017 European Society for Medical Oncology Congress using the same search terms to identify results of any clinical trials that were not yet published in the peer-reviewed literature. We identified one randomised phase 3 trial of anti-programmed death 1 (PD-1) or anti-programmed death ligand 1 (PD-L1) monotherapy for squamous cell carcinoma of the head and neck—the CheckMate 141 study of nivolumab versus investigator's choice of docetaxel, methotrexate, or cetuximab for patients with recurrent or metastatic disease following platinum-based chemotherapy. Phase 1 and phase 2 studies of anti-PD-1 or anti-PD-L1 monotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck were identified, including the phase 1 KEYNOTE-012 and phase 2 KEYNOTE-055 studies of pembrolizumab, a phase 1 study of atezolizumab (NCT01375842), and the phase 2 HAWK study of durvalumab.

Added value of this study

To our knowledge, these data are the first published report of a randomised, controlled trial of pembrolizumab as therapy for recurrent or metastatic squamous cell carcinoma of the head and neck. Pembrolizumab provides a clinically meaningful prolongation of overall survival and has a favourable safety profile compared with standard-of-care therapy with methotrexate, docetaxel, or cetuximab. There was a clear relationship between higher PD-L1 expression and the benefit of pembrolizumab relative to standard-of-care therapy. Receipt of an immune checkpoint inhibitor by patients in the standard-of-care group appeared to decrease the treatment effect of pembrolizumab, a finding that has implications for future oncology studies, particularly those done in patients with cancer for which immune checkpoint inhibitors have received regulatory approval.

Implications of all the available evidence

Anti-PD-1 and anti-PD-L1 monotherapy have a favourable benefit-to-risk profile in patients with recurrent or metastatic squamous cell carcinoma of the head and neck that progress after platinum-based chemotherapy. The benefit of pembrolizumab monotherapy appears to be greater in patients whose tumours express PD-L1 than in patients whose tumours do not express the ligand. The survival benefit and safety profile of monotherapy with anti-PD-1 and anti-PD-L1 therapies in the recurrent or metastatic setting support the evaluation of monotherapy in earlier stages of disease and the evaluation of combination regimens that include PD-1 and PD-L1 inhibitors.

with squamous cell carcinoma of the head and neck on the basis of their antitumour activity and safety profiles.[8–14] The anti-PD-1 monoclonal antibody pembrolizumab had a manageable safety profile and produced objective responses in 16–18% of patients with recurrent or metastatic head-and-neck squamous cell carcinoma in the phase 1b KEYNOTE-012[8,9] and phase 2 KEYNOTE-055[12] studies. On the basis of these data, we initiated the international, randomised, open-label, phase 3 KEYNOTE-040 trial to compare the efficacy and safety of pembrolizumab with those of an investigator's choice of methotrexate, docetaxel, or cetuximab (standard of care) in patients with recurrent or metastatic squamous cell carcinoma of the head and neck that progressed during or after platinum-based chemotherapy.

Methods

Study design and participants

This randomised, open-label, phase 3 study was done at 97 medical centres in 20 countries. Patients were eligible for enrolment if they met the following criteria: aged 18 years or older; had histologically or cytologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, incurable by local therapies; had disease progression during or after platinum-containing treatment for recurrent or metastatic disease (or both) or had recurrence or progression within 3–6 months of previous multimodal therapy containing platinum for locally advanced disease; received two or fewer lines of therapy for recurrent or metastatic disease; had known human papilloma virus (HPV) p16 status for oropharyngeal cancer; had known programmed death ligand 1 (PD-L1) expression status; had at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1;[15] and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (on a five-point scale, with 0 indicating no symptoms and higher numbers indicating greater disability).[16] Patients were ineligible if their disease progressed within 3 months of completing definitive treatment for locoregionally advanced or recurrent disease or had received previous immune checkpoint inhibitor therapy. Full eligibility criteria are listed in the trial protocol, which is available in the appendix.

See Online for appendix

The trial protocol and all amendments were approved by the appropriate ethics body at each centre. The study was done in accordance with the protocol and its amendments and Good Clinical Practice guidelines. All patients provided written informed consent before enrolment.

Randomisation

Patients were enrolled by the study investigators and randomly allocated in a 1:1 ratio using a central interactive voice response and integrated web response system (Almac Clinical Technologies, Souderton, PA, USA) to receive pembrolizumab or investigator's choice of methotrexate, docetaxel, or cetuximab. Randomisation was stratified by ECOG performance status (0 *vs* 1), p16 status in the oropharynx (positive *vs* negative), and PD-L1 tumour proportion score (≥50% *vs* <50%). Treatment was allocated in blocks of four in each stratum. The allocation schedule was generated by the system vendor using a computerised random list generator. Neither patients nor investigators were masked to group assignment.

Procedures

Patients assigned to pembrolizumab received 200 mg every 3 weeks intravenously. Those assigned to investigator's choice received either methotrexate 40 mg/m² per week intravenously (could be increased to 60 mg/m² per week in the absence of toxicity), docetaxel 75 mg/m² every 3 weeks intravenously, or cetuximab 250 mg/m² per week intravenously following a loading dose of 400 mg/m². Patients received treatment until disease progression, development of unacceptable toxicity, withdrawal of consent, or physician decision; the maximum duration of pembrolizumab treatment was 24 months. Clinically stable patients with radiological disease progression could continue study treatment until progression was confirmed on a scan obtained at least 4 weeks later. There was no planned crossover on disease progression. Tumour imaging was done at baseline, week 9, then every 6 weeks during year 1 and every 9 weeks thereafter. Patients were contacted every 12 weeks to assess survival during follow-up. Adverse events and laboratory abnormalities were collected throughout treatment and for 30 days thereafter (90 days for serious adverse events and those of special interest to pembrolizumab treatment) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Oropharyngeal p16 status was assessed as a surrogate of HPV association using the CINtec p16 Histology assay (Ventana Medical Systems, Tucson, AZ, USA) with a cutoff point for positivity of 70% of cells. PD-L1 expression was assessed at a central laboratory in formalin-fixed tumour samples during screening using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA). Expression was categorised by the tumour proportion score, defined as the percentage of tumour cells with membranous PD-L1 staining, and by the combined positive score, defined as the number of PD-L1-positive cells (tumour cells, lymphocytes, and macrophages) divided by the total number of tumour cells multiplied by 100. The combined positive score was previously reported as a percentage but is now reported as a unitless measure.

