**Type:** Original article

**Title:** Pembrolizumab versus investigator's choice of methotrexate, docetaxel, or cetuximab for recurrent or metastatic head and neck squamous cell carcinoma that progressed or recurred following platinum-based therapy (KEYNOTE-040): a multicentre, randomised, open-label, phase 3 study

**Authors:** Ezra E. W. Cohen, M.D.,[1*] Denis Soulières, M.D.,[2] Christophe Le Tourneau, M.D.,[3*] José Dinis, M.D.,[4] Lisa Licitra, M.D.,[5*] Myung-Ju Ahn, M.D.,[6*] Ainara Soria, M.D.,[7] Jean-Pascal Machiels, M.D.,[8*] Nicolas Mach, M.D.,[9] Ranee Mehra, M.D.,[10] Barbara Burtness, M.D.,[11*] Pingye Zhang, Ph.D.,[12] Jonathan Cheng, M.D.,[12] Ramona Swaby, M.D.,[12] Kevin J. Harrington, Ph.D.,[13*] on behalf of the KEYNOTE-040 Investigators

*Indicates full professor or the equivalent.

**Affiliations:** [1]University of California, San Diego Moores Cancer Center, La Jolla, CA, USA; [2]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada; [3]Department of Drug Development and Innovation, Institut Curie, Paris & Saint-Cloud, INSERM U900 Research Unit, Saint-Cloud, and Versailles-Saint-Quentin-en-Yvelines University, Montigny-le-Bretonneux, all France; [4]Instituto Português de Oncologia do Porto Francisco Gentil, Porto, Portugal; [5]Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; [6]Samsung Medical Center, Seoul, South Korea; [7]Hospital Universitario Ramón y Cajal, Madrid, Spain; [8]Cliniques Universitaires Saint-Luc, Brussels and Université catholique de

Louvain, Louvain-la-Neuve, Belgium; [9]Hôpitaux Universitaires de Genève, Geneva, Switzerland; [10]Fox Chase Cancer Center, Philadelphia, PA, USA (currently at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA); [11]Yale University School of Medicine and Yale Cancer Center, New Haven, CT, USA; [12]Merck & Co., Inc., Kenilworth, NJ, USA; [13]The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, London, UK

**Correspondence to:**

Ezra Cohen, MD

Moores Cancer Center at University of California, San Diego

3855 Health Sciences Drive

La Jolla, CA 92093

Tel: +1 858-657-7000

Email: ecohen@ucsd.edu

## Summary

**Background:** Effective treatment options are limited for patients with recurrent and/or metastatic head and neck squamous cell carcinoma. Pembrolizumab demonstrated antitumour activity and manageable toxicity in early-phase trials in this population.

**Methods:** We did this 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 and/or metastatic disease or recurred or progressed within 3 to 6 months of previous multimodal therapy containing platinum for locally advanced disease were randomly assigned (1:1) in blocks of 4 per stratum with an interactive voice-response/integrated web-response system to receive pembrolizumab 200 mg every 3 weeks or investigator's choice of standard doses of methotrexate, docetaxel, or cetuximab. Primary endpoint was overall survival in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, number NCT02252042.

**Findings:** Between Dec 24, 2014, and May 13, 2016, 495 patients were randomly allocated to pembrolizumab (n=247) or standard-of-care (n=248). As of May 15, 2017, 388 patients 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 (95% CI 5·9–8·0) with standard-of-care (hazard ratio 0·80; 95% CI 0·65–0·98; nominal p=0·0161). Fewer patients treated with pembrolizumab compared with standard-of-care experienced grade ≥3 treatment-related adverse events (13·4% vs 36·3%).

**Interpretation:** Pembrolizumab provides a clinically meaningful prolongation of overall survival and has a lower incidence of treatment-related adverse events compared with standard-of-care therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma.

**Funding:** Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

**Research in context panel**

**Evidence before this study:** We searched PubMed on Apr 11, 2018, using the following terms: "PD-1 OR PD-L1 OR MK-3475 OR lambrolizumab OR pembrolizumab OR Keytruda OR BMS-936558 OR nivolumab OR Opdivo OR MPDL3280A OR atezolizumab OR Tecentriq OR MEDI4736 OR durvalumab OR Imfinzi OR MSB0010718C OR avelumab OR Bavencio" AND "head and neck cancer." There were no limits applied 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–PD-1 or anti–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. The following phase 1 and 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: the phase 1 KEYNOTE-012 and phase 2 KEYNOTE-055 studies of pembrolizumab, a phase 1 study of atezolizumab (ClinicalTrials.gov identifier NCT01375842), and the phase 2 HAWK study of durvalumab.

**Added value of this study:** 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 levels of 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 conducted 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 progressed following platinum-based chemotherapy. The benefit of pembrolizumab monotherapy appears to be greater in patients whose tumours express PD-L1. 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, as well as the evaluation of combination regimens that include PD-1 and PD-L1 inhibitors.

## Introduction

Despite multimodal therapy including platinum-based chemoradiotherapy,[1,2] >50% of patients with locoregionally advanced squamous cell carcinoma of the head and neck (HNSCC) experience recurrence and/or metastasis within 3 years of treatment.[2,3] Platinum-based combination chemotherapy regimens and cetuximab are commonly used in the first-line recurrent and/or metastatic setting.[1,2] The EXTREME regimen, which consists of platinum, 5-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 recently, treatment options for recurrent and/or 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.[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 with HNSCC based on their antitumour activity and safety profiles.[8-14] The anti–PD-1 monoclonal antibody pembrolizumab had a manageable safety profile and provided objective responses in 16% to 18% of patients with recurrent and/or metastatic HNSCC in the phase 1b KEYNOTE-012[8,9] and phase 2 KEYNOTE-055[12] studies. Based on 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 investigator's choice of methotrexate, docetaxel, or cetuximab in patients with recurrent and/or metastatic HNSCC that progressed during or after platinum-based chemotherapy.

## Methods

### Study design and participants

This randomised, open-label, phase 3 study was conducted at 97 medical centres in 20 countries (Australia, Belgium, Canada, France, Germany, Hungary, Ireland, Italy, Lithuania, Mexico, Netherlands, Poland, Portugal, Russia, South Korea, Spain, Sweden, Switzerland, United Kingdom, and United States). Patients were eligible for enrolment if they were ≥18 years of age; 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 and/or metastatic disease or had recurrence or progression within 3 to 6 months of previous multimodal therapy containing platinum for locally advanced disease; received ≤2 lines of therapy for recurrent and/or metastatic disease; had known human papilloma virus (HPV) p16 status for oropharyngeal cancer; had known 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 5-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.

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 and masking

Patients were randomly allocated in a 1:1 ratio using a central interactive voice-response/integrated web-response system to receive pembrolizumab 200 mg every 3 weeks or investigator's choice of methotrexate 40 mg/m$^2$ weekly (could be increased to 60 mg/m$^2$ weekly in the absence of toxicity), docetaxel 75 mg/m$^2$ every 3 weeks, or cetuximab 250 mg/m$^2$ weekly following a loading dose of 400 mg/m$^2$. All treatments were administered intravenously. 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 4 in each stratum. The allocation schedule was generated by the system vendor using a computerised random list generator.

