Title: Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous-cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study

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Summary

Background: Pembrolizumab is active in head-and-neck squamous-cell carcinoma (HNSCC), with PD-L1 expression associated with improved response.

Methods: This randomised, open-label, phase 3 study of participants with untreated locally incurable recurrent/metastatic HNSCC was conducted at 200 sites in 37 countries. Participants were stratified by PD-L1 expression, p16 status, and performance status and allocated 1:1:1 to pembrolizumab, pembrolizumab plus a platinum and 5-fluorouracil ("pembrolizumab-chemotherapy"), or cetuximab plus a platinum and 5-fluorouracil ("cetuximab-chemotherapy"). There were 14 primary hypotheses: superiority of pembrolizumab and pembrolizumab-chemotherapy versus cetuximab-chemotherapy for overall survival (OS) and progression-free survival (PFS) in the PD-L1 combined positive score (CPS) ≥20, CPS ≥1, and total populations and noninferiority of pembrolizumab and pembrolizumab-chemotherapy versus cetuximab-chemotherapy for OS in the total population. Statistical testing was completed for 11 hypotheses at the second interim analysis and for 3 hypotheses at final analysis. This study is registered at ClinicalTrials.gov, number NCT02358031.

Findings: Between April 2015, and January 2017, 882 participants were allocated to pembrolizumab (n=301), pembrolizumab-chemotherapy (n=281), or cetuximab-chemotherapy (n=300); 754 (85%) had CPS ≥1 and 381 (43%) had CPS ≥20. At the second interim analysis (IA2), pembrolizumab significantly improved OS vs cetuximab-chemotherapy in the CPS ≥20 (median 14·9 vs 10·7 months, HR 0·61 [95% CI, 0·45–0·83]; p=0·0007) and CPS ≥1 (12·3 vs 10·3 months, 0·78 [0·64–0·96], p=0·0086) populations and was noninferior in the total population (11·6 vs 10·7 months, 0·85 [0·71-1·03]). Pembrolizumab-chemotherapy significantly improved OS vs cetuximab-chemotherapy in the total population (13·0 vs 10·7 months, HR 0·77 [95% CI, 0·63–0·93], p=0·0034) at IA2 and in the CPS ≥20 (14·7 vs 11·0 months, 0·60 [0·45–

0·82], p=0·0004) and CPS ≥1 (13·6 vs 10·4 months, 0·65 [0·53–0·80], p<0·0001) populations at final analysis. Neither pembrolizumab nor pembrolizumab-chemotherapy improved PFS at IA2. At final analysis, grade ≥3 all-cause adverse events occurred in 164 (55%) of 300 treated participants in the pembrolizumab group, 235 (85%) of 276 in the pembrolizumab-chemotherapy group, and 239 (83%) of 287 in the cetuximab-chemotherapy group.

Interpretation: Based on the observed efficacy and safety, pembrolizumab plus platinum and 5-fluorouracil is an appropriate first-line treatment for recurrent/metastatic HNSCC and pembrolizumab monotherapy is an appropriate first-line treatment for PD-L1–positive recurrent/metastatic HNSCC.

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Research in context

Evidence before this study: We searched PubMed on May 28, 2019, using the following terms: “PD-1 OR PD-L1 OR (MK-3475 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) OR (cetuximab OR Erbitux AND chemotherapy)” AND “recurrent OR metastatic AND locally incurable” AND “(first line) OR (previously untreated)” AND “head and neck squamous cell carcinoma OR HNSCC OR SCCHN.” There were no limits applied to the search. We also searched the abstracts for the 2017, 2018, and 2019 American Association for Cancer Research Annual Meeting, American Society of Clinical Oncology Annual Meeting, and 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 a subgroup analysis of the phase 3 CheckMate 141 study of nivolumab vs investigator’s choice of therapy for platinum-refractory recurrent or metastatic HNSCC that showed that nivolumab was associated with an overall survival benefit in participants whose disease progressed within 6 months of platinum-based therapy given for locally advanced disease. We did not focus on this report because our study excluded patients whose disease progressed within 6 months of curatively intended systemic therapy given as a component of locoregionally advanced disease management. We also identified several studies of cetuximab given in combination with various chemotherapy regimens and a phase 3 study of bevacizumab plus platinum-doublet chemotherapy vs platinum-doublet chemotherapy alone. We focused on the phase 3 EXTREME study that showed an overall survival benefit for cetuximab in combination with a platinum and 5-fluorouracil because this is the standard regimen for first-line treatment of recurrent or metastatic HNSCC. This regimen was used as the control arm in several other studies, including the phase 2 ADVANTAGE study of cilengitide plus cetuximab, a platinum, and 5-

fluorouracil, the phase 2 Active8 study of motolimod plus cetuximab, cisplatin, and 5-fluorouracil, and the phase 2 TPExtreme study of cetuximab plus cisplatin and docetaxel.

Added value of this study: The randomised, open-label, phase 3 KEYNOTE-048 study of pembrolizumab given alone or in combination with a chemotherapy regimen of platinum and 5-fluorouracil establishes anti–PD-1–based therapy as a first-line treatment option for patients with locally incurable recurrent or metastatic HNSCC. Pembrolizumab monotherapy was associated with a significant overall survival benefit in participants with a PD-L1 combined positive score (CPS) ≥20 or ≥1 and had noninferior overall survival in the total study population compared with standard-of-care therapy with cetuximab, a platinum, and 5-flurouracil. Pembrolizumab given with a platinum and 5-fluorouracil significantly improved overall survival in the PD-L1 CPS ≥20, PD-L1 CPS ≥1, and total populations compared with cetuximab, a platinum, and 5-fluorouracil. Compared with standard therapy, the incidence of adverse events of any grade and of grade 3, 4, or 5 was lower with pembrolizumab monotherapy and similar with pembrolizumab plus chemotherapy.

Implications of all the available evidence: Our findings of a significant survival benefit for pembrolizumab monotherapy in participants with PD-L1 CPS ≥20 and ≥1 and a favourable safety profile relative to standard-of-care therapy suggest that pembrolizumab monotherapy is a new treatment option for patients with PD-L1–positive recurrent or metastatic HNSCC. Our findings of a significant survival benefit for pembrolizumab combined with a platinum and 5-fluorouracil in the total and PD-L1–positive populations along with a manageable safety profile compared with standard therapy suggest that pembrolizumab plus chemotherapy is a new standard-of-care treatment for patients recurrent or metastatic HNSCC.

INTRODUCTION

Head and neck squamous-cell carcinoma (HNSCC) includes cancers of the oral cavity, oropharynx, hypopharynx, and larynx. Locoregional HNSCC is treated with curative intent, although functional sequelae may be severe, and many patients succumb to recurrence or metastasis.[1,2] Standard first-line treatment for recurrent or metastatic disease not amenable to local therapy is cetuximab plus chemotherapy with platinum and 5-fluorouracil, which provides median overall survival (OS) of approximately 10 months and is associated with substantial toxicity.[3]

Immune checkpoint inhibitors have demonstrated efficacy and manageable safety in HNSCC.[4-8] Monotherapy with the programmed cell death protein 1 (PD-1) inhibitors pembrolizumab and nivolumab improved OS compared with standard-of-care in participants with recurrent or metastatic HNSCC that progressed during or after platinum-based chemotherapy[5,6]; PD-1 ligand 1 (PD-L1) expression on tumour cells and associated immune cells predicted better outcomes for pembrolizumab.[5] Chemotherapy is a rational combination partner for immune checkpoint inhibitors in HNSCC because it disrupts tumour architecture, potentially reducing immune exclusion, results in antigen shedding, and induces rapid disease control.[9]

We performed the KEYNOTE-048 study to determine whether pembrolizumab as monotherapy or in combination with chemotherapy improves OS compared with cetuximab-chemotherapy in participants with previously untreated recurrent or metastatic HNSCC.

METHODS

Study design and participants

This randomised, open-label, phase 3 study was done at 200 medical centres in 37 countries (appendix). Participants were eligible for enrolment if they were aged ≥18 years, had

pathologically confirmed squamous-cell carcinoma of the oropharynx, oral cavity, hypopharynx, or larynx that was recurrent or metastatic and not curable by local therapy, had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1, had ≥1 tumour lesion measurable per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, had known p16 expression for oropharyngeal cancers, and provided a tumour sample for PD-L1 testing. Participants were excluded if they experienced progressive disease within 6 months of curatively intended systemic treatment given for locoregionally advanced disease management, had symptomatic central nervous system metastases, had a history of non-infectious pneumonitis that required glucocorticoids, or had active autoimmune disease. Full eligibility criteria are included in the trial protocol (appendix).

The study protocol and all amendments were approved by the appropriate ethics committee at each centre. The study was conducted in accordance with the protocol, its amendments, and standards of Good Clinical Practice. All participants provided written informed consent before enrolment.