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation to death from any cause in the total population. Secondary endpoints were overall survival in the population with a PD-L1 combined positive score of 1 or higher and the following endpoints in all participants and those with a PD-L1 combined positive score of 1 or higher: safety; progression-free survival, defined as the time from randomisation to disease progression or death from any cause, assessed according to RECIST version 1.1[15] and modified RECIST (which is the same as RECIST version 1.1 except that a confirmatory assessment of disease progression done at least 4 weeks after the initial progressive disease assessment is required) by masked, independent central radiological review; objective response rate, defined as the percentage of patients who had a complete or partial response, regardless of confirmation, assessed according to RECIST version 1.1 by masked, independent central radiological review; duration of confirmed response, defined as the time from the first documentation of complete or partial response to disease progression or death, assessed according to RECIST version 1.1 by masked, independent central radiological review; and time to progression, defined as the time from randomisation to first documented disease progression, assessed according to RECIST version 1.1 by masked, independent central radiological review. Protocol-specified exploratory endpoints included overall and progression-free survival and the proportion of patients with an objective response in the population with a PD-L1 tumour proportion score of 50% or higher. The full list of exploratory endpoints is available in the protocol.

Statistical analysis

The protocol specified two interim analyses and a final analysis. The independent data monitoring committee (appendix) recommended that the study continue as planned after reviewing the results of both interim analyses, which were done by an unmasked statistician. The protocol-specified final analysis was planned for when approximately 340 deaths had occurred. Assuming median overall survival of 6·2 months in the standard-of-care group and 340 total events at final analysis, we calculated that enrolment of 466 patients would provide the study with 90% power to show a hazard ratio (HR) for death of 0·70 or better for the comparison of overall survival in the pembrolizumab group versus the standard-of-care group in the total population. The family-wise type I error rate was strictly controlled at a one-sided α of 0·025 using the Hwang-Shih-DeCani α-spending function with a γ parameter of –4. α was allocated in a stepwise manner starting with the comparison of overall survival in the total population (appendix). The protocol-specified final analysis was done on the basis of a data cutoff date of May 15, 2017 (efficacy boundary for overall survival in the total population, one-sided α of 0·0175). At

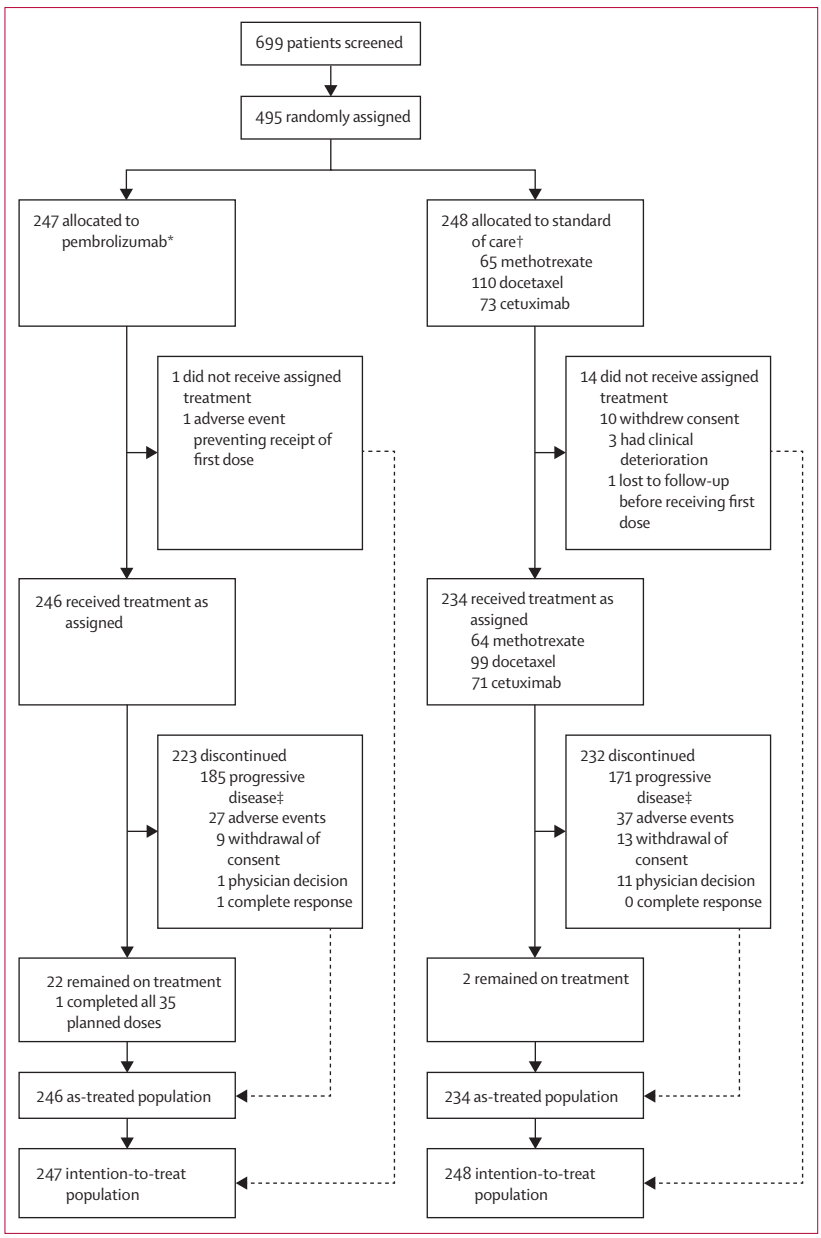


Figure 1: **Trial profile**

*Major protocol deviations that were determined to be clinically relevant were reported for five patients: receipt of three or more previous therapies for advanced disease (n=2), absence of documented failure of platinum therapy (n=2), and progressive disease more than 6 months after platinum-containing multimodal therapy for locally advanced disease (n=1). †Major protocol deviations that were determined to be clinically relevant were reported for five patients: receipt of three or more previous therapies for advanced disease (n=2), progressive disease after platinum-containing multimodal therapy for locally advanced disease did not occur within 6 months (n=2), and absence of progressive disease documented by radiography (n=1). ‡Includes patients who had radiographic or clinical progression.

the time of the protocol-specified final analysis, survival status was not confirmed for 12 patients. A post-hoc analysis of overall survival based on the same cutoff date (ie, May 15, 2017) was done after confirming the survival status of all 495 randomly allocated patients, including the aforementioned 12 patients.

Overall survival, progression-free survival, objective response rate, and time to progression were assessed in the intention-to-treat population, which included all patients randomly allocated to study treatment. Duration of response was analysed in all patients who had a best response of complete or partial response. Safety was assessed in the as-treated population, which included all patients who received at least one dose of study treatment.