## Procedures

Patients received treatment for up to 35 cycles (approximately 2 years; pembrolizumab only) or until disease progression, development of unacceptable toxicity, withdrawal of consent, or physician decision to discontinue therapy. 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 performed 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 events and those of special interest to pembrolizumab) 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 human papillomavirus association using the CINtec p16 Histology assay (Ventana Medical Systems, Oro Valley, AZ, USA) with a cutpoint 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 categorized 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, macrophages) divided by the total number of tumour cells × 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 randomization to death from any cause, in the total population. Secondary endpoints were overall survival in the PD-L1 combined positive score ≥1 population and the following in the total and PD-L1 combined positive score ≥1 populations: 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 according to modified RECIST (same as RECIST version 1.1 except that a confirmatory assessment of disease progression performed at least 4 weeks after the initial progressive disease assessment is required), both by blinded, independent central radiologic

review; 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 blinded, independent central radiologic 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 blinded, independent central radiologic review; and time to progression, defined as the time from randomisation to first documented disease progression, assessed according to RECIST version 1.1 by blinded, independent central radiologic review. Protocol-specified exploratory endpoints included overall and progression-free survival and response rate in the PD-L1 tumour proportion score ≥50% population. The full list of exploratory endpoints is available in the protocol.

Overall survival, progression-free survival, 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.

**Statistical analysis**

The protocol specified two interim analyses and a final analysis. The independent data monitoring committee (appendix p 9) recommended that the study continue as planned after reviewing the results of both interim analyses, which were performed 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 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 alpha of 0·025 using the Hwang-Shih-DeCani alpha-spending function with the gamma parameter of –4. Alpha was allocated in a stepwise manner starting with the comparison of overall survival in the total population (appendix p 10). The protocol-specified final analysis was performed based on a data cutoff date of May 15, 2017 (efficacy boundary for overall survival in the total population, one-sided alpha of 0·0175). At the time of the protocol-specified final analysis, survival status was not confirmed for 11 patients. A post-hoc analysis of overall survival based on the same cutoff date (i.e., May 15, 2017) was performed after confirming survival status of all 495 randomly allocated patients, including the aforementioned 11 patients.

All statistical analyses were performed 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 radiographic evidence of progression were censored at the time of the last radiographic assessment showing response. For both progression-free survival and duration of response, data for patients who started new anticancer therapy without radiographic 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. Hazard ratios and their associated 95% confidence intervals (CIs) were calculated using a stratified Cox proportional hazards model and Efron's method of handling ties.[17] Differences in response rate were assessed with the stratified Miettinen and Nurminen method.[18] The same stratification factors applied to randomization were applied to all stratified efficacy analyses. An exploratory analysis of the interaction of subgroups with treatment effect was performed using the likelihood ratio test.

This study is registered with ClinicalTrials.gov, NCT02252042.

**Role of the funding source**

The funder contributed to study design, analysis and interpretation of the data, and the preparation of the manuscript. The funder maintained the study database. All authors had access to the data and had responsibility for the decision to submit for publication.

## Results

*Patients*

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, 246 and 234, respectively, 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 ≥1 was observed in 196 of 247 patients (79·4%) in the pembrolizumab group and 191 of 248 patients (77·0%) in the standard-

of-care group. Baseline demographics and disease characteristics for the PD-L1 combined positive score ≥1 and tumour proportion score ≥50% populations are summarized on appendix pp 16–17.

The median duration of follow-up from randomization to data cutoff or death, whichever came first, was 7·5 months (IQR 3·4–13·3). Overall, 22 of 247 patients (8·9%) in the pembrolizumab group and 2 of 248 patients (0·9%) in the standard-of-care group remained on study treatment at the time of data cutoff (figure 1).

*Efficacy*

At the time of the protocol-specified final analysis, which was based on a data cutoff of May 15, 2017, 377 deaths had occurred in 495 patients, with survival status unconfirmed for 11 patients. The hazard ratio for death for pembrolizumab versus standard-of-care was 0·82 (95% CI 0·67–1·01) (one-sided p=0·0316) (appendix p 11), which did not meet the efficacy boundary. After confirming the survival status of the 11 outstanding patients based on the same data cutoff, the number of deaths in the intention-to-treat population increased to 388, and the hazard ratio 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 (95% CI 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) and 26·5% (95% CI 21·2–32·2), respectively. The hazard ratio for death was mostly similar across most subgroups examined, with all 95% confidence intervals overlapping that of the overall population (figure 2B).

With 300 deaths among the 387 patients with a PD-L1 combined positive score ≥1, the hazard ratio 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 (95% CI 5·7–8·3) with standard-of-care. The estimated proportion of patients surviving at 12 months was 40·1% (95% CI 33·2–46·9) and 26·1% (95% CI 20·0–32·5), respectively. With 84 deaths among the 104 patients with a combined positive score <1, the hazard ratio was 1·28 (95% CI 0·80–2·07) and median overall survival was 6·3 months (95% CI 3·9–8·9) and 7·0 months (95% CI 5·1–9·0), respectively (figure 3B). The nominal, two-sided p value for the interaction of treatment effect and PD-L1 combined positive score was 0·07. In the PD-L1 tumour proportion score ≥50% population, there were 97 deaths among 129 patients, and the hazard ratio for death was 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 (95% CI 4·8–9·2) with standard-of-care, and estimated overall survival rates at 12 months were 46·6% (95% CI 34·0–58·2) and 25·4% (95% CI 15·5–36·6). In the tumour proportion score <50% population, 287 of 362 patients had died, and the hazard ratio for death was 0·93 (95% CI 0·73–1·17); median overall survival was 6·5 months (95% CI 5·6–8·8) and 7·1 months (95% CI 5·7–8·1), respectively (figure 3D). The nominal, two-sided p value for the interaction of treatment effect and PD-L1 tumour proportion score was 0·015..

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, and the response rate was 14·6% (95% CI 10·4–19·6) and 10·1% (95% CI 6·6–14·5), respectively (nominal p=0.0610) (appendix pp 18–20). 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) and 2·2 months (IQR 2·1–3·5), respectively. The median duration of response was 18·4 months (95% CI 5·8–18·4) with pembrolizumab and 5.0 months (95% CI 3·6–18·8) with standard-of-care (appendix pp 18–20). The response rate in the pembrolizumab group was higher in patients whose tumours expressed PD-L1, whereas the response rate in the standard-of-care group was similar regardless of PD-L1 expression (appendix pp 18–20). Duration of response was not affected by PD-L1 expression, although the medians fluctuated due to the low number of responses overall (appendix ppXX).

