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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 programmed cell death ligand 1 (PD-L1) expression associated with improved response.

Methods KEYNOTE-048 was a randomised, phase 3 study of participants with untreated locally incurable recurrent or metastatic HNSCC done at 200 sites in 37 countries. Participants were stratified by PD-L1 expression, p16 status, and performance status and randomly allocated (1:1:1) to pembrolizumab alone, pembrolizumab plus a platinum and 5-fluorouracil (pembrolizumab with chemotherapy), or cetuximab plus a platinum and 5-fluorouracil (cetuximab with chemotherapy). Investigators and participants were aware of treatment assignment. Investigators, participants, and representatives of the sponsor were masked to the PD-L1 combined positive score (CPS) results; PD-L1 positivity was not required for study entry. The primary endpoints were overall survival (time from randomisation to death from any cause) and progression-free survival (time from randomisation to radiographically confirmed disease progression or death from any cause, whichever came first) in the intention-to-treat population (all participants randomly allocated to a treatment group). There were 14 primary hypotheses: superiority of pembrolizumab alone and of pembrolizumab with chemotherapy versus cetuximab with chemotherapy for overall survival and progression-free survival in the PD-L1 CPS of 20 or more, CPS of 1 or more, and total populations and non-inferiority (non-inferiority margin: 1·2) of pembrolizumab alone and pembrolizumab with chemotherapy versus cetuximab with chemotherapy for overall survival in the total population. The definitive findings for each hypothesis were obtained when statistical testing was completed for that hypothesis; this occurred at the second interim analysis for 11 hypotheses and at final analysis for three hypotheses. Safety was assessed in the as-treated population (all participants who received at least one dose of allocated treatment). This study is registered at ClinicalTrials.gov, number NCT02358031.

Findings Between April 20, 2015, and Jan 17, 2017, 882 participants were allocated to receive pembrolizumab alone (n=301), pembrolizumab with chemotherapy (n=281), or cetuximab with chemotherapy (n=300); of these, 754 (85%) had CPS of 1 or more and 381 (43%) had CPS of 20 or more. At the second interim analysis, pembrolizumab alone improved overall survival versus cetuximab