All statistical analyses were done using SAS, version 9.4. Overall survival, progression-free survival, and duration of response were estimated using the Kaplan-Meier method. Data for patients who were alive or lost to follow-up were censored at the time of last contact for estimation of overall survival. Data for patients without disease progression or who were lost to follow-up were censored at the time of last tumour imaging for estimation of progression-free survival. Data for patients who were alive without evidence of disease progression who discontinued the study without radiographical evidence of progression were censored at the time of the last radiographical assessment showing response. For both progression-free survival and duration of response, data for patients who started new anticancer therapy without radiographical evidence of progression were censored at the time of the last tumour assessment before new anticancer therapy was initiated. Between-group differences in overall and progression-free survival were tested using the stratified log-rank test. HRs and their associated 95% CIs were calculated using a stratified Cox proportional hazards model and Efron's method of handling ties.[17] Differences in the proportion of patients with an objective response were assessed with the stratified Miettinen and Nurminen method.[18] The same stratification factors that were applied to randomisation were applied to all stratified efficacy analyses. A post-hoc exploratory analysis of the interaction of subgroups with treatment effect was done using the likelihood ratio test. This study is registered with ClinicalTrials.gov, number NCT02252042.

Role of the funding source

The funder contributed to study design, data collection, data analysis, data interpretation, and the writing of this report. The funder maintained the study database. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 24, 2014, and May 13, 2016, 495 patients were randomly allocated to pembrolizumab (n=247) or to investigator's choice of standard-of-care therapy (n=248) at one of 97 sites in 20 countries. Of these participants, 246 in the pembrolizumab group and 234 in the standard-of-care group received study treatment (figure 1). Baseline demographics and disease characteristics were generally balanced between the two treatment groups (table 1). A PD-L1 combined positive score of 1 or higher was

observed in 196 (79%) of 247 patients in the pembrolizumab group and 191 (77%) of 248 patients in the standard-of-care group. Baseline demographics and disease characteristics for the population with a PD-L1 combined positive score of 1 or higher and the population with a tumour proportion score of 50% or higher are summarised in the appendix.

The median duration of follow-up from randomisation to data cutoff or death, whichever came first, was 7·5 months (IQR 3·4–13·3; 8·4 months [3·3–14·5] in the pembrolizumab group and 7·1 months [3·7–12·4] in the standard-of-care group). Overall, 22 (9%) of 247 patients in the pembrolizumab group and two (1%) of 248 patients in the standard-of-care group remained on study treatment at the time of data cutoff (figure 1).

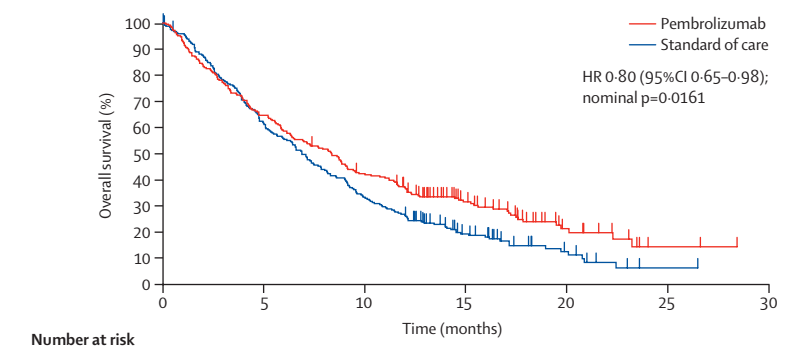
At the time of the protocol-specified final analysis, which was based on a data cutoff of May 15, 2017, death had occurred in 179 (72%) of 247 patients in the pembrolizumab group and 198 (80%) of 248 patients in the standard-of-care group, with survival status unconfirmed for 12 patients (three in the pembrolizumab group and nine in the standard-of-care group). The HR for death for pembrolizumab versus standard-of-care was 0·82 (95% CI 0·67–1·01; one-sided p=0·0316; appendix), which did not meet the efficacy boundary. After confirming the survival status of the 12 outstanding patients based on the same data cutoff, the number of deaths in the intention-to-treat population increased to 181 (73%) of 247 in the pembrolizumab group and 207 (83%) of 248 in the standard-of-care group, and the HR for death was 0·80 (95% CI 0·65–0·98; nominal p=0·0161; figure 2A). Median overall survival was 8·4 months (95% CI 6·4–9·4) with pembrolizumab and 6·9 months (5·9–8·0) with standard of care; the estimated proportion of patients who were alive at 12 months was 37·0% (95% CI 31·0–43·1) in the pembrolizumab group and 26·5% (21·2–32·2) in the standard-of-care group. The HR for death was similar across most subgroups examined, with all 95% CIs overlapping those of the overall population (figure 2B).

With 300 deaths among the 387 patients with a PD-L1 combined positive score of 1 or higher (138 [70%] of 196 in the pembrolizumab group and 162 [85%] of 191 in the standard-of-care group), the HR for death was 0·74 (95% CI 0·58–0·93; nominal p=0·0049; figure 3A). Median overall survival was 8·7 months (95% CI 6·9–11·4) with pembrolizumab and 7·1 months (5·7–8·3) with standard of care. The estimated proportion of patients surviving at 12 months was 40% (95% CI 33–47) in the pembrolizumab group and 26% (20–33) in the standard-of-care. With 84 deaths among the 104 patients with a combined positive score less than 1 (42 [84%] of 50 in the pembrolizumab group and 42 [78%] of 54 in the standard-of-care group), the HR was 1·28 (95% CI 0·80–2·07; p=0·8476) and median overall survival was 6·3 months (3·9–8·9) in the pembrolizumab group and 7·0 months (5·1–9·0) in the standard-of-care group (figure 3B). The nominal, two-sided p value for the interaction of treatment effect and PD-L1 combined positive score was 0·07 (figure 2B). In the population with a PD-L1 tumour proportion score of 50% or higher, 97 deaths occurred in 129 patients (41 [64%] of 64 in the pembrolizumab group and 56 [86%] of 65 in the standard-of-care group; HR 0·53, 95% CI 0·35–0·81; nominal p=0·0014; figure 3C). Median overall survival was 11·6 months (95% CI 8·3–19·5) with pembrolizumab and 6·6 months (4·8–9·2) with standard of care, and estimated overall survival at 12 months was 47% (34–58) and 25% (16–37). In the population with a tumour proportion score of less than 50%, 287 of 362 patients (139 [76%] of 182 in the pembrolizumab