Randomisation and masking

The randomisation schedule was produced by a computerised random list generator and housed centrally. Treatment assignments were obtained using an interactive voice-response/integrated web-response system (Almac Clinical Technologies, Souderton, PA, USA). Randomization was stratified by the percentage of PD-L1–expressing tumour cells (≥50% vs <50%), p16 status for oropharyngeal cancers (positive vs negative; participants with non-oropharyngeal tumours were considered p16 negative), and ECOG performance-status score (0 vs 1). Participants were assigned 1:1:1 in blocks of 3 per stratum to receive pembrolizumab alone, pembrolizumab plus platinum and 5-fluorouracil (“pembrolizumab-chemotherapy”), or

cetuximab plus platinum and 5-fluorouracil ("cetuximab-chemotherapy"). Neither participants nor investigators were masked to treatment assignment.

Procedures

In the pembrolizumab and pembrolizumab-chemotherapy groups, pembrolizumab (200 mg) was administered once every 3 weeks until disease progression, intolerable toxicity, physician or participant decision, or 35 cycles, whichever occurred first. Participants in the cetuximab group received cetuximab (400 mg/m^2 loading dose, then 250 mg/m^2/week) until disease progression, intolerable toxicity, or physician or participant decision, whichever occurred first. Participants in the pembrolizumab-chemotherapy and cetuximab-chemotherapy groups also received carboplatin (AUC 5 mg/m^2) or cisplatin (100 mg/m^2) and 5-fluorouracil (1000 mg/m^2/day for 4 days) every 3 weeks for 6 cycles. All treatments were administered intravenously. Participants who experienced confirmed complete response and had received ≥24 weeks of therapy, including 2 doses of pembrolizumab beyond the first evidence of complete response, could discontinue pembrolizumab; clinically stable participants with unconfirmed disease progression could remain on treatment at the discretion of the investigator until progression was confirmed with imaging performed ≥28 days later.

PD-L1 expression in archival or newly obtained, formalin-fixed tumour samples was assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA) and characterized by the combined positive score (CPS), defined as the number of PD-L1–positive cells (tumour cells, lymphocytes, macrophages) divided by the total number of tumour cells × 100; a minimum of 100 viable tumour cells must have been present for the specimen to be considered evaluable.[10] Investigators, participants, and representatives of the sponsor were masked to CPS results; PD-L1 positivity was not required for study entry. p16 status for oropharyngeal cancers was assessed as a surrogate of HPV association using the

CINtec p16 Histology assay (Ventana Medical Systems, Tucson, AZ, USA) with strong and diffuse nuclear and cytoplasmic staining in ≥70% of cells used as the cutpoint for positivity.

Adverse events (AEs) and laboratory abnormalities were collected regularly throughout treatment and for 30 days thereafter (90 days for serious adverse events and events of interest) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Tumour imaging was performed at baseline, week 9, every 6 weeks through year 1, and every 9 weeks thereafter. Response was assessed according to RECIST v1.1 by masked and independent central review. Participants were contacted to assess survival every 12 weeks during follow-up.

Outcomes

The primary endpoints were OS, defined as the time from randomisation to death from any cause, and progression-free survival (PFS), defined as the time from randomisation to radiographically confirmed disease progression or death from any cause, whichever occurred first. Secondary endpoints were safety and tolerability, the proportion of participants with objective response, defined as radiographically confirmed complete or partial response, the proportion of participants who were progression-free at 6 and 12 months, change from baseline in global health status/quality of life (reported elsewhere), and time to deterioration in global health status/quality of life, pain, and swallowing (reported elsewhere). Duration of response, defined as the time from first documented complete or partial response to radiographically confirmed disease progression or death from any cause, whichever occurred first, was an exploratory endpoint. A full list of exploratory endpoints is found in the protocol and the summary of its amendments (appendix). Response and disease progression were assessed according to RECIST v1.1, by masked, independent central review. All endpoints were evaluated for pembrolizumab vs cetuximab-chemotherapy and for pembrolizumab-

chemotherapy vs cetuximab-chemotherapy in participants with PD-L1 CPS ≥20, in participants with PD-L1 CPS ≥1, and in the total population; the exception is safety, which was only evaluated in the total population.

Statistical analysis

OS, PFS, and objective response were assessed in the intention-to-treat population, defined as all participants randomly allocated to a treatment group. Duration of response was assessed in all participants who had confirmed complete or partial response. Safety was assessed in the as-treated population, defined as all participants who received ≥1 dose of allocated study treatment.

All statistical analyses were done using SAS version 9.4. OS, PFS, and duration of response were estimated using the Kaplan-Meier method and the censoring rules outlined in the protocol (appendix). The stratified log-rank test was used to assess between-group differences in OS and PFS. A stratified Cox proportional hazards model with Efron's method of tie handling[11] was used to estimate hazard ratios (HRs) and associated 95% CIs. The randomisation stratification factors were applied to all stratified analyses. The consistency of the OS treatment effect in subgroups was assessed descriptively using HRs and nominal 95% CIs calculated with a non-stratified Cox proportional hazards model with Efron's method of tie handling. In accordance with the intention-to-treat principle, participants allocated to the cetuximab-chemotherapy group during the pembrolizumab-chemotherapy enrolment hold (described in the Results) were excluded from all efficacy comparisons between pembrolizumab-chemotherapy and cetuximab-chemotherapy. The Kaplan-Meier method was used to estimate OS, PFS, and duration of response.

The evolution of the statistical analysis plan can be found in the protocol and summary of its amendments (appendix). In the final protocol, there were 14 primary hypotheses: superiority of pembrolizumab and of pembrolizumab-chemotherapy, each vs cetuximab-chemotherapy, for OS and PFS in the CPS ≥20 population; noninferiority of pembrolizumab-chemotherapy for OS and superiority of pembrolizumab-chemotherapy for PFS, each vs cetuximab-chemotherapy, in the total population; non-inferiority of pembrolizumab vs cetuximab-chemotherapy for OS in the total population; superiority of pembrolizumab vs cetuximab-chemotherapy for OS and PFS in the CPS ≥1 and total populations; and superiority of pembrolizumab-chemotherapy vs cetuximab-chemotherapy for OS and PFS in the CPS ≥1 population and OS in the total population (appendix). The graphical method of Maurer and Bretz[12] was used to control the family-wise type I error rate at α=0.025 (one-sided) across all primary hypotheses and interim analyses. As detailed in the appendix, the following six hypotheses were tested in parallel: superiority of pembrolizumab vs cetuximab-chemotherapy for PFS and OS, superiority of pembrolizumab-chemotherapy vs cetuximab-chemotherapy for PFS and OS in the PD-L1 CPS ≥20 population; superiority of pembrolizumab-chemotherapy vs cetuximab-chemotherapy for PFS in the total population; and the noninferiority of pembrolizumab-chemotherapy vs cetuximab-chemotherapy for OS in the total population. The remaining 8 primary hypotheses were tested according to the pre-specified multiplicity strategy if the hypotheses with initial alpha allocations were positive. Pembrolizumab and pembrolizumab-chemotherapy were considered effective if they showed superior OS or PFS compared with cetuximab-chemotherapy in any of the protocol-specified populations or if they showed non-inferior OS in the total population. Planned enrolment was 825 participants. The assumptions that contributed to the planned enrolment and the power for all 14 primary hypotheses are summarized in the appendix.

The protocol specified two interim analyses and a final analysis. The first interim analysis was planned to occur ≥9 months after the last patient was enrolled and used a data cutoff of Oct 17,

2017. The data and safety monitoring committee recommended that the study continue as planned after reviewing the first interim analysis. The second interim analysis, which was the final analysis of PFS, was planned to occur approximately 17 months after the last patient was enrolled and used a data cutoff of Jun 13, 2018. The one-sided p-value boundaries for testing superiority of pembrolizumab vs cetuximab-chemotherapy at the second interim analysis were 0·0016 for PFS in the CPS ≥20 population, 0·0024 for OS in the CPS ≥20 population, 0·0109 for OS in the CPS ≥1 population, and 0·0117 for OS in the total population. The one-sided p-value boundaries for testing superiority of pembrolizumab-chemotherapy versus cetuximab-chemotherapy at the second interim analysis were 0·0017 for PFS in the PD-L1 CPS ≥20 population, 0·0002 for PFS in the total population, and 0·0018 for OS in the CPS ≥20 population, and 0·0041 for OS in the total population. The noninferiority boundary for OS in the total population for both pembrolizumab and for pembrolizumab-chemotherapy vs cetuximab-chemotherapy was 1·2; the statistical criterion for the success of the noninferiority hypothesis is that if the upper bound of the confidence interval, based on the alpha level allocated to the analysis, for the hazard ratio is <1·2. Results from the second interim analysis are presented for the 11 primary hypotheses for which statistical testing was completed at the second interim analysis. To complete statistical testing for the 3 remaining primary hypotheses, the study continued to the final analysis, which was planned to occur approximately 44 months after the first patient was enrolled and used a data cutoff of Feb 25, 2019. The one-sided p-value boundaries for testing superiority of the 3 remaining primary hypotheses at the final analysis were 0·0023 for OS superiority of pembrolizumab-chemotherapy vs cetuximab-chemotherapy in the PD-L1 CPS ≥20 population, 0·0026 for OS superiority of pembrolizumab-chemotherapy vs cetuximab-chemotherapy in the CPS ≥1 population, and 0·0059 for OS superiority of pembrolizumab vs cetuximab-chemotherapy in the total population. Results from the final analysis are presented for the 3 primary hypotheses that completed statistical testing at the final analysis, all secondary hypotheses, and safety; to provide more mature overall survival for

those hypotheses that completed statistical testing at the second interim analysis, an additional exploration of overall survival from the final analysis is also presented. This trial is registered with ClinicalTrials.gov, number NCT02358031.