With 442 events of death or disease progression assessed according to RECIST version 1.1 in the total population, there was no difference in progression-free survival between treatment groups (hazard ratio 0·96; 95% CI 0·79–1·16; nominal p=0·3250) (figure 4). Median progression-free survival was 2·1 months (95% CI 2·1–2·3) with pembrolizumab and 2·3 months (95% CI 2·1–2·8) with standard-of-care. Progression-free survival in the PD-L1 combined positive score ≥1 population was similar to that of the total population, whereas progression-free survival was longer with pembrolizumab in the PD-L1 tumour proportion score ≥50% population (figure 4); progression-free survival appeared to be shorter with pembrolizumab in the combined positive score <1 and tumour proportion score ≥50% populations. Median progression-free survival was longer in both treatment groups when assessed according to modified RECIST, and the hazard ratios were close to 1·00 in both the total and PD-L1 combined positive score ≥1 populations (appendix pp XX). There was no difference in time to progression assessed according to RECIST version 1.1 in either the total or PD-L1 combined positive score ≥1 populations (appendix pp XX).

*Subsequent therapy*

In the intention-to-treat population, 84 of 247 patients (34·0%) in the pembrolizumab group and 101 of 248 patients (40·7%) in the standard-of-care group received subsequent therapy, including 11 of 247 (4·5%) and 31 of 248 patients (12·5%), respectively, who received subsequent therapy with an immune checkpoint inhibitor (appendix p 21). 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 p 15). 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 hazard ratio for death was 0·72 (95% CI 0·58–0·88; nominal p=0·0008) (figure 4). In this analysis, median overall survival was 8·3 months (95% CI 6·4–9·4) with pembrolizumab and 6·6 months (95% CI 5·4–7·5) with standard-of-care.

*Safety*

In the as-treated population, treatment-related adverse events occurred in 155 of 246 patients (63·0%) treated with pembrolizumab and 196 of 234 patients (83·8%) treated with standard-of-care (table 2). These events were of grade 3-5 severity in 33 of 246 (13·4%) pembrolizumab-treated patients and 85 of 234 (36·3%) standard-of-care–treated patients and led to treatment discontinuation in 15 (6·1%) and 12 (5·1%) patients, respectively. The incidence of treatment-related adverse events was similar in patients with a PD-L1 combined positive score ≥1, with events of any grade occurring in 128 of 195 patients (65·6%) treated with pembrolizumab and

150 of 183 patients (82·0%) treated with standard-of-care, events of grade 3-5 severity occurring in 31 (15·9%) and 71 (38·8%), respectively, and events leading to discontinuation occurring in 13 (6·7%) and 10 (5·5%), respectively. 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 ≥1.

The most common treatment-related adverse event was hypothyroidism (33 of 246 patients [13·4%]) with pembrolizumab and fatigue (43 of 234 patients [18·4%]) with standard-of-care (table 2). In the pembrolizumab group, there were 4 treatment-related adverse events of grade 3-5 severity that occurred in ≥2 patients each compared with 19 such events in the standard-of-care group. A summary of all treatment-related adverse events is available in appendix pp 22-47. The adverse events of interest with regard to pembrolizumab, regardless of attribution to treatment by the investigator, are summarized in table 2. One of 246 (0·4%) patients experienced a grade 5 event, which was a severe skin reaction (Stevens-Johnson syndrome).

## Discussion

In this randomised, open-label, phase 3 study, pembrolizumab prolonged overall survival compared with investigator's choice of methotrexate, docetaxel, or cetuximab in patients with recurrent and/or metastatic HNSCC. The benefit of pembrolizumab compared with standard-of-

care therapy was greater in patients with PD-L1 expression on their tumours and/or in the tumour microenvironment. 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 rate was low overall (4 of 246 [1·6%] in the pembrolizumab group, 2 of 234 [0·9%] 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 and/or metastatic setting was the lack of a progression-free survival benefit for pembrolizumab compared with standard-of-care therapy.[10,19-21]

In an exploratory analysis not adjusted for multiplicity, there appeared to be an interaction between the treatment effect for overall survival and PD-L1 expression such that benefit of pembrolizumab was greater in patients with a combined positive score ≥1 vs those with a combined positive score <1 and those with a tumour proportion score ≥50% vs <50%. Although not formally tested, the progression-free survival and response rate benefit of pembrolizumab compared with standard-of-care therapy was greater in patients whose tumours had PD-L1 expression. 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 ≥1. Treatment differences were even larger in patients with a PD-L1 tumour proportion score ≥50%. 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.

These data share similarities and differences with those of the CheckMate 141 study, in which the anti–PD-1 monoclonal antibody nivolumab demonstrated superior overall survival compared with investigator's choice of methotrexate, docetaxel, or cetuximab in a similar patient population enrolled in KEYNOTE-040 (hazard ratio 0·70; 97·73% CI 0·51-0·96; p=0·01).[10] 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 (44·6%) and KEYNOTE-040 (44·4%), the doses administered were different. In CheckMate 141, docetaxel was administered at a dose of 30-40 mg/m$^2$ per week, compared with 75 mg/m$^2$ every 3 weeks in KEYNOTE-040. This difference may be relevant given data from patients with HNSCC,[23,24] non–small-cell lung cancer,[25] and prostate cancer[26] that suggest although docetaxel is better tolerated when administered at lower doses weekly, it has less efficacy than higher doses administered once every 3 weeks. Although neither KEYNOTE-040 or CheckMate 141 were powered to compare outcomes in the experimental group with the individual therapies in the standard-of-care group, it is noteworthy that the relative treatment effect of pembrolizumab for overall survival in KEYNOTE-040 was less apparent compared with docetaxel (hazard ratio

0·86) than with methotrexate (hazard ratio 0·75) or cetuximab (hazard ratio 0·56); the hazard ratios in the CheckMate 141 study were 0·82, 0·64, and 0·47, respectively. Moreover, although 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 and 6 months, patients with locally advanced disease in KEYNOTE-040 may have had a better prognosis than those in CheckMate 141. Interestingly, patients whose only prior systemic therapy was definitive and administered in the locally advanced setting, appeared to experience a greater treatment effect with pembrolizumab compared to standard of care than the overall study population. This 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 HNSCC. Despite the differences in eligibility criteria between the studies, the estimated survival at 1 year in the pembrolizumab group of KEYNOTE-040 (37·0%) was nearly identical to that of the nivolumab group of CheckMate 141 (36·0%).[10]

To further understand the better-than-expected overall survival observed in patients receiving standard-of-care therapy, we performed several post-hoc exploratory analyses. At least one subsequent immune checkpoint inhibitor was received by 12·5% of patients in the standard-of-care group, compared with only 4·5% 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 2-times longer than that of patients who received subsequent therapy

other than a checkpoint inhibitor and 4-times longer than that of patients who received no subsequent therapy (20·1 vs 9·7 vs 4·5 months). In an analysis of overall survival in which patients in both treatment groups were censored at the time 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 hazard ratio 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 arm and confounded analysis of overall survival. Future studies of immunotherapy, particularly those conducted in patients with cancers for which checkpoint inhibitors are already approved, should adequately account for subsequent immunotherapy use during study design, particularly as it pertains to power calculations.

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 and/or metastatic HNSCC that progressed during or after platinum-based therapy. Post-study crossover in the standard-of-care group appeared to confound the analysis and may 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 HNSCC.