	Pembrolizumab group (n=247)	Standard-of-care group (n=248)
Age (years)	60·0 (55–66)	60·0 (54–66)
Sex		
Male	207 (84%)	205 (83%)
Female	40 (16%)	43 (17%)
Region of enrolment		
Europe	147 (60%)	158 (64%)
North America	73 (30%)	60 (24%)
Rest of the world	27 (11%)	30 (12%)
ECOG performance status score		
0	71 (29%)	67 (27%)
1	176 (71%)	180 (73%)
2	0	1 (<1%)
Current or former smoker	179 (72%)	182 (73%)
p16 positive in the oropharynx	61 (25%)	58 (23%)
PD-L1 tumour proportion score*		
<50%	182 (74%)	180 (72·6%)
≥50%	64 (26%)	65 (26%)
Missing	1 (<1%)	3 (1%)
PD-L1 combined positive score†		
<1	50 (20%)	54 (22%)
≥1	196 (79%)	191 (77%)
Missing	1 (<1%)	3 (1%)
Current disease stage		
II	5 (2%)	7 (3%)
III	9 (4%)	17 (7%)
IV	233 (94%)	224 (90%)
Chemotherapy before enrolment		
Curative intent	34 (14%)	40 (16%)
First-line recurrent or metastatic	141 (57%)	141 (57%)
Second-line recurrent or metastatic	69 (28%)	64 (26%)
Third line recurrent or metastatic	3 (1%)	3 (1%)
Previous cetuximab	145 (59%)	140 (56%)

Data are median (interquartile range) or n (%). ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed death ligand 1. *The PD-L1 tumour proportion score was defined as the percentage of tumour cells with membranous PD-L1 expression. †The PD-L1 combined positive score was defined as the number of PD-L1-positive cells (tumour cells, lymphocytes, and macrophages) out of the total number of tumour cells, multiplied by 100.

Table 1: **Demographic and disease characteristics at baseline in the intention-to-treat population**



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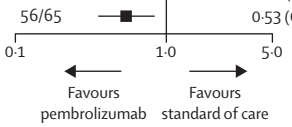
	Events/patients		Hazard ratio (95% CI)	$p_{interaction}$ value
	Pembrolizumab	Standard of care		
Overall	181/247	207/248	0·80 (0·65–0·98)	
Sex				0·50
Male	152/207	177/205	0·77 (0·62–0·96)	
Female	29/40	30/43	0·94 (0·54–1·63)	
Age (years)				0·07
<65	126/165	141/167	0·94 (0·73–1·20)	
≥65 to <75	40/63	58/69	0·57 (0·37–0·87)	
≥75	15/19	8/12	1·13 (0·42–3·02	
Race				0·63
White	149/207	170/207	0·80 (0·64–1·00)	
Non-white	18/24	22/26	0·93 (0·45–1·92)	
Region of enrolment				0·05
Europe	107/147	141/158	0·68 (0·52–0·88)	
North America	52/73	38/60	1·27 (0·82–1·97)	
Rest of the world	22/27	28/30	0·67 (0·36–1·26)	
ECOG performance status				0·61
0	44/71	51/67	0·87 (0·57–1·32)	
1	137/176	155/180	0·78 (0·62–0·98)	
Smoking status				0·87
Current	22/32	31/36	0·71 (0·38–1·31)	
Former	107/147	120/146	0·78 (0·60–1·02)	
Never	52/68	56/66	0·90 (0·60–1·35)	
p16 status in the oropharynx				0·47
Positive	44/61	45/58	0·97 (0·63–1·49)	
Negative	137/186	162/190	0·77 (0·61–0·97)	
Previous lines of therapy				0·32
Curative intent	21/34	33/40	0·77 (0·42–1·43)	
1	103/141	120/141	0·77 (0·59–1·00)	
≥2	57/72	54/67	0·96 (0·65–1·43)	
Previous cetuximab				0·38
Yes	109/145	113/140	0·89 (0·68–1·16)	
No	72/102	94/108	0·78 (0·56–1·07)	
Choice of chemotherapy				0·32
Methotrexate	51/70	54/65	0·75 (0·50–1·13)	
Docetaxel	94/123	91/110	0·86 (0·64–1·17)	
Cetuximab	36/54	62/73	0·56 (0·36–0·89)	
Combined positive score				0·07
<1	42/50	42/54	1·28 (0·80–2·10)	
≥1	138/196	62/191	0·74 (0·58–0·93)	
Tumour proportion score				0·015
<50%	139/182	148/180	0·93 (0·73–1·17)	
≥50%	41/64	56/65	0·53 (0·35–0·81)	



group and 148 [82%] of 180 in the standard-of-care group) had died (HR 0·93, 95% CI 0·73–1·17; p=0·2675); median overall survival was 6·5 months (95% CI 5·6–8·8) with pembrolizumab and 7·1 months (5·7–8·1) with standard of care (figure 3D). The nominal, two-sided p value for the interaction of treatment effect and PD-L1 tumour proportion score was 0·015 (figure 2B).

In the intention-to-treat population, 36 of 247 patients in the pembrolizumab group and 25 of 248 in the standard-of-care group had a confirmed or unconfirmed response, resulting in a response rate of 14·6% (95% CI 10·4–19·6) and 10·1% (6·6–14·5), respectively (nominal p=0·0610; appendix). Among the 26 patients in the pembrolizumab group and 18 patients in the standard-of-care group who had a confirmed response, median time to response was 4·5 months (IQR 2·3–6·4) with pembrolizumab and 2·2 months (2·1–3·5) with standard of care. The median duration of response was 18·4 months (95% CI 5·8–18·4) with pembrolizumab and 5·0 months (3·6–18·8) with standard of care (appendix). The proportion of patients who had an objective response in the pembrolizumab group was higher in patients whose tumours expressed PD-L1 than in those whose tumours did not, whereas the proportion in the standard-of-care group was similar regardless of PD-L1 expression (appendix). Duration of response was not affected by PD-L1 expression, although the medians fluctuated because of the low number of responses overall (appendix).

With 442 events of death or disease progression assessed according to RECIST version 1.1 in the total population (218 [88%] of 247 in the pembrolizumab group and 224 [90%] of 248 in the standard of care group), no difference in progression-free survival between treatment groups was observed (figure 4). Median progression-free survival was 2·1 months (95% CI 2·1–2·3) with pembrolizumab and 2·3 months (2·1–2·8) with standard

Figure 2: **Overall survival in the intention-to-treat population**
Kaplan-Meier estimates of overall survival according to treatment group in the total population (A) and forest plot of the overall survival findings in subgroups (B). (A) Tick marks represent patients who had data censored at the last time at which they were known to be alive. (B) All subgroups were prespecified except for previous cetuximab treatment, age (prespecified categories were ≤65 years *vs* >65 years), and region of enrolment (prespecified categories were east Asia *vs* the rest of the world). Although not a prespecified subgroup analysis, the PD-L1 combined positive score breakdown of less than 1 versus 1 or higher was included for completeness. *Subgroups are based on what the investigator chose before the patient was randomly allocated to treatment with either pembrolizumab or standard of care (investigators were required to select a standard-of-care therapy for all patients before random allocation should they be allocated to that group). The hazard ratios for death for the comparison of pembrolizumab versus standard-of-care therapy in all subgroups were calculated using a Cox proportional hazards model stratified by the randomisation stratification factors. The interaction of each subgroup with treatment was a post-hoc exploratory analysis done using the likelihood ratio test. The two-sided p values are not adjusted for multiplicity and, therefore, nominal only; small p values suggest that the treatment effect varies across subgroups. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. PD-L1=programmed death ligand 1.