Role of the funding source

The study funder participated in study design, data collection, analysis, and interpretation, and writing of the report. All authors had access to all study data and approved the decision so submit for publication.

RESULTS

Of the 1228 individuals screened for eligibility, 882 were randomly allocated to pembrolizumab (n=301), pembrolizumab-chemotherapy (n=281), or cetuximab-chemotherapy (n=300) between April 20, 2015, and January 17, 2017 (figure 1, appendix). Based on consultation between the sponsor and data and safety monitoring committee after 3 deaths (2 from disease progression, 1 from an adverse event) occurred in the first 14 participants in the pembrolizumab-chemotherapy group, allocation to this group was held starting August 13, 2015. After the data and safety monitoring committee reviewed safety data from 20 participants in the pembrolizumab-chemotherapy group who completed 2 cycles of study treatment, allocation to this group resumed as of October 2, 2015. Among the 882 allocated participants, 381 (43%) had PD-L1 CPS ≥20 and 754 (85%) had PD-L1 CPS ≥1. Carboplatin was the chosen platinum for 160 (57%) of 281 participants in the pembrolizumab-chemotherapy group and 170 (57%) of 300 participants in the cetuximab-chemotherapy group. Baseline demographics and disease characteristics were as expected and similar between groups and across the PD-L1 CPS and total populations (table 1, appendix).

The study profile for the total population is found in figure 1. The intention-to-treat population for the evaluation of pembrolizumab vs cetuximab-chemotherapy included all 301 participants allocated to pembrolizumab and all 300 participants allocated to cetuximab-chemotherapy. The intention-to treat population for the evaluation of pembrolizumab-chemotherapy vs cetuximab-chemotherapy included all 281 participants allocated to pembrolizumab-chemotherapy and the 278 participants allocated to cetuximab-chemotherapy while the pembrolizumab-chemotherapy arm was available for allocation. Study treatment was received by 300 participants in the pembrolizumab group, 276 in the pembrolizumab-chemotherapy group, and 287 in the cetuximab-chemotherapy group. As of the final analysis (data cutoff, Feb 25, 2019), no participants in the pembrolizumab or pembrolizumab-chemotherapy groups remained on pembrolizumab, with 31 (10%) of 300 treated participants in the pembrolizumab group and 27 (10%) of 276 treated participants in the pembrolizumab-chemotherapy group having completed all 35 cycles of pembrolizumab. In the cetuximab-chemotherapy group, 9 (3%) of 287 treated participants remained on cetuximab. Trial profiles for the PD-L1 CPS ≥20 and CPS ≥1 populations are in the appendix. In the intention-to-treat population at the final analysis, ≥1 subsequent anticancer therapy was received by 148 (49%) of 301 participants in the pembrolizumab group, 115 (41%) of 281 in the pembrolizumab-chemotherapy group, and 159 (53%) of 300 in the cetuximab-chemotherapy group, including 17 (6%), 17 (6%), and 74 (25%), respectively, who received a subsequent PD-1 or PD-L1 inhibitor (appendix).

Median follow-up duration, defined as the time from randomization to death or data cutoff, whichever occurred first, was 11·7 months (IQR 5·1-20·8) in the pembrolizumab group, 13·0 months (IQR 6·4-21·5) in the pembrolizumab-chemotherapy group, and 10·7 months (IQR 6·6-18·1) in the cetuximab-chemotherapy group at the second interim analysis. At final analysis, median (IQR) follow-up was 11·5 months (5·1-25·7), 13·0 months (6·4-26·6), and 10·7 months (6·6-19·7), respectively.

At the second interim analysis and compared with cetuximab-chemotherapy, pembrolizumab significantly prolonged OS in the PD-L1 CPS ≥20 and CPS ≥1 populations (figure 2). In the CPS ≥20 population and with 177 (69%) of 255 participant having died, HR was 0·61 (95% CI 0·45-0·83; p=0·0007); median (95% CI) OS was 14·9 months (11·6-21·5) in the pembrolizumab group versus 10·7 months (8·8-12·8) in the cetuximab-chemotherapy group. In the PD-L1 CPS ≥1 population and with 383 (75%) of 512 participant having died, HR was 0·78 (95% CI 0·64-0·96; p=0·0086); median (95% CI) OS was 12·3 months (10·8-14·9) versus 10·3 months (9·0-11·5). The benefit of pembrolizumab compared with cetuximab-chemotherapy in the CPS ≥20 and CPS ≥1 populations was maintained at the final analysis (appendix). At the second interim analysis in the total population and with 453 (75%) of 601 participants having died, pembrolizumab demonstrated noninferior, but not superior, OS compared with cetuximab-chemotherapy (HR 0·85, 95% CI 0·71-1·03, p=0·0456); median (95% CI) OS was 11·6 months (10·5-13.6) in the pembrolizumab group vs 10·7 months (9·3-11·7) in the cetuximab-chemotherapy group. At final analysis and with 501 (83%) of 601 participants having died, the threshold for demonstrating superior OS for pembrolizumab vs cetuximab-chemotherapy in the total population was not met (HR 0·83, 95% CI 0·70-0·99; p=0·0199); median (95% CI) OS was 11·5 months (10·3-13·4) versus 10·7 months (9·3-11·7) (figure 2). All HRs favoured pembrolizumab except for the recurrent disease subgroup of the total and PD-L1 CPS ≥1 populations (appendix).

At the second interim analysis in the total population, 420 (75%) of 559 participants allocated to pembrolizumab-chemotherapy and cetuximab-chemotherapy had died, and pembrolizumab-chemotherapy significantly prolonged OS (HR 0·77, 95% CI 0·63-0·93, p=0·0034) (figure 2); median (95% CI) OS was 13·0 months (10·9-14·7) in the pembrolizumab-chemotherapy group versus 10·7 months (9·3-11·7) in the cetuximab-chemotherapy group. The survival benefit was

maintained at the final analysis (appendix). The superiority threshold for an OS benefit of pembrolizumab-chemotherapy versus cetuximab-chemotherapy in the CPS ≥20 population was not met at the second interim analysis, and per the analysis plan, formal statistical testing in the CPS ≥1 population was not performed. At final analysis, pembrolizumab-chemotherapy significantly improved OS versus cetuximab-chemotherapy in the CPS ≥20 and CPS ≥1 populations (figure 2). With 182 (77%) of 236 participants having died in the CPS ≥20 population, HR was 0·60 (95% CI 0·45-0·82, p=0·0004), and median (95% CI) OS was 14·7 months (10·3-19·3) with pembrolizumab-chemotherapy versus 11·0 months (9·2-13·0) in the cetuximab-chemotherapy group. With 390 (82%) of 477 participants having died in the CPS ≥1 population, HR was 0·65 (95% CI 0·53-0·80, p<0·0001), and median (95% CI) OS was 13·6 months (10·7-15·5) versus 10·4 months (9·1-11·7). All HRs favoured pembrolizumab-chemotherapy (appendix).

At the second interim analysis (final analysis of progression-free survival) and compared with cetuximab-chemotherapy, pembrolizumab did not significantly improve PFS in the PD-L1 CPS ≥20 population (HR 0·99, 95% CI 0·75-1·29; p=0·4562), and pembrolizumab-chemotherapy did not significantly improve PFS in the CPS ≥20 (HR 0·73, 95% CI 0·55-0·97, p=0·0162) or total populations (HR 0·92, 95% CI 0·77-1·10, p=0·1697) (figure 3). Because superiority was not demonstrated for these comparisons, no formal statistical testing was done for pembrolizumab versus cetuximab-chemotherapy in the PD-L1 CPS ≥1 (HR 1·16, 95% CI 0·96-1·39) or total (HR 1·34, 95% CI 1·13-1·59) populations or for pembrolizumab-chemotherapy versus cetuximab-chemotherapy in the CPS ≥1 population (HR 0·82, 95% CI 0·67-1·00) (figure 3). Median PFS and estimated rates of participants alive and without disease progression at 6 and 12 months are summarized in table 2.