## Acknowledgments

This trial was funded by Merck Sharp & Dohme, Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

We thank the patients and their families and caregivers for participating in this trial; all the investigators and site personnel; the staff of Agilent Technologies for developing the PD-L1 IHC 22C3 pharmDx assay; Joy Ge and Christine Gause (Merck Sharp & Dohme, Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA) for assistance with statistical analyses; Alba Tuozzo (Merck Sharp & Dohme, Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA) for contributions to study conduct; and Melanie A. Leiby (Merck Sharp & Dohme, Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA) for medical writing and editorial assistance.

## Contributors

EEW Cohen, B Burtness, J Cheng, and KJ Harrington conceived and designed the study. EEW Cohen, J-P Machiels, P Zhang, J Cheng, R Swaby, and KJ Harrington analysed the data. EEW Cohen, D Soulières, C Le Tourneau, J Dinis, L Licitra, A Soria, J-P Machiels, N Mach, R Mehra, R Swaby, and KJ Harrington acquired the data. EEW Cohen, P Zhang, R Swaby, and KJ Harrington wrote the first draft of the manuscript. EEW Cohen, D Soulières, L Licitra, M-J Ahn, A Soria, J-P Machiels, R Mehra, B Burtness, P Zhang, J Cheng, R Swaby, and KJ Harrington interpreted the data. All authors contributed to reviewing or revising the manuscript. All authors approved the final version.

**Declaration of interests**

EEW Cohen reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work and serving in an advisory role for AstraZeneca, Bristol-Myers Squibb, Eisai, Merck, Human Longevity, Inc., and Pfizer, all outside the submitted work.

D Soulières 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.

C Le Tourneau 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 advisor or for lectures from Amgen, Bristol-Myers Squibb, Merck Serono, MSD, Nanobiotix, Novartis, and Roche, all outside the submitted work.

J Dinis reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work.

L Licitra 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, 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, Sobi; and travel support for medical meetings from Bayer, Bristol-Myers Squibb, Debiopharm, Merck-Serono, MSD, Sobi, all outside the submitted work.

M-J Ahn reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work.

A Soria 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-P Machiels 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.

N Mach reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work.

R Mehra reports grant support to the institution from Merck Sharp & Dohme for clinical research related to the submitted work and previous employment by spouse at GlaxoSmithKline and serving as an advisory board member for Bayer, Bristol-Myers Squibb, Genentech, and InnatePharma, all outside the submitted work.

B Burtness 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.

P Zhang personal fees in the form of salary as a full-time employee of Merck & Co., Inc., Kenilworth, NJ, USA.

J Cheng reports personal fees in the form of salary as a full-time employee of Merck & Co., Inc., Kenilworth, NJ, USA, and stock options from the same.

R Swaby reports personal fees in the form of salary as a full-time employee of Merck & Co., Inc., Kenilworth, NJ, USA, and stock options from the same.

KJ Harrington 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.

## References


1. Licitra L, Felip E, Group EGW. Squamous cell carcinoma of the head and neck: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009; **20 Suppl 4**: 121-2.

2. National Comprehensive Cancer Network I. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Head and Neck Cancers, version 2.2017. 2017. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf (accessed October 3, 2017.

3. Blanchard P, Baujat B, Holostenco V, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiother Oncol* 2011; **100**(1): 33-40.

4. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008; **359**(11): 1116-27.

5. Guardiola E, Peyrade F, Chaigneau L, et al. Results of a randomised phase II study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer. *Eur J Cancer* 2004; **40**(14): 2071-6.

6. Vermorken JB, Herbst RS, Leon X, Amellal N, Baselga J. Overview of the efficacy of cetuximab in recurrent and/or metastatic squamous cell carcinoma of the head and neck in patients who previously failed platinum-based therapies. *Cancer* 2008; **112**(12): 2710-9.

7. Argiris A, Ghebremichael M, Gilbert J, et al. Phase III randomized, placebo-controlled trial of docetaxel with or without gefitinib in recurrent or metastatic head and neck cancer: an eastern cooperative oncology group trial. *J Clin Oncol* 2013; **31**(11): 1405-14.

8. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol* 2016.

9. Chow LQ, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: Results from the phase Ib KEYNOTE-012 expansion cohort. *J Clin Oncol* 2016; **34**(32): 3838-45.

10. Ferris RL, Blumenschein G, Jr., Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016; **375**: 1856-67.

11. Moy JD, Moskovitz JM, Ferris RL. Biological mechanisms of immune escape and implications for immunotherapy in head and neck squamous cell carcinoma. *Eur J Cancer* 2017; **76**: 152-66.

12. Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. *J Clin Oncol* 2017; **35**(14): 1542-9.

13. Bahleda R, Braiteh FS, Balmanoukian AS, et al. Long-term safety and clinical outcomes of atezolizumab in head and neck cancer: phase Ia trial results. *Ann Oncol* 2017; **28**(suppl_5): 1044O.

14. Zandberg D, Algazi A, Jimeno A, et al. Durvalumab for recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): preliminary results from a single-arm, phase 2 study. *Ann Oncol* 2017; **28**(suppl_5): 1042O.

15. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**(2): 228-47.

16. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**(6): 649-55.

17. Efron B. The efficiency of Cox's likelihood function for censored data. *J Am Stat Assoc* 1977; **72**: 557-65.

18. Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med* 1985; **4**(2): 213-26.

19. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015; **373**(19): 1803-13.

20. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; **387**(10027): 1540-50.

21. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017; **376**(11): 1015-26.