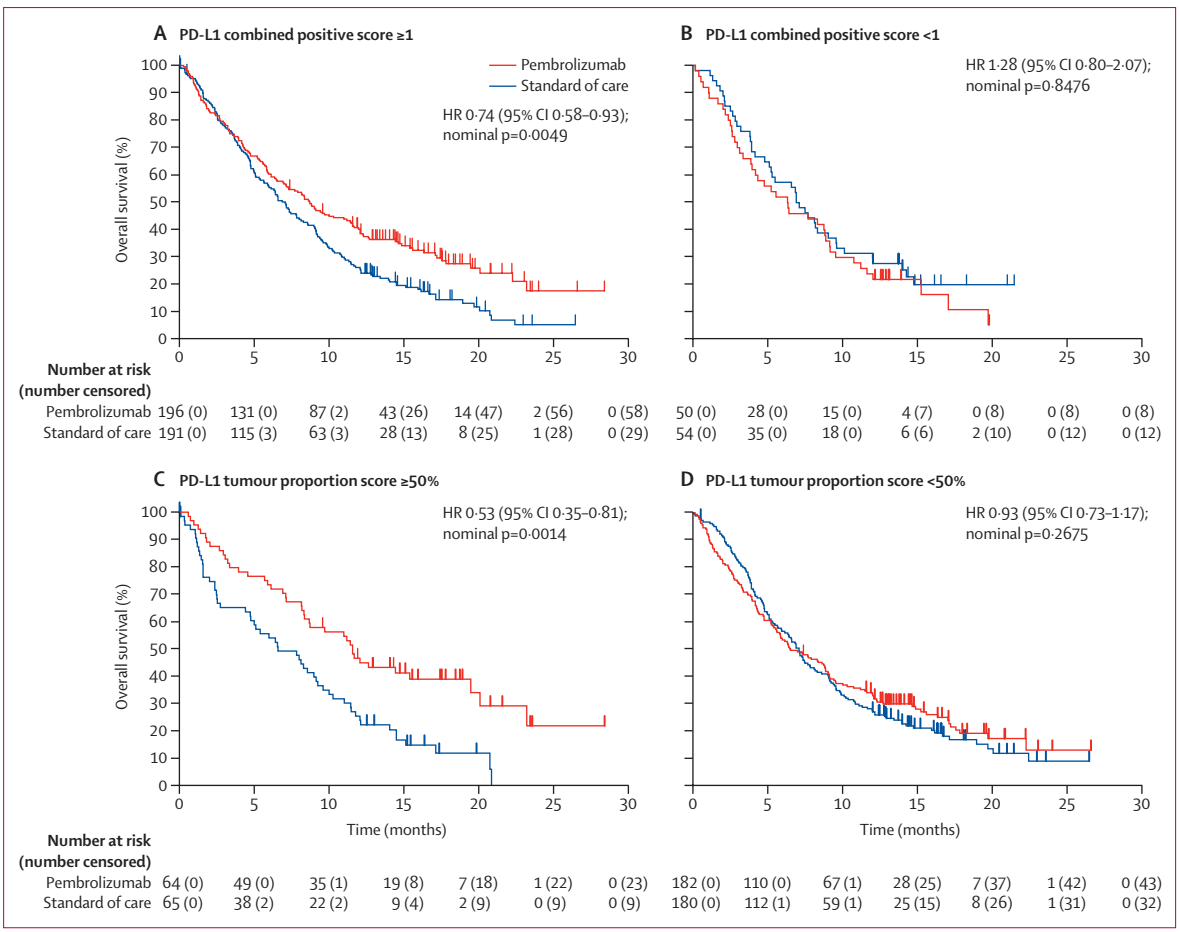


Figure 3: **Overall survival in the intention-to-treat populations according to PD-L1 expression category**
Kaplan-Meier estimates of overall survival according to treatment group in the population with a combined positive score of 1 or more (A), the population with a combined positive score of less than 1 (B), the population with a tumour proportion score of 50% or more (C), and the population with a tumour proportion score of less than 50% (D). Tick marks represent patients who had data censored at the last time a which they were known to be alive. HR=hazard ratio. PD-L1=programmed death ligand 1.

of care. Progression-free survival in the population with a PD-L1 combined positive score of 1 or higher was similar to that of the total population, whereas progression-free survival was longer with pembrolizumab in the population with a PD-L1 tumour proportion score of 50% or higher (figure 4); progression-free survival appeared to be shorter with pembrolizumab than with standard of care in the populations with a combined positive score of less than 1 and tumour proportion score of less than 50%. Median progression-free survival was longer in both treatment groups when assessed according to modified RECIST than when assessed with standard RECIST, and the HRs were close to 1·00 in both the total population and population with a PD-L1 combined positive score of 1 or higher (appendix). No difference in time to progression assessed according to RECIST version 1.1 was observed in either the total population or the population with a PD-L1 combined positive score of 1 or higher (appendix).

In the intention-to-treat population, 84 (34%) of 247 patients in the pembrolizumab group and 101 (41%) of 248 patients in the standard-of-care group received subsequent therapy, including 11 (4%) of 247 patients in the pembrolizumab group and 31 (13%) of 248 patients in the standard-of-care group who received subsequent therapy with an immune checkpoint inhibitor (appendix). In a post-hoc exploratory analysis in the standard-of-care group, the 31 patients who received subsequent immune checkpoint inhibition had longer overall survival than the 70 patients who received other subsequent therapy and the 147 patients who received no subsequent therapy (median overall survival of 20·1 months *vs* 9·7 months *vs* 4·5 months; appendix). In a post-hoc sensitivity analysis in which patients in both treatment groups were censored at the time of first subsequent immune checkpoint inhibitor, the HR for death was 0·72 (95% CI 0·58–0·88; nominal p=0·0008; appendix). In this analysis, median overall survival was 8·3 months (95% CI 6·4–9·4) with pembrolizumab and 6·6 months (5·4–7·5) with standard of care.