At final analysis, the proportion of participants with objective response in the pembrolizumab and cetuximab-chemotherapy groups was 31 (23%) of 133 and 44 (36%) of 122, respectively, in the PD-L1 CPS ≥20 population, 49 (19%) of 257 and 89 (35%) of 255, respectively, in the CPS ≥1 population, and 51 (17%) of 301 and 108 (36%) of 300, respectively, in the total population. Median response duration in the pembrolizumab and cetuximab-chemotherapy groups was 22·6 months and 4·2 months, respectively, in the CPS ≥20 population, 23·4 months and 4·5 months, respectively, in the CPS ≥1 population, and 22·6 months and 4·5 months, respectively, in the total population (appendix). At final analysis, the proportion of participants with objective response in the pembrolizumab-chemotherapy and cetuximab-chemotherapy groups was 54 (43%) of 126 and 42 (38%) of 110, respectively, in the CPS ≥20 population, 88 (36%) of 242 and 84 (36%) of 235, respectively, in the CPS ≥1 population, and 100 (36%) of 281 and 101 (36%) of 278, respectively, in the total population. Median response duration in the pembrolizumab-chemotherapy and cetuximab-chemotherapy groups was 7·1 and 4·2 months, respectively, in the CPS ≥20 population, 6·7 and 4·3 months, respectively, in the CPS ≥1 population, and 6·7 and 4·3 months, respectively, in the total population (appendix).

At final analysis in the as-treated population, the median (IQR) duration of any study therapy was 3·5 months (1·4-7·6) in the pembrolizumab group, 5·8 months (2·8-9·7) in the pembrolizumab-chemotherapy group, and 4·9 months (2·5-7·4) in the cetuximab-chemotherapy group. In the as-treated population, grade ≥3 AEs of any cause occurred in 164 (55%) of 300 participants in the pembrolizumab group, 235 (85%) of 276 in the pembrolizumab-chemotherapy group, and 239 (83%) of 287 in the cetuximab-chemotherapy group; these AEs were attributed to study treatment by the investigator in 51 (17%), 198 (72%), and 199 (69%) participants, respectively. Grade ≥3 AEs of any cause that occurred in ≥5 participants in any group are summarized in the appendix; there were 13 such events in the pembrolizumab group, 36 in the pembrolizumab-chemotherapy group, and 34 in the cetuximab-chemotherapy group. In the

pembrolizumab group, AEs of any cause led to treatment discontinuation in 36 (12%) of 300 participants. In the pembrolizumab-chemotherapy and cetuximab-chemotherapy groups, AEs of any cause led to discontinuation of any treatment in 90 (33%) of 276 participants and 79 (28%) of 287 participants, respectively, and of all treatment in 23 (8%) and 26 (9%), respectively. Twenty-five (8%) participants in the pembrolizumab group, 32 (12%) in the pembrolizumab-chemotherapy group, and 28 (10%) in the cetuximab-chemotherapy group died from AEs, including 3 (1%), 11 (4%), and 8 (3%), respectively, who died from treatment-related AEs (appendix).

The most common AEs with pembrolizumab were fatigue and anaemia (table 3); the most common treatment-related AEs were fatigue and hypothyroidism (appendix). Anaemia and nausea were the most common AEs of any cause and those attributed to study treatment with pembrolizumab-chemotherapy and cetuximab-chemotherapy (table 3, appendix). Pembrolizumab was associated with a greater risk of hypothyroidism than cetuximab-chemotherapy, whereas cetuximab-chemotherapy was associated with a greater risk of 20 AEs (appendix). Pembrolizumab-chemotherapy was associated with a greater risk of anaemia, hypothyroidism, and cough than cetuximab-chemotherapy, whereas risks of hypokalaemia, hypomagnesaemia, rash, and acneiform dermatitis were greater with cetuximab-chemotherapy (appendix). Exposure-adjusted rates of all-cause AEs are summarized in the appendix. AEs of interest, which were based on a list of terms specified by the sponsor and included regardless of treatment attribution by the investigator, occurred in 93 (31%) of 300 participants in the pembrolizumab group, 73 (26%) of 276 participants in the pembrolizumab-chemotherapy group, and 68 (24%) of 287 participants in the cetuximab-chemotherapy group; these were of grade ≥3 in 21 (7%), 15 (5%), and 30 (10%), respectively (appendix). One participant each in the pembrolizumab and pembrolizumab-chemotherapy groups died from pneumonitis. Bleeding from the tumour site occurred in 20 (7%) of 300 participants in the pembrolizumab group, 24

(9%) of 276 participants in the pembrolizumab-chemotherapy group, and 15 (5%) of 287 participants in the cetuximab-chemotherapy group (appendix).

DISCUSSION

In this randomised phase 3 study of participants with untreated recurrent or metastatic HNSCC and compared with cetuximab plus platinum and 5-fluorouracil, pembrolizumab monotherapy significantly prolonged OS in the PD-L1 CPS ≥20 and CPS ≥1 populations and had non-inferior OS in the total population, whereas pembrolizumab plus platinum and 5-fluorouracil significantly prolonged OS in the PD-L1 CPS ≥20, PD-L1 CPS ≥1, and total populations. The OS observed in the cetuximab-chemotherapy group was consistent with that observed for cetuximab-chemotherapy in the phase 3 EXTREME study.[3]

Neither pembrolizumab nor pembrolizumab-chemotherapy improved PFS or objective response compared with cetuximab-chemotherapy, and rates of progressive disease as best response were higher with pembrolizumab than with cetuximab-chemotherapy. PFS and objective response were similar for pembrolizumab-chemotherapy and cetuximab-chemotherapy. The statistical analysis plan specified one-sided testing only, but numerically, PFS and objective response favoured the cetuximab-chemotherapy group in the CPS ≥1 and total populations. Although there were no PFS or objective response benefits, pembrolizumab and pembrolizumab-chemotherapy were associated with more complete responses and a longer duration of response. Pembrolizumab improved median response duration by >16 months vs cetuximab-chemotherapy. The improvement in median response duration with pembrolizumab-chemotherapy was a more modest 2·5 months, likely reflecting a mix of shorter chemotherapy-driven and longer pembrolizumab-driven responses.

As has been previously observed for immune checkpoint inhibition, profound OS benefits for pembrolizumab monotherapy in participants with PD-L1–positive tumours and for pembrolizumab-chemotherapy in all participants were observed without improvements in PFS or objective response.[5,6,13-15] The substantial survival advantages demonstrated for pembrolizumab monotherapy in the PD-L1 CPS ≥20 and ≥1 populations and for pembrolizumab-chemotherapy in the CPS ≥20, CPS ≥1, and total populations were seen despite the fact that the OS benefit emerged only after approximately 7 months. The observed survival benefit reflects the remarkable response durability and is partially driven by a subset of patients who remain progression-free at 3 years. However, the proportion of participants alive at 3 years exceeds the proportion who are progression-free at 1 and 2 years to a degree that would not be expected based on historical data for second-line chemotherapy, cetuximab, or even immunotherapy.[5,6,16-18] This observation raises the possibility that early exposure to pembrolizumab may induce durable alterations in the tumour microenvironment, altering the natural history of the cancer and sensitizing it to subsequent therapy.[19] Support for this hypothesis comes from retrospective analyses showing that outcomes of therapy given after immune checkpoint inhibition exceed those predicted by historical data, even in patients whose disease did not respond to checkpoint inhibition.[20-25] Further clinical and translational analyses and prospective studies are needed to explore this hypothesis.

The observed AEs were as expected based on the known toxicity profiles of the individual treatment components. Pembrolizumab had a favourable safety profile compared with cetuximab-chemotherapy. The incidences of grade ≥3 AEs and those leading to treatment discontinuation were lower with pembrolizumab than with cetuximab-chemotherapy, as was the incidence of treatment-related death. The incidence of grade ≥3 AEs and those leading to discontinuation and death were similar in the pembrolizumab-chemotherapy and cetuximab-chemotherapy groups. Pembrolizumab did not appear to exacerbate AEs associated with

chemotherapy or vice versa. Tumour bleeding did not appear to be substantially increased with pembrolizumab or with pembrolizumab-chemotherapy.

This study was powered to compare pembrolizumab monotherapy with cetuximab-chemotherapy and to compare pembrolizumab-chemotherapy with cetuximab-chemotherapy; it was not powered to compare pembrolizumab monotherapy with pembrolizumab-chemotherapy, and the protocol did not specify any comparisons of these two groups. Although outcomes were not directly compared and both pembrolizumab strategies showed a survival benefit, certain findings may direct the choice of pembrolizumab monotherapy or pembrolizumab-chemotherapy. For example, while pembrolizumab monotherapy had a favourable toxicity profile compared with cetuximab-chemotherapy, the proportion of participants with an objective response was lower and progression-free survival was shorter. Conversely, the proportion of participants with objective response and progression-free survival were similar for pembrolizumab-chemotherapy and cetuximab-chemotherapy. For pembrolizumab monotherapy, greater PD-L1 expression levels were associated with greater response. Overall, pembrolizumab monotherapy may be preferred for PD-L1–positive cancers that are associated with a lesser symptom burden, whereas pembrolizumab-chemotherapy may be preferred for patients whose symptom burden indicates a greater importance of objective response or those who have low PD-L1 expression or recurrent-only disease. Patient preference will also be an important element in choosing between pembrolizumab monotherapy and pembrolizumab-chemotherapy. Exploratory analyses of clinical characteristics, additional PD-L1 subgroups, and biomarkers beyond PD-L1 expression would be of value in helping to inform the choice of therapy.