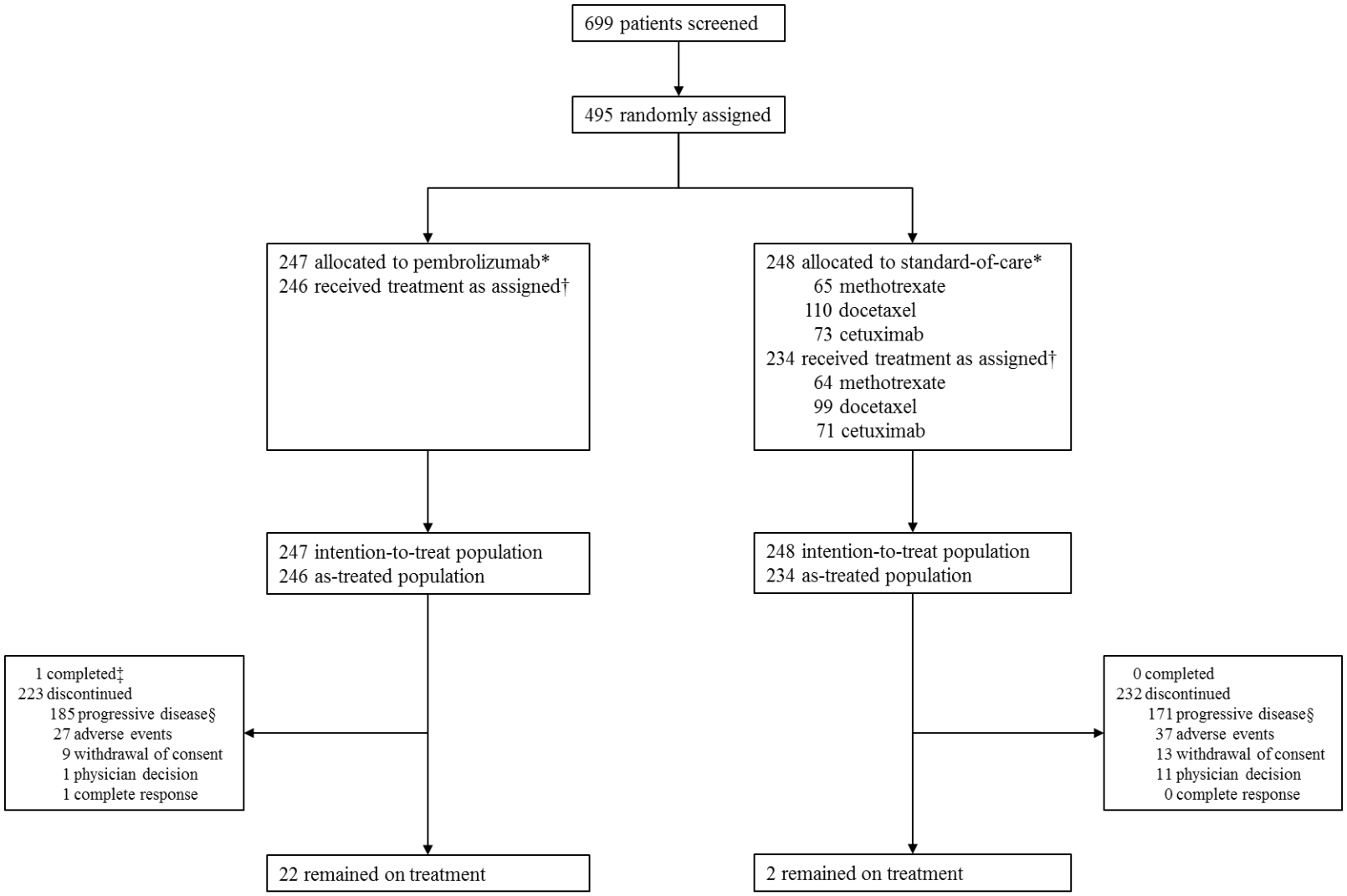
22. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015; **372**(21): 2018-28.

23. Hitt R, Amador ML, Quintela-Fandino M, et al. Weekly docetaxel in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Cancer* 2006; **106**(1): 106-11.

24. Seiwert TY, Cohen EE, Haraf DJ, et al. A phase I trial of docetaxel based induction and concomitant chemotherapy in patients with locally advanced head and neck cancer. *Cancer Invest* 2007; **25**(6): 435-44.

615 25. Camps C, Massuti B, Jimenez A, et al. Randomized phase III study of 3-weekly versus
616 weekly docetaxel in pretreated advanced non-small-cell lung cancer: a Spanish Lung Cancer
617 Group trial. *Ann Oncol* 2006; **17**(3): 467-72.
618 26. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus
619 prednisone for advanced prostate cancer. *N Engl J Med* 2004; **351**(15): 1502-12.
620
621

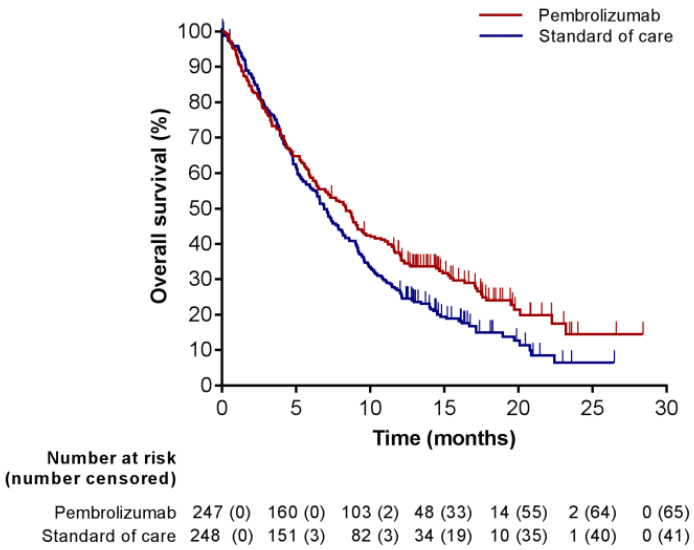
**Figure 1: Trial profile.** *Major protocol deviations that were determined to be clinically relevant were reported for five patients allocated to the pembrolizumab group and five patients allocated to the standard-of-care group. In the pembrolizumab group, the deviations were receipt of ≥3 prior therapies for advanced disease (n=2), lack of documented failure of platinum therapy (n=2), and progressive disease >6 months after platinum-containing multimodal therapy for locally advanced disease (n=1). In the standard-of-care group, the deviations were receipt of ≥3 prior 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 lack of progressive disease documented by radiography (n=1).†One patient allocated to the pembrolizumab group experienced an adverse event after random assignment that prevented them from receiving the first dose of study treatment. In the standard-of-care group, 10 patients withdrew consent, 3 patients experienced clinical deterioration, and 1 patient was lost to follow-up before receiving the first dose of study treatment. ‡Includes patients who received all 35 planned doses of pembrolizumab. §Includes patients who experienced radiographic or clinical progression.


699 patients screened
495 randomly assigned
247 allocated to pembrolizumab*
246 received treatment as assigned†
248 allocated to standard-of-care*
65 methotrexate
110 docetaxel
73 cetuximab
234 received treatment as assigned†
64 methotrexate
99 docetaxel
71 cetuximab
247 intention-to-treat population
246 as-treated population
248 intention-to-treat population
234 as-treated population
1 completed‡
223 discontinued
185 progressive disease§
27 adverse events
9 withdrawal of consent
1 physician decision
1 complete response
0 completed
232 discontinued
171 progressive disease§
37 adverse events
13 withdrawal of consent
11 physician decision
0 complete response
22 remained on treatment
2 remained on treatment

633

**Figure 2: Overall Survival in the Intention-to-Treat Population. Shown are Kaplan-Meier estimates of overall survival according to treatment group in the total population (Panel A) and in subgroups (Panel B).** Tick marks in panel A represent patients who had data censored at the last time that they were known to be alive. In panel B, all subgroups were prespecified except for previous cetuximab, age (prespecified categories were ≤65 years vs. >65 years), and region of enrolment (prespecified categories were east Asia vs. rest of world). Although not a prespecified subgroup analysis, the PD-L1 combined positive score breakdown of <1 vs. ≥1 was included for completeness. The subgroups for the choice of standard-of-care therapy 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 prior to 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 stratified Cox proportional hazards model stratified by the randomisation stratification factors. The interaction of each subgroup with treatment was an exploratory analysis performed using the likelihood ratio test. The 2-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. PD-L1 = programmed death ligand 1.