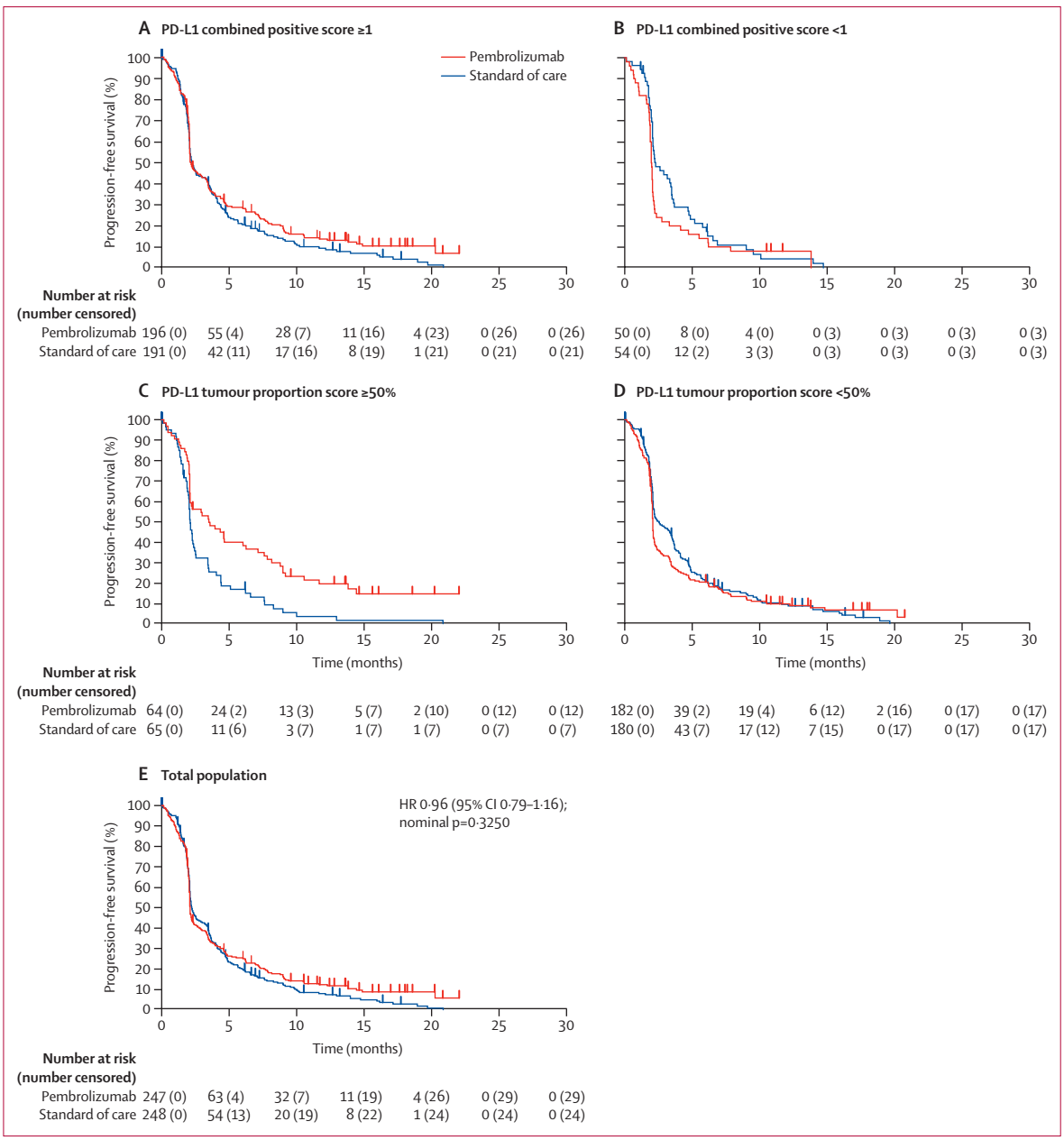


Figure 4: **Progression-free survival in the intention-to-treat population**
Kaplan-Meier estimates of progression-free survival according to treatment group in the total population (A), the population with a PD-L1 combined positive score of 1 or more (B), the population with a combined positive score of less than 1 (C), the population with a PD-L1 tumour proportion score of 50% or more (D), and the population with a PD-L1 tumour proportion score of less than 50% (E). Tick marks represent patients who had data censored at the last time at which they were known to be alive and without disease progression. HR=hazard ratio. PD-L1=programmed death ligand 1.

In the as-treated population, treatment-related adverse events occurred in 155 (63%) of 246 patients treated with pembrolizumab and 196 (84%) of 234 patients treated with standard of care (table 2). These events were of grade 3–5 severity in 33 (13%) of 246 patients treated with pembrolizumab and 85 (36%) of 234 patients treated with standard of care, and led to treatment discontinuation in 15 (6%) of 246 and 12 (5%) of 234 patients, respectively. The incidence of treatment-related adverse events was similar in patients with a PD-L1 combined positive score of 1 or higher, with events of any grade occurring in 128 (66%) of 195 patients treated with pembrolizumab and 150 (82%) of 183 patients treated with standard of care, events of grade 3–5 severity occurring in 31 (16%) of 195 patients treated with pembrolizumab and 71 (39%) of 183 patients treated with standard of care, and events leading to discontinuation occurring in 13 (7%) of 195 patients treated with pembrolizumab and ten (5%) of

183 patients treated with standard of care. In the total population, four patients treated with pembrolizumab and two patients treated with standard of care died from adverse events attributed by the investigator to treatment. The treatment-related events that led to death were death of unspecified cause, large intestine perforation, malignant neoplasm progression, and Stevens-Johnson syndrome in the pembrolizumab group and malignant neoplasm progression and pneumonia in the standard-of-care group. All but one of the deaths in the pembrolizumab group occurred in patients with a combined positive score of 1 or higher.

The most common treatment-related adverse event was hypothyroidism (33 of 246 patients [13%]) with pembrolizumab and fatigue (43 of 234 patients [18%]) with standard of care (table 2). In the pembrolizumab group, there were four treatment-related adverse events of grade 3–5 severity that occurred in two or more patients each compared with 19 such events in the standard-of-care group. A summary of all treatment-related adverse events is available in the appendix. The adverse events of interest with regard to pembrolizumab, regardless of attribution to treatment by the investigator, are summarised in table 2; one of 246 (<1%) patients had a grade 5 event (ie, resulting in death), which was a severe skin reaction (Stevens-Johnson syndrome).