One limitation of this study is the open-label design, which may have resulted in the higher proportion of participants in the cetuximab-chemotherapy group who did not receive the

assigned therapy. Other limitations are the inconsistent access to second-line PD-1 inhibitors across the countries that enrolled participants and the aforementioned lack of statistical power to compare outcomes in the pembrolizumab and pembrolizumab-chemotherapy groups.

In conclusion, first-line therapy with pembrolizumab monotherapy significantly improved OS in the PD-L1 CPS ≥20 and CPS ≥1 populations, had non-inferior OS in the total population, was associated with a substantially longer duration of response in all populations, and had a favourable safety profile compared with cetuximab-chemotherapy as first-line therapy for recurrent or metastatic advanced HNSCC. First-line therapy with pembrolizumab in combination with platinum and 5-fluorouracil significantly improved OS in the PD-L1 CPS ≥20, CPS ≥1, and total populations, was associated with a longer duration of response, and had a comparable safety profile vs cetuximab-chemotherapy. Based on the observed efficacy and safety, pembrolizumab platinum and 5-fluorouracil is an appropriate first-line treatment for recurrent/metastatic HNSCC and pembrolizumab monotherapy is an appropriate first-line treatment for PD-L1–positive recurrent/metastatic HNSCC.

Contributors

BB, KJH, JDC, FJ contributed to study conception, design, and planning. BB, KJH, RG, DS, MT, GC Jr, AP, NB, PN, ÅB, TF, BGMH, RM, NN, TR, WZWI, R-LH, RGM, and DR acquired the data. AR and YZ did the statistical analysis. BB, AR, and FJ prepared the first draft of the article. All authors interpreted the results, provided critical review and revision of the article, and approved the decision to submit for publication.

Declaration of interests

BB has received honoraria and travel support for steering committee activities from Boehringer-Ingelheim, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD), has received personal fees for serving as an advisor from Amgen, Alligator Biosciences, Aduro, Bayer, AstraZeneca, Celgene, Debiopharm, Cure Biosciences, Maverick Therapeutics, GlaxoSmithKline, VentiRx, Bristol-Myers Squibb, and Genentech/Roche, has received travel support for advisory activities from Celgene, Debiopharm, Maverick Therapeutics, and Genentech/Roche, has received honoraria and travel support for data safety monitoring committee activities from IDDI (for AstraZeneca/MedImmune), and has received funding to the institution to support study conduct from Boehringer-Ingelheim and MSD.

KJH has received personal fees for serving as an advisory board member from MSD, AstraZeneca, Amgen, Boehringer-Ingelheim, Merck-Serono, Mersana, Oncolys, Pfizer, Replimmune, and Vyriad, has received personal fees for serving as a speaker from MSD, AstraZeneca, Amgen, Merck-Serono, has received honoraria from MSD, AstraZeneca, Amgen, Boehringer-Ingelheim, Merck-Serono, Pfizer, Replimmune, and Vyriad, and has received funding to the institution to support study conduct from MSD.

RG has received honoraria and travel support for serving in a consultant/advisory role from MSD and has received funding to the institution to support study conduct from MSD.

DS has received personal fees for serving as an advisor and a speaker from MSD and has received funding to the institution to support study conduct from MSD.

MT has received personal fees from Merck Serono, Bristol-Myers Squibb, Eisai, Ono Pharmaceutical, AstraZeneca, Pfizer, Rakuten Aspyrian Therapeutics, Celgene, Amgen, and Bayer, has received grants from Bristol-Myers Squibb, Ono Pharmaceutical, AstraZeneca,

Pfizer, Rakuten Aspyrian Therapeutics, Bayer, LOXO, and Novartis, and has received funding to the institution to support study conduct from MSD.

GC, Jr. has received personal fees for serving as a speaker from MSD, AstraZeneca, Bristol-Myers Squibb, and Merck Serono, has received personal fees for presentations from AstraZeneca and Teva, has received travel and accommodation support from MSD, Bristol-Myers Squibb, and Merck Serono, and has received funding to the institution to support study conduct from MSD, Bristol-Myers Squibb, and Merck Serono.

AP has received personal fees for advisory boards from MSD, Bristol-Myers Squibb, Roche, and Genesis, has received travel support from MSD, Bristol-Myers Squibb, Roche, and Merck Serono, has received honoraria from MSD, Bristol-Myers Squibb, and Roche, has received grants from Bristol-Myers Squibb, Roche, Boehringer-Ingelheim, Pfizer, Merck Serono, Genesis, and KURA, and has received funding to the institution to support study conduct from MSD.

NB has received personal fees from Bristol-Myers Squibb, Nanobiotix, and Merck Serono, has received non-financial support from Bristol-Myers Squibb, Nanobiotix, AstraZeneca, Merck Serono, Boehringer Ingelheim, Novartis, MSD, ISA Therapeutics, Debiopharm, and Roche, and has received funding to the institution to support study conduct from MSD.

PN has received funding to the institution to support study conduct from MSD.

ÅB has received funding to the institution to support study conduct from MSD.

TF has received honoraria and travel support to support advisory activities from MSD, Merck KGaA, Roche, Bristol-Myers Squibb, and Boehringer-Ingelheim, has received honoraria for

lectures from Accord, AstraZeneca, Novartis, Sanofi, and Boehringer-Ingelheim, has received research grants from MSD and Merck KGaA, and has received funding to the institution to support study conduct from MSD, Bristol-Myers Squibb, Merck KGaA, AstraZeneca, Novartis, Sanofi, Roche, Amgen, and Pfizer.

BGMH has served as an advisory board member for MSD, Bristol-Myers Squibb, Pfizer, Roche, AstraZeneca, Eisai, and Boehringer-Ingelheim and has received funding to the institution to support study conduct from MSD.

RM has served in an advisory role for AstraZeneca, MSD, Merck, Bristol-Myers Squibb, Roche, and Nanobiotix, has received honoraria for conferences from MSD, Bristol-Myers Squibb, and Merck, and has received funding to the institution to support study conduct from MSD.

NN has received personal fees from Roche, AstraZeneca, Novartis, Amgen, Boehringer-Ingelheim, Eisai, Taiho, and Bristol-Myers Squibb, has received non-financial support from Roche, Novartis, Amgen, Boehringer-Ingelheim, Eisai, Merck, and Taiho, and funding to the institution to support study conduct from MSD, Pfizer, and AstraZeneca.

TR has received personal fees for serving on an advisory board from MSD, has received funding to the institution to support study conduct from MSD.

WZWI has received personal fees for advisory board member ship from Merck Serono, Eisai Malaysia, MSD Malaysia, Roche Malaysia, Boehringer-Ingelheim, Eli Lilly Malaysia, and Mundipharma Malaysia, has received travel grants from Merck Serono, Eisai Malaysia, MSD Malaysia, Roche Malaysia, Eli Lilly Malaysia, Mundipharma Malaysia, and Pfizer, has received honorarium for lectures from Merck Serono, Eisai Malaysia, MSD Malaysia, Roche Malaysia,

Boehringer-Ingelheim, Eli Lilly Malaysia, and Mundipharma Malaysia, and has received funding to the institution to support study conduct from MSD.

R-LH has received non-financial support from MSD, and received consulting fees from MSD, and has received funding to the institution to support study conduct from MSD.

RGM has received funding to the institution to support study conduct from MSD.

AR is an employee of MSD and owns MSD stock.

YZ is an employee of MSD.

BG is an employee of MSD and owns MSD stock.

JDC is an employee of MSD and owns MSD stock.

FJ is an employee of MSD and owns MSD stock.

DR has served as an uncompensated advisor for MSD, Regeneron, Bristol-Myers Squibb, GlaxoSmithKline, and Sanofi, has received non-financial support from MSD, has received grants from Roche, GlaxoSmithKline, Regeneron, and Bristol-Myers Squibb, and has received funding to the institution to support study conduct from MSD.

Data sharing

Data will be available according to Merck Sharp & Dohme's data sharing policy, which, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for

access to the clinical study data can be submitted through the EngageZone site or via email to dataacess@merck.com.

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Figure 1: Trial profile of the total population at final analysis. For the profiles of the PD-L1 CPS ≥20 and PD-L1 CPS ≥1 populations, see the appendix. *No participants were eligible to continue treatment in the pembrolizumab or pembrolizumab-chemotherapy groups because all participants were enrolled long enough to receive the maximum 35 cycles of pembrolizumab. †No participants were eligible to complete treatment in the cetuximab-chemotherapy group because there is no maximum duration of cetuximab. CPS=combined positive score. ITT=intention-to-treat. PD-L1=programmed death ligand 1.