**A. Total Population**



## B. Subgroups

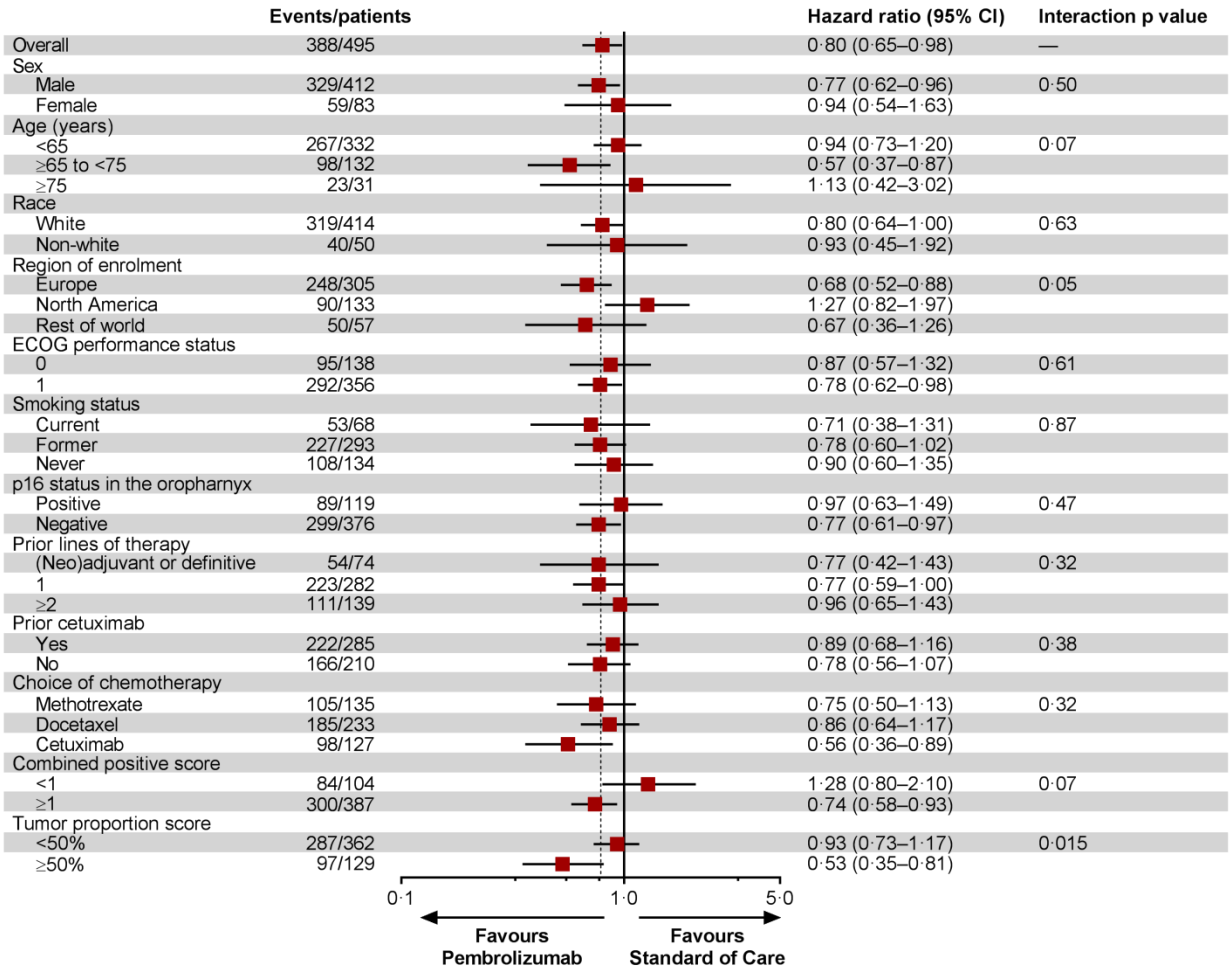
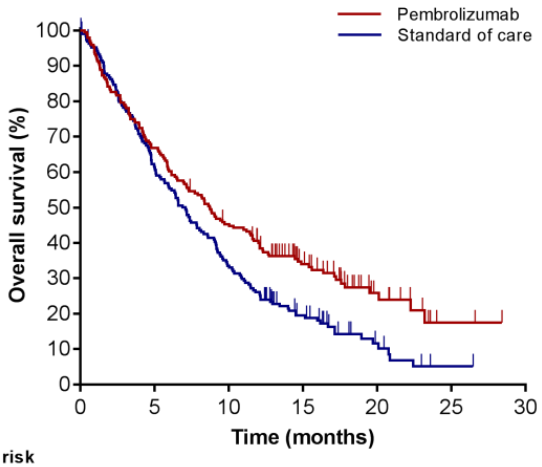


**Figure 3. Overall Survival in the PD-L1 Combined Positive Score and Tumour Proportion Score Intention-to-Treat Populations. Shown are Kaplan-Meier estimates of overall survival according to treatment group in the combined positive score of 1 or more population (Panel A), combined positive score of less than 1 population (Panel B), tumour proportion score of 50% or more population (Panel C), and tumour proportion score of less than 50% population (Panel D).** Tick marks represent patients who had data censored at the last time that they were known to be alive.

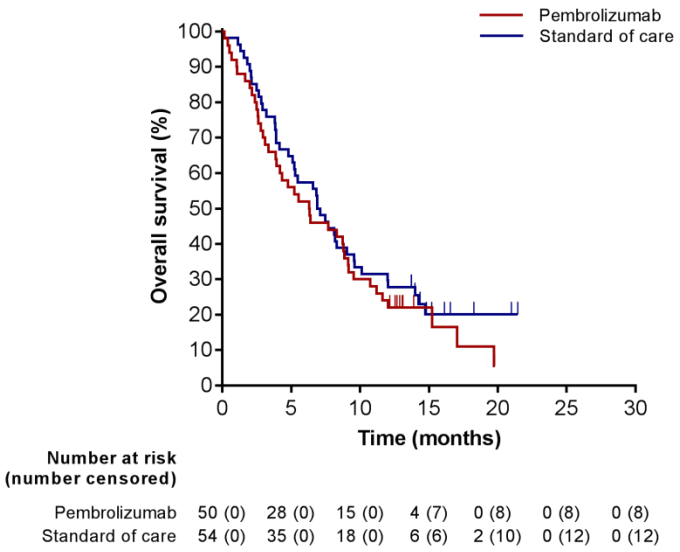
**A. PD-L1 Combined Positive Score ≥1 Population**