	Pembrolizumab group (n=246)		Standard-of-care group (n=234)	
	Any grade	Grade 3, 4, or 5	Any grade	Grade 3, 4, or 5
Treatment-related event*				
Any event	155 (63%)	33 (13%)	196 (84%)	85 (36%)
Event leading to treatment discontinuation	15 (6%)	12 (5%)	12 (5%)	9 (4%)
Event leading to death	4 (2%)	4 (2%)	2 (1%)	2 (1%)
Event occurring in 10% or more of patients in either group				
Hypothyroidism	33 (13%)	1 (<1%)	2 (1%)	0
Fatigue	31 (13%)	4 (2%)	43 (18%)	2 (1%)
Diarrhoea	20 (8%)	4 (2%)	24 (10%)	1 (<1%)
Rash	19 (8%)	1 (<1%)	34 (15%)	1 (<1%)
Asthenia	18 (7%)	1 (<1%)	28 (12%)	4 (2%)
Anaemia	17 (7%)	1 (<1%)	33 (14%)	9 (4%)
Nausea	12 (5%)	0	29 (12%)	1 (<1%)
Mucosal inflammation	9 (4%)	1 (<1%)	30 (13%)	5 (2%)
Stomatitis	6 (2%)	1 (<1%)	28 (12%)	11 (5%)
Neutrophil count decreased	3 (1%)	1 (<1%)	25 (11%)	20 (9%)
Alopecia	1 (<1%)	0	25 (11%)	0
Event of interest†				
Any	63 (26%)	11 (4%)	28 (12%)	11 (5%)
Hypothyroidism	37 (15%)	1 (<1%)	9 (4%)	0
Pneumonitis	10 (4%)	3 (1%)	3 (1%)	3 (1%)
Infusion-related reaction	8 (3%)	1 (<1%)	7 (3%)	1 (<1%)
Severe skin reaction	7 (3%)	4 (2%)	9 (4%)	7 (3%)
Hyperthyroidism	5 (2%)	0	1 (<1%)	0
Colitis	2 (1%)	0	1 (<1%)	0
Guillain-Barré syndrome	2 (1%)	1 (<1%)	0	0
Hepatitis	2 (1%)	1 (<1%)	0	0

The median duration of treatment in this population was 2·8 months (IQR 1·2–6·8) for pembrolizumab, 1·4 months (0·7–2·2) for methotrexate, 1·7 months (1·2–3·9) for docetaxel, and 2·3 months (1·6–5·0) for cetuximab. *Events were attributed to treatment by the investigator and are listed as indicated by the investigator on the case report form and are in descending order of frequency in the pembrolizumab group. †Events of interest are those with an immune-related cause and are considered regardless of attribution to study treatment by the investigator. These events are listed in descending order of frequency in the pembrolizumab group. In addition to the specific preferred terms listed, related terms were also included. Data are number of patients with at least one event (% of patients).

Table 2: **Adverse events in the as-treated population**

Discussion

In the randomised, open-label, phase 3 KEYNOTE-040 trial, pembrolizumab prolonged overall survival compared with investigator's choice of methotrexate, docetaxel, or cetuximab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. The benefit of pembrolizumab compared with standard-of-care therapy was greater in patients with PD-L1 expression on their tumours or in the tumour microenvironment than in those without PD-L1 expression. Pembrolizumab had a better safety profile than standard of care, with overall profiles consistent with those previously observed and no new or unexpected toxicities. The frequency of adverse events of grade 3–5 severity that were attributed to study treatment by the investigator was 2·7 times lower with pembrolizumab than with standard of care. More patients in the pembrolizumab group died from treatment-related adverse events, although the proportion was low overall (four [2%] of 246 in the pembrolizumab group and two [1%] of 234 in the standard-of-care group).

As previously observed for pembrolizumab and other immune checkpoint inhibitors,[8–10,12–14] responses to pembrolizumab were durable. The median duration of response was 18·4 months in the pembrolizumab group, compared with only 5·0 months in the standard-of-care group. Also consistent with previous studies of immune checkpoint inhibitors in the PD-L1–unselected recurrent or metastatic setting was the absence of a progression-free survival benefit for pembrolizumab compared with standard-of-care therapy.[10,19–21]

In a post-hoc exploratory analysis not adjusted for multiplicity, an interaction between the treatment effect for overall survival and PD-L1 expression appeared to be present, such that benefit of pembrolizumab was greater in patients with a combined positive score of 1 or higher versus those with a combined positive score of less than 1 and those with a tumour proportion score of 50% or higher versus those with a score of less than 50%. Although not formally tested, the benefits on progression-free survival and objective response of pembrolizumab compared with standard-of-care therapy were greater in patients whose tumours had PD-L1 expression than in those who did not express the ligand. Of note, all four complete responses and 30 of 32 partial responses in the pembrolizumab group occurred in patients with a PD-L1 combined positive score of 1 or higher. Treatment differences were even greater in patients with a PD-L1 tumour proportion score of 50% or higher. The benefit of

pembrolizumab has been shown to be enriched in patients with PD-L1 expression on their tumours in other advanced malignancies, including non-small-cell lung cancer.[22] These data suggest that PD-L1 expression could be used as an enrichment strategy in future trials of PD-1 blockade.

Our data share similarities and differences with those of the CheckMate 141 study,[10] in which the anti-PD-1 monoclonal antibody nivolumab showed superior overall survival compared with investigator's choice of methotrexate, docetaxel, or cetuximab in a similar patient population to that enrolled in KEYNOTE-040 (HR 0·70, 97·73% CI 0·51–0·96, p=0·01). KEYNOTE-040 and CheckMate 141 used the same comparator treatments of methotrexate, cetuximab, and docetaxel. Although docetaxel was the chosen chemotherapy for a similar proportion of patients in the standard-of-care group in CheckMate 141 (45%) and KEYNOTE-040 (44%) trials, the doses administered were different. In CheckMate 141, docetaxel was administered at a dose of 30–40 mg/m² per week, compared with 75 mg/m² every 3 weeks in KEYNOTE-040. This difference might be relevant given that data from patients with head-and-neck squamous cell carcinoma,[23,24] non-small-cell lung cancer,[25] and prostate cancer[26] suggest that lower weekly doses of docetaxel have less efficacy than higher doses administered once every 3 weeks. Although neither KEYNOTE-040 nor CheckMate 141 was powered to compare outcomes in the experimental group with the individual therapies in the standard-of-care group, of note is that the relative treatment effect of pembrolizumab for overall survival in KEYNOTE-040 was less apparent compared with docetaxel (HR 0·86) than with methotrexate (HR 0·75) or cetuximab (HR 0·56); the HRs in the CheckMate 141 study were 0·82 for docetaxel, 0·64 for methotrexate, and 0·47 for cetuximab. Both KEYNOTE-040 and CheckMate 141 enrolled patients with locally advanced disease that progressed within 6 months of receiving platinum-based therapy with curative intent. However, because eligibility in KEYNOTE-040 was restricted to platinum-refractory disease that progressed between 3 months and 6 months, patients with locally advanced disease in KEYNOTE-040 might have had a better prognosis than those in CheckMate 141. Patients whose only previous systemic therapy was definitive and administered in the locally advanced setting appeared to have a greater treatment effect with pembrolizumab compared with standard of care than the overall study population. This finding raises speculation not only about the reasons that the standard-of-care group in KEYNOTE-040 had a higher than expected survival, with 1 year survival estimates of 26·5% in KEYNOTE-040 and 16·6% in CheckMate 141,[10] but also the prospect that adjuvant therapy with PD-1 or PD-L1 inhibitors might be effective in patients with locally advanced squamous cell carcinoma of the head and neck. Despite the differences in eligibility criteria between the studies, the estimated survival at 1 year in the pembrolizumab group of KEYNOTE-040 (37%) was nearly identical to that of the nivolumab group of CheckMate 141 (36%).[10]