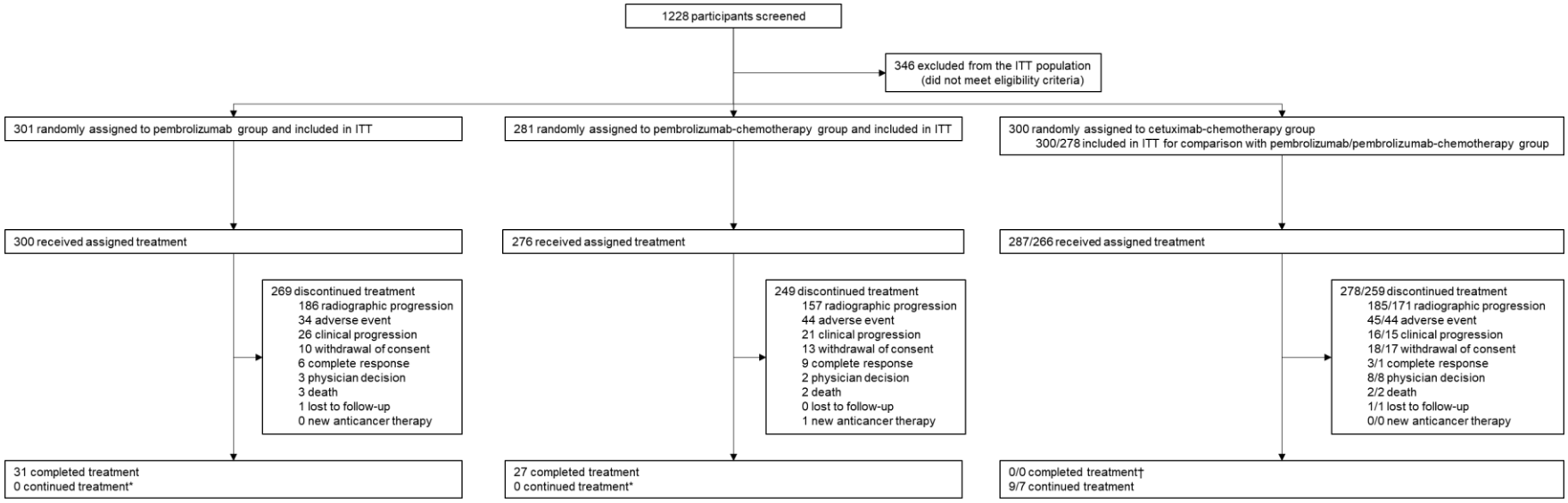
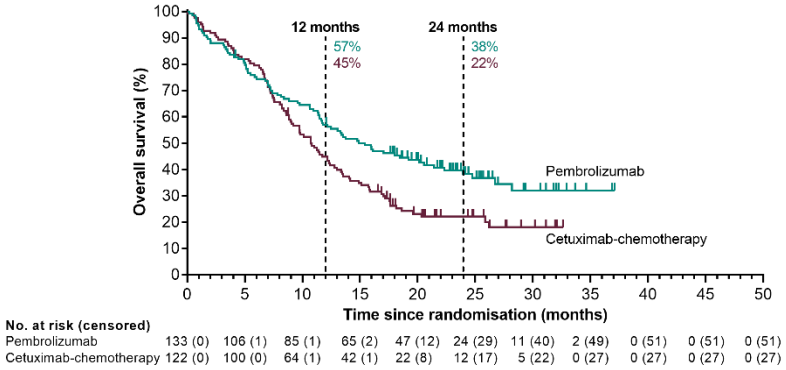
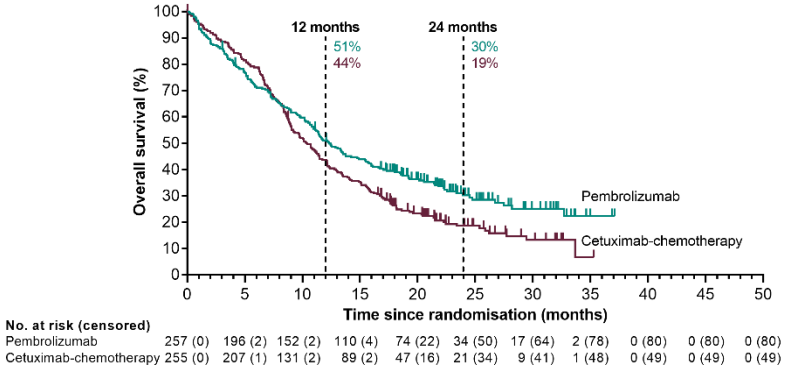


Figure 2. Kaplan-Meier estimates of overall survival. Tick marks indicate censoring of the data at the last time the patient was known to be alive. CPS=combined positive score. FA=final analysis. IA2= second interim analysis. PD-L1=programmed death ligand 1.

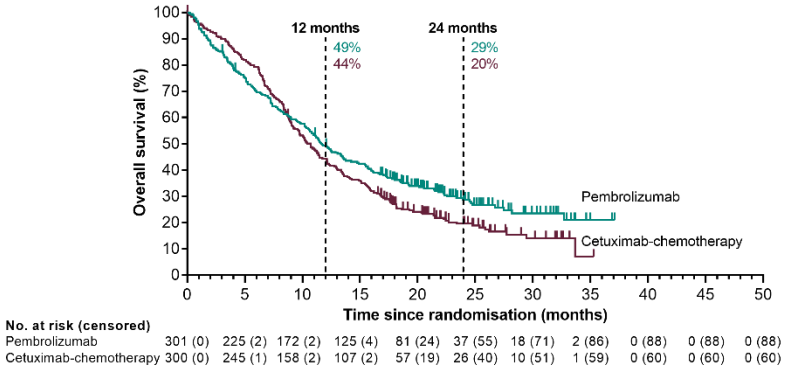
A. Pembrolizumab vs cetuximab-chemotherapy, PD-L1 CPS ≥20 population, IA2



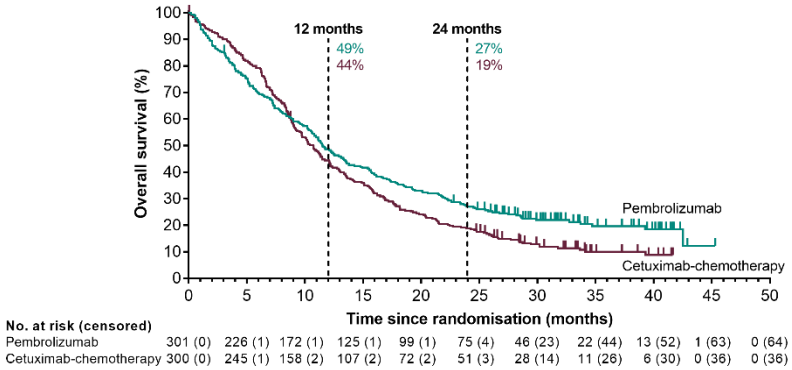
B. Pembrolizumab vs cetuximab-chemotherapy, PD-L1 CPS ≥1 population, IA2



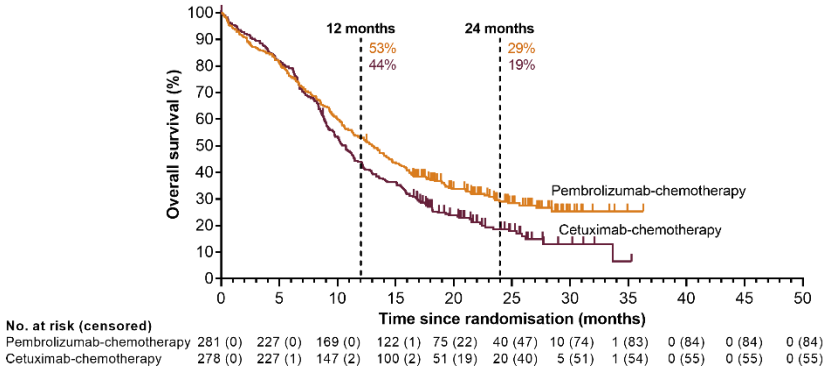
C. Pembrolizumab vs cetuximab-chemotherapy, total population, IA2



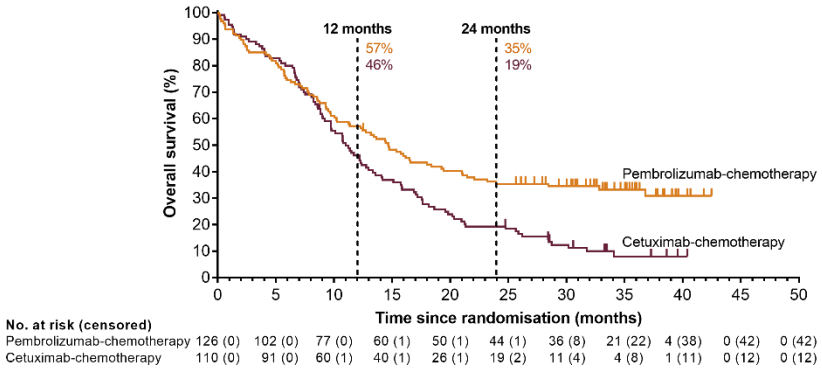
D. Pembrolizumab vs cetuximab-chemotherapy, total population, FA