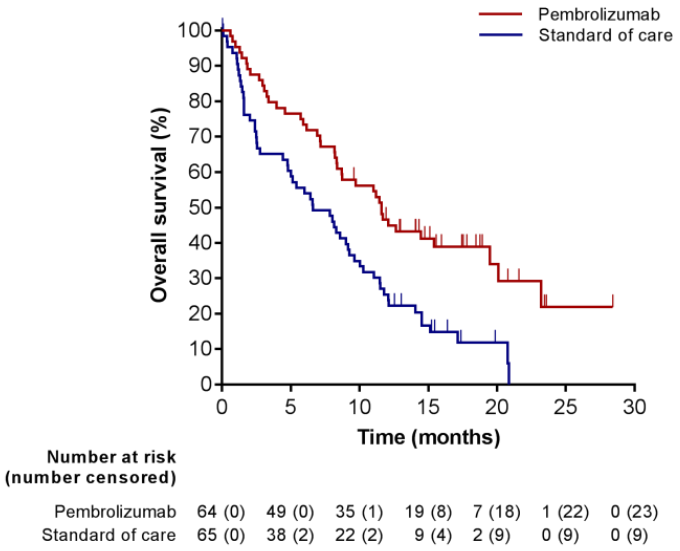

Number at risk (number censored)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pembrolizumab | 196 (0) | 131 (0) | 87 (2) | 43 (26) | 14 (47) | 2 (56) | 0 (58) |
| Standard of care | 191 (0) | 115 (3) | 63 (3) | 28 (13) | 8 (25) | 1 (28) | 0 (29) |

**B. PD-L1 Combined Positive Score <1 Population**




**C. PD-L1 Tumour Proportion Score ≥50% Population**



## D. PD-L1 Tumour Proportion Score <50% Population

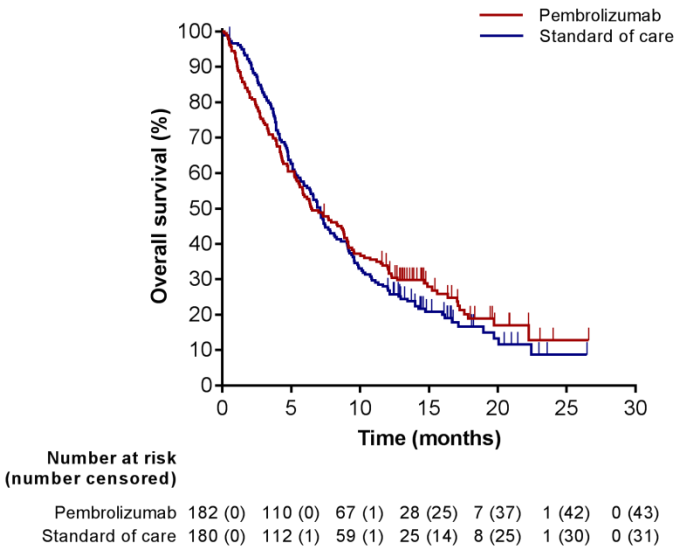
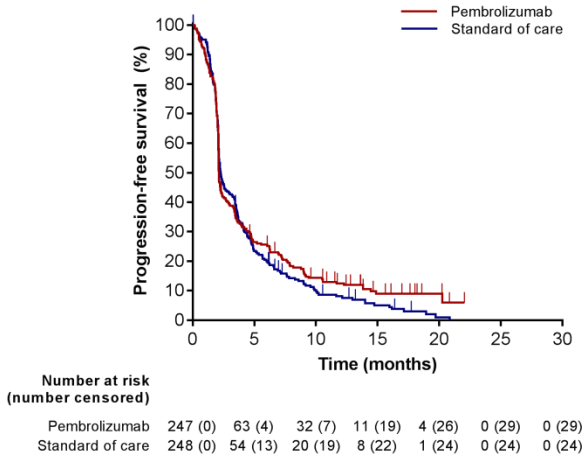
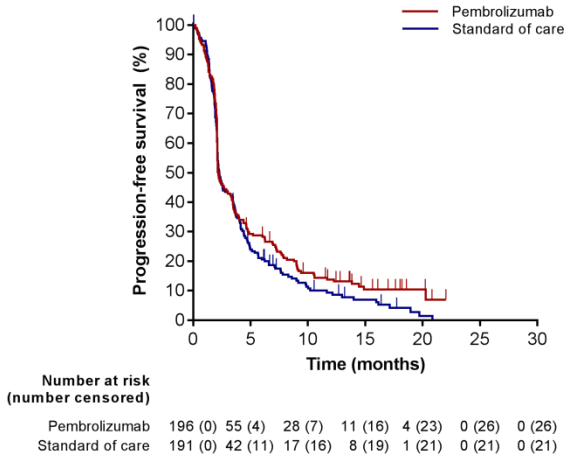


**Figure 4.** Progression-free Survival in the Intention-to-Treat Population. Shown are the Kaplan-Meier estimates of progression-free survival according to treatment group in the total population (Panel A), programmed cell death ligand 1 (PD-L1) combined positive score of 1 or more population (Panel B), combined positive score of less than 1 population (Panel C), PD-L1 tumour proportion score of 50% or more population (Panel D), and PD-L1 tumour proportion score of less than 50% population. Tick marks represent patients who had data censored at the last time that they were known to be alive and without disease progression.

**A. Total Population**

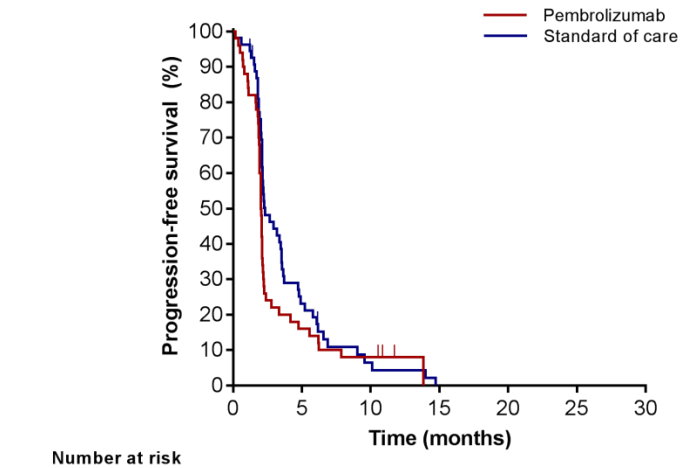



**B. PD-L1 Combined Positive Score ≥1 Population**



688

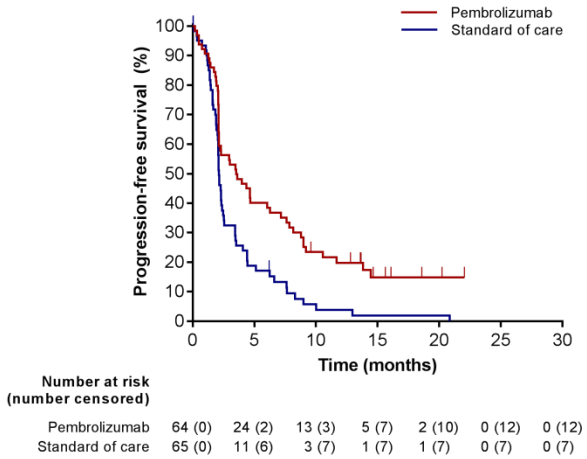
689 **B. PD-L1 Combined Positive Score <1 Population**