To further understand the better-than-expected overall survival observed in patients receiving standard-of-care therapy, we did several post-hoc exploratory analyses. With a minimum follow-up of 12·2 months since the last patient enrolled, one or more subsequent immune checkpoint inhibitors were received by 13% of patients in the standard-of-care group, compared with only 5% of patients in the pembrolizumab group. The patients in the standard-of-care group who received a subsequent immune checkpoint inhibitor had a median overall survival that was two times longer than that of patients who received subsequent therapy other than a checkpoint inhibitor, and four times longer than that of patients who received no subsequent therapy (20·1 months *vs* 9·7 months *vs* 4·5 months, respectively). In an analysis of overall survival in which patients in both treatment groups were censored at the time at which they started subsequent immune checkpoint therapy, median overall survival in the standard-of-care group decreased to 6·6 months, which was closer to the predicted overall survival of 6·2 months based on historical data, and the HR for death decreased to 0·72 (95% CI 0·58–0·88). These data strongly suggest that subsequent immunotherapy influenced outcomes in the standard-of-care group and confounded analysis of overall survival. To the best of our knowledge, a similar analysis was not done in CheckMate-141, in which 5·3% of patients in the nivolumab group and 10·1% of patients in the standard-of-care group received a subsequent checkpoint inhibitor with a minimum follow-up of 24·2 months since the last patient enrolled.[27] Future studies of immunotherapy, particularly those done in patients with cancers for which checkpoint inhibitors are already approved, should adequately account for subsequent immunotherapy use during study design, particularly as this factor pertains to power calculations.

The results of this study solidify the role of PD-1 checkpoint inhibition in the treatment of head and neck squamous cell carcinoma. The large population size and ability to collect tissue samples from the majority of participants helped show that PD-L1 expression is a predictive biomarker in this population. Limitations of the data include the inability to assess the efficacy and safety of pembrolizumab in patients who did not receive platinum-based therapy, a group that represents a substantial minority of patients with head and neck cancer. Moreover, several hypotheses arise from these data that will need to be tested to explain the outcomes observed in various subgroup analyses, including the subgroups based on HPV status and geographical region of enrolment.

Our findings suggest that pembrolizumab provides a clinically meaningful survival benefit compared with investigator's choice of methotrexate, docetaxel, or

cetuximab in patients with recurrent or metastatic head-and-neck squamous cell carcinoma that progressed during or after platinum-based therapy. Post-study crossover in the standard-of-care group appeared to confound the analysis and might have decreased the apparent magnitude of the benefit of pembrolizumab on overall survival. Pembrolizumab had a favourable safety profile compared with standard-of-care therapy, and no new safety signals were observed. Together, these data support the benefit of pembrolizumab for patients with recurrent or metastatic head-and-neck squamous cell carcinoma.

Contributors

EEWC, BB, JC, and KJH conceived and designed the study. EEWC, J-PM, PZ, JC, RFS, and KJH analysed the data. EEWC, DS, CLT, JD, LL, AS, J-PM, NM, RM, RFS, and KJH acquired the data. EEWC, PZ, RFS, and KJH wrote the first draft of the manuscript. EEWC, DS, LL, M-JA, AS, J-PM, RM, BB, PZ, JC, RFS, and KJH interpreted the data. All authors contributed to reviewing or revising the manuscript and approved the final version.

Declaration of interests

EEWC reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work and serving an advisory role for AstraZeneca, Bristol-Myers Squibb, Eisai, Merck, Human Longevity, and Pfizer, all outside the submitted work. DS reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work and personal fees for advisory board membership from Merck outside the submitted work. CLT reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work and personal fees for serving as a consultant or adviser or for lectures from Amgen, Bristol-Myers Squibb, Merck Serono, MSD, Nanobiotix, Novartis, and Roche, all outside the submitted work. JD reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work. LL reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work and grants to the institution for clinical studies and research from AstraZeneca, Boehringer Ingelheim, Eisai, Merck-Serono, MSD, Novartis, and Roche, personal fees for serving as a consultant or advisor or for lectures from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Debiopharm, Eisai, Merck Serono, MSD, Novartis, Roche, and Sobi, and travel support for medical meetings from Bayer, Bristol-Myers Squibb, Debiopharm, Merck-Serono, MSD, and Sobi, all outside the submitted work. M-JA reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work. AS reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work and personal fees for giving lectures from Bristol-Myers Squibb, Novartis, and Roche, all outside the submitted work. J-PM reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work and serving as an uncompensated advisory board member for MSD. NM reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work. RM reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work, previous employment of RM's spouse at GlaxoSmithKline, and serving as an advisory board member for Bayer, Bristol-Myers Squibb, Genentech, and InnatePharma, all outside the submitted work. BB reports research funding to the institution and receipt of personal fees for serving on a steering committee for the work under consideration for publication and research funding to the institution from Advaxis and Bristol-Myers Squibb, receiving personal fees for serving on a data safety monitoring committee for IDDI, receiving personal fees for serving on an advisory board for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, and Genentech, and travel support from Boehringer Ingelheim, all outside the submitted work. PZ reports personal fees in the form of salary as a full-time employee from Merck & Co. JC reports personal fees in the form of salary as a full-time employee of Merck & Co and stock options from the same company. RFS reports personal fees in the form of salary as a full-time employee of Merck & Co and stock options from the same company. KJH reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work and fees to the institution from Amgen, AstraZeneca, Bristol-Myers Squibb, Merck, MSD, Pfizer, and Viralytics and grants to the institution from AstraZeneca and MSD, all outside the submitted work.

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