E. Pembrolizumab-chemotherapy vs cetuximab-chemotherapy, total population, IA2



F. Pembrolizumab-chemotherapy vs cetuximab-chemotherapy, PD-L1 CPS ≥20 population, FA



G. Pembrolizumab-chemotherapy vs cetuximab-chemotherapy, PD-L1 CPS ≥1 population, FA

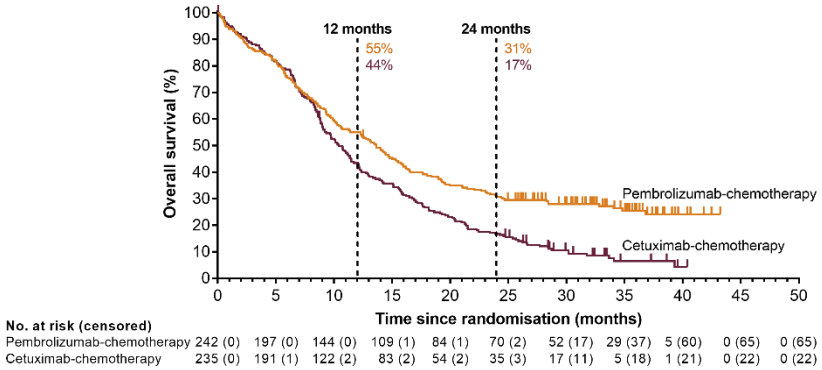
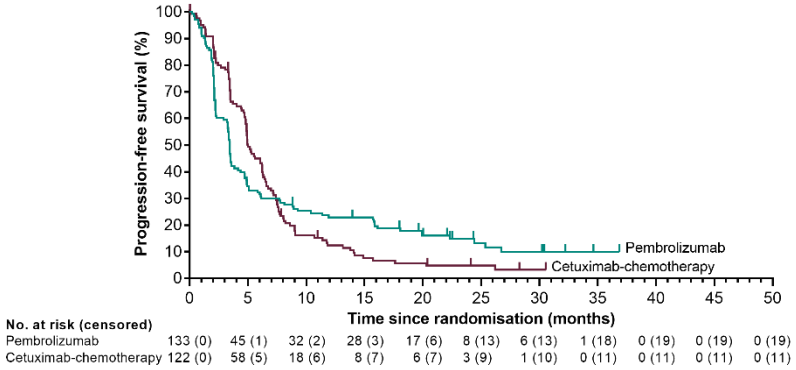
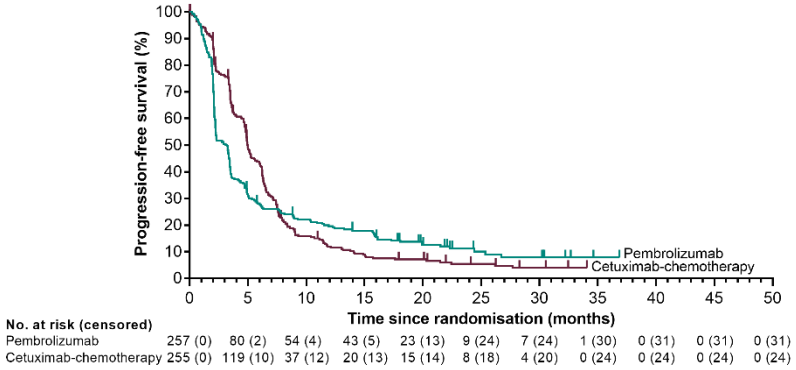


Figure 3. Kaplan-Meier estimates of progression-free survival at the second interim analysis. Tick marks indicate censoring of the data at the time of the last imaging assessment. CPS=combined positive score. PD-L1=programmed death ligand 1.

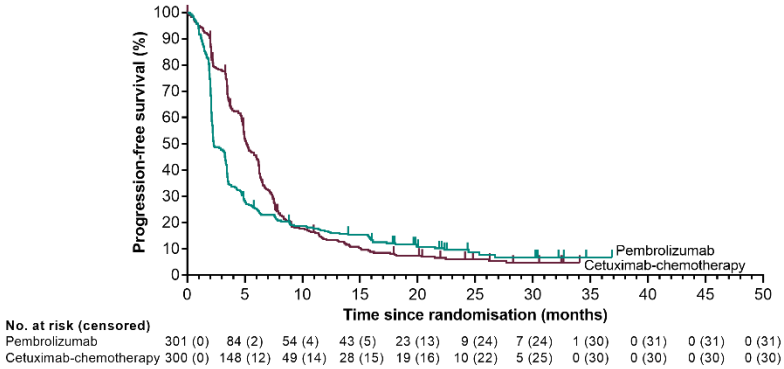
A. Pembrolizumab vs cetuximab-chemotherapy, PD-L1 CPS ≥20 population



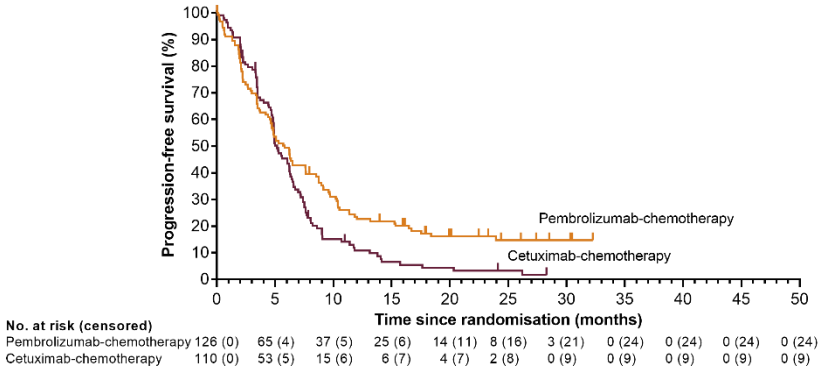
B. Pembrolizumab vs cetuximab-chemotherapy, PD-L1 CPS ≥1 population



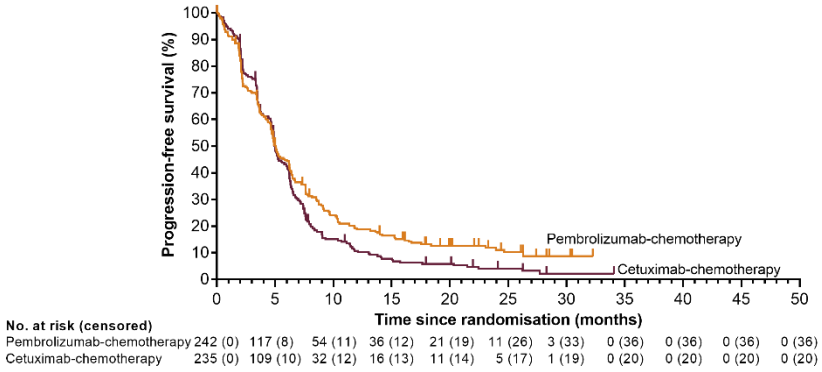
C. Pembrolizumab vs cetuximab-chemotherapy, total population



D. Pembrolizumab-chemotherapy vs cetuximab-chemotherapy, PD-L1 CPS ≥20 population



E. Pembrolizumab-chemotherapy vs cetuximab-chemotherapy, PD-L1 CPS ≥1 population



F. Pembrolizumab-chemotherapy vs cetuximab-chemotherapy, total population

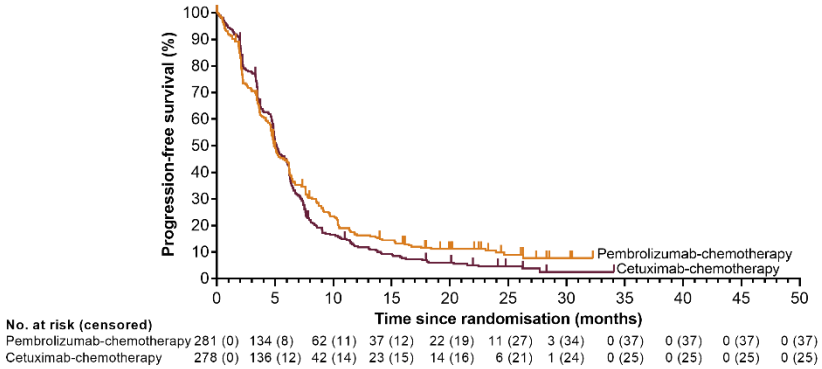


Table 1: Baseline characteristics in the total intention-to-treat populations for pembrolizumab vs cetuximab-chemotherapy and pembrolizumab-chemotherapy vs cetuximab-chemotherapy