690

691

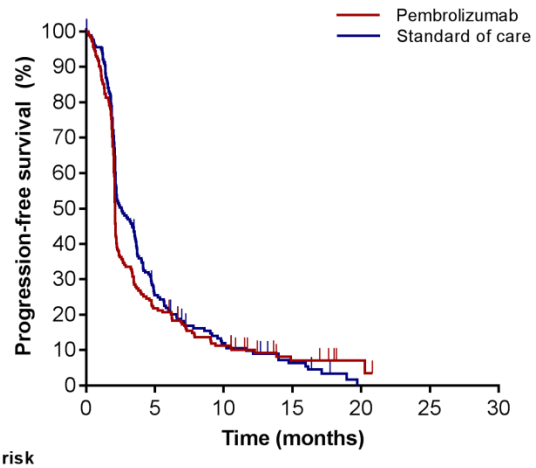
692 **D. PD-L1 Tumour Proportion Score ≥50% Population**




693

694

695 **E. PD-L1 Tumour Proportion Score <50% Population**




| Number at risk (number censored) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pembrolizumab | 182 (0) | 39 (2) | 19 (4) | 6 (12) | 2 (16) | 0 (17) | 0 (3) |
| Standard of care | 180 (0) | 43 (7) | 17 (12) | 7 (15) | 0 (17) | 0 (17) | 0 (17) |

696

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

| Characteristic | Pembrolizumab Group (N=247) | Standard-of-Care Group (N=248) |
|---|---|---|
| Age, years | 60·0 (55–66) | 60·0 (54–66) |
| Male sex | 207 (83·8%) | 205 (82·7%) |
| Region of enrolment | | |
| Europe | 147 (59·5%) | 158 (63·7%) |
| North America | 73 (29·6%) | 60 (24·2%) |
| Rest of world | 27 (10·9%) | 30 (12·1%) |
| ECOG performance status score | | |
| 0 | 71 (28·7%) | 67 (27·0%) |
| 1 | 176 (71·3%) | 180 (72·6%) |
| 2 | 0 | 1 (0·4%) |
| Current or former smoker | 179 (72·5%) | 182 (73·4%) |
| p16 positive in the oropharynx | 61 (24·7%) | 58 (23·4%) |
| PD-L1 tumour proportion score* | | |
| <50% | 182 (73·7%) | 180 (72·6%) |
| ≥50% | 64 (25·9%) | 65 (26·2%) |
| Missing | 1 (0·4%) | 3 (1·2%) |
| PD-L1 combined positive score† | | |
| <1 | 50 (20·2%) | 54 (21·8%) |

| | | |
|---|---|---|
| ≥1 | 196 (79·4%) | 191 (77·0%) |
| Missing | 1 (0·4%) | 3 (1·2%) |
| Current disease stage | | |
| II | 5 (2·0%) | 7 (2·8%) |
| III | 9 (3·6%) | 17 (6·9%) |
| IV | 233 (94·3%) | 224 (90·3%) |
| Previous therapy | | |
| (Neo)adjuvant or definitive | 34 (13·8%) | 40 (16·1%) |
| First line | 141 (57·1%) | 141 (56·9%) |
| Second line | 69 (27·9%) | 64 (25·8%) |
| Third line | 3 (1·2%) | 3 (1·2%) |
| Previous cetuximab | 145 (58·7%) | 140 (56·5%) |

699 Data are median (IQR) or n (%). ECOG = Eastern Cooperative Oncology Group.

700 *The programmed death ligand 1 (PD-L1) tumour proportion score was defined as the

701 percentage of tumour cells with membranous PD-L1 expression.

702 †The PD-L1 combined positive score was defined as the number of PD-L1–positive cells

703 (tumour cells, lymphocytes, and macrophages) out of the total number of tumour cells × 100.

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

| Event | 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 (63·0%) | 33 (13·4%) | 196 (83·8%) | 85 (36·3%) |
| Event leading to treatment discontinuation | 15 (6·1%) | 12 (4·9%) | 12 (5·1%) | 9 (3·8%) |
| Event leading to death | 4 (1·6%) | 4 (1·6%) | 2 (0·9%) | 2 (0·9%) |
| Event occurring in ≥10% of patients in either group | | | | |
| Hypothyroidism | 33 (13·4%) | 1 (0·4%) | 2 (0·9%) | 0 |
| Fatigue | 31 (12·6%) | 4 (1·6%) | 43 (18·4%) | 2 (0·9%) |
| Diarrhoea | 20 (8·1%) | 4 (1·6%) | 24 (10·3%) | 1 (0·4%) |
| Rash | 19 (7·7%) | 1 (0·4%) | 34 (14·5%) | 1 (0·4%) |
| Asthenia | 18 (7·3%) | 1 (0·4%) | 28 (12·0%) | 4 (1·7%) |
| Anaemia | 17 (6·9%) | 1 (0·4%) | 33 (14·1%) | 9 (3·8%) |

| | | | | |
|---|---|---|---|---|
| Nausea | 12 (4·9%) | 0 | 29 (12·4%) | 1 (0·4%) |
| Mucosal inflammation | 9 (3·7%) | 1 (0·4%) | 30 (12·8%) | 5 (2·1%) |
| Stomatitis | 6 (2·4%) | 1 (0·4%) | 28 (12·0%) | 11 (4·7%) |
| Neutrophil count decreased | 3 (1·2%) | 1 (0·4%) | 25 (10·7%) | 20 (8·5%) |
| Alopecia | 1 (0·4%) | 0 | 25 (10·7%) | 0 |
| Event of interest† | | | | |
| Any | 63 (25·6%) | 11 (4·5%) | 28 (12·0%) | 11 (4·7%) |
| Hypothyroidism | 37 (15·0%) | 1 (0·4%) | 9 (3·8%) | 0 |
| Pneumonitis | 10 (4·1%) | 3 (1·2%) | 3 (1·3%) | 3 (1·3%) |
| Infusion-related reaction | 8 (3·3%) | 1 (0·4%) | 7 (3·0%) | 1 (0·4%) |
| Severe skin reaction | 7 (2·8%) | 4 (1·6%) | 9 (3·8%) | 7 (3·0%) |
| Hyperthyroidism | 5 (2·0%) | 0 | 1 (0·4%) | 0 |
| Colitis | 2 (0·8%) | 0 | 1 (0·4%) | 0 |
| Guillain-Barré syndrome | 2 (0·8%) | 1 (0·4%) | 0 | 0 |
| Hepatitis | 2 (0·8%) | 1 (0·4%) | 0 | 0 |

Data are presented as n (%). The median duration of treatment in this population was 2·8 months (IQR 1·2–6·8) for pembrolizumab, 1·4 months (IQR 0·7–2·2) for methotrexate, 1·7 months (IQR 1·2–3·9) for docetaxel, and 2·3 months (IQR 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 in descending order of frequency in the pembrolizumab group.

†The events of interest are those with an immune-related cause and are considered regardless of attribution to study treatment by the investigator. They are listed in descending order of frequency in the pembrolizumab group. In addition to the specific preferred terms listed, related terms were also included.