Characteristic	Pembrolizumab vs Cetuximab-Chemotherapy		Pembrolizumab-Chemotherapy vs Cetuximab-Chemotherapy*	
	Pembrolizumab (N=301)	Cetuximab-Chemotherapy (N=300)	Pembrolizumab-Chemotherapy (N=281)	Cetuximab-Chemotherapy (N=278)
Age (years)	62·0 (56·0–68·0)	61·0 (54·5–68·0)	61·0 (55·0–68·0)	61·0 (55·0–68·0)
Male sex	250 (83)	261 (87)	224 (80)	242 (87)
Region of enrolment				
Europe	87 (29)	105 (35)	88 (31)	94 (34)
North America	75 (25)	62 (21)	60 (21)	59 (21)
Rest of world	139 (46)	133 (44)	133 (47)	125 (45)
ECOG performance-status score				
0	118 (39)	117 (39)	110 (39)	108 (39)
1	183 (61)	183 (61)	171 (61)	170 (61)
Smoking status				
Current or former	239 (79)	234 (78)	224 (80)	215 (77)
Never	62 (21)	64 (21)	57 (20)	61 (22)
Unknown	0	2 (<1)	0	2 (<1)
Oropharyngeal p16 positive	63 (21)	67 (22)	60 (21)	61 (22)
Tumour cells with PD-L1 expression				
≥50%	67 (22)	66 (22)	66 (23)	62 (22)
<50%	234 (78)	234 (78)	215 (77)	216 (78)
PD-L1 CPS				
≥1	257 (85)	255 (85)	242 (86)	235 (85)
≥20	133 (44)	122 (41)	126 (45)	110 (40)
Disease status				
Metastatic	216 (72)	203 (68)	201 (72)	187 (67)
Recurrent only†	82 (27)	94 (31)	76 (27)	88 (32)
Newly diagnosed, nonmetastatic	3 (1)	3 (1)	4 (1)	3 (1)
Primary tumour location				
Hypopharynx	38 (13)	39 (13)	44 (16)	36 (13)
Larynx	74 (25)	61 (20)	46 (16)	56 (20)

Oral cavity	82 (27)	91 (30)	82 (29)	84 (30)
Oropharynx	113 (38)	114 (38)	113 (40)	107 (38)
Investigator's choice of platinum for study treatment‡				
Carboplatin	181 (60)	170 (57)	160 (57)	156 (56)
Cisplatin	120 (40)	130 (43)	121 (43)	122 (44)

Data are median (IQR) or n (%). Chemotherapy included investigator's choice of carboplatin or cisplatin and 5-fluorouracil.

* Only includes those participants randomly allocated to the cetuximab-chemotherapy group while the pembrolizumab-chemotherapy group was open for enrolment.

† Recurrent only includes participants with locally recurrent disease and disease that spread to cervical lymph nodes.

‡ Investigators were required to choose which platinum would be administered before participants were randomized to study treatment.

Table 2: Summary of Kaplan-Meier estimates of median progression-free survival and progression-free survival rates at 6 and 12 months at the second interim analysis.

Characteristic	Pembrolizumab vs Cetuximab-Chemotherapy		Pembrolizumab-Chemotherapy vs Cetuximab-Chemotherapy*	
	Pembrolizumab	Cetuximab-Chemotherapy	Pembrolizumab-Chemotherapy	Cetuximab-Chemotherapy
PD-L1 CPS ≥20 population	N=133	N=122	N=126	N=110
Median (months)	3·4 (3·2-3·8)	5·0 (4·8-6·2)	5·8 (4·7-7·6)	5·2 (4·8-6·2)
6-month estimate	32% (24-40)	45% (36-54)	49% (40-58)	45% (36-54)
12-month estimate	23% (16-30)	12% (7-19)	24% (16-31)	11% (6-18)
PD-L1 CPS ≥1 population	N=257	N=255	N=242	N=235
Median (months)	3·2 (2·2-3·4)	5·0 (4·8-5·8)	5·0 (4·7-6·2)	5·0 (4·8-5·8)
6-month estimate	28% (23-34)	43% (37-49)	45% (38-51)	42% (36-49)
12-month estimate	20% (15-25)	12% (8-16)	19% (14-24)	11% (7-15)
Total population	N=301	N=300	N=281	N=278
Median (months)	2·3 (2·2-3·3)	5·2 (4·9-6·0)	4·9 (4·7-6·0)	5·1 (4·9-6·0)
6-month estimate	25% (20-30)	45% (39-51)	45% (39-50)	44% (38-50)
12-month estimate	17% (13-21)	14% (10-18)	17% (12-21)	12% (8-16)

CPS=combined positive score. PD-L1=programmed death ligand 1.

828 **Table 3:** Adverse events of any cause that occurred in ≥15% of participants in the as-treated population at the final analysis

Event	Pembrolizumab (N=300)		Pembrolizumab-Chemotherapy (N=276)		Cetuximab-Chemotherapy (N=287)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
Blood and lymphatic system disorders	78 (26%)	20 (7%)	206 (75%)	131 (47%)	189 (66%)	113 (39%)
Anaemia	62 (21%)	14 (5%)	161 (58%)	70 (25%)	134 (47%)	49 (17%)
Neutropenia	6 (2%)	1 (<1%)	93 (34%)	49 (18%)	94 (33%)	61 (21%)
Thrombocytopenia	6 (2%)	1 (<1%)	79 (29%)	25 (9%)	71 (25%)	26 (9%)
Endocrine disorders	65 (22%)	5 (2%)	51 (18%)	2 (<1%)	22 (8%)	0
Hypothyroidism	55 (18%)	0	44 (16%)	0	18 (6%)	0
Gastrointestinal disorders	170 (57%)	23 (8%)	228 (83%)	68 (25%)	239 (83%)	55 (19%)
Constipation	59 (20%)	1 (<1%)	102 (37%)	0	95 (33%)	4 (1%)
Diarrhoea	46 (15%)	2 (<1%)	78 (28%)	8 (3%)	99 (34%)	8 (3%)
Nausea	49 (16%)	0	141 (51%)	16 (6%)	147 (51%)	17 (6%)
Stomatitis	9 (3%)	0	74 (27%)	23 (8%)	81 (28%)	10 (3%)
Vomiting	33 (11%)	1 (<1%)	90 (33%)	10 (4%)	80 (28%)	8 (3%)
General disorders and administration site conditions	162 (54%)	22 (7%)	209 (76%)	62 (22%)	210 (73%)	40 (14%)
Asthenia	17 (6%)	3 (1%)	46 (17%)	9 (3%)	45 (16%)	9 (3%)
Fatigue	83 (28%)	9 (3%)	95 (34%)	20 (7%)	102 (36%)	14 (5%)
Mucosal inflammation	13 (4%)	4 (1%)	85 (31%)	27 (10%)	81 (28%)	15 (5%)
Pyrexia	38 (13%)	1 (<1%)	45 (16%)	2 (<1%)	35 (12%)	0
Investigations	107 (36%)	31 (10%)	154 (56%)	70 (25%)	158 (55%)	61 (21%)
Neutrophil count decreased	1 (<1%)	0	50 (18%)	30 (11%)	57 (20%)	37 (13%)
Platelet count decreased	3 (1%)	0	55 (20%)	15 (5%)	49 (17%)	10 (3%)
Weight decreased	44 (15%)	7 (2%)	44 (16%)	8 (3%)	60 (21%)	3 (1%)
White blood cell count decreased	4 (1%)	0	36 (13%)	15 (5%)	47 (16%)	26 (9%)
Metabolism and nutrition disorders	122 (41%)	43 (14%)	166 (60%)	74 (27%)	187 (65%)	71 (25%)
Decreased appetite	45 (15%)	3 (1%)	80 (29%)	13 (5%)	85 (30%)	10 (3%)
Hypokalaemia	23 (8%)	6 (2%)	32 (12%)	18 (7%)	53 (18%)	17 (6%)
Hypomagnesaemia	12 (4%)	0	44 (16%)	5 (2%)	116 (40%)	14 (5%)

Respiratory, thoracic and mediastinal disorders	139 (46%)	34 (11%)	130 (47%)	37 (13%)	126 (44%)	20 (7%)
Cough	40 (13%)	0	53 (19%)	0	37 (13%)	0
Skin and subcutaneous tissue disorders	96 (32%)	10 (3%)	98 (36%)	7 (3%)	235 (82%)	28 (10%)
Dermatitis acneiform	8 (3%)	0	1 (<1%)	0	83 (29%)	6 (2%)
Rash	30 (10%)	2 (<1)	29 (11%)	1 (<1%)	111 (39%)	17 (6%)

Adverse events are presented by the Medical Dictionary for Regulatory Affairs system organ class. Only those system organ classes in which an individual event occurred with incidence ≥15% in any group are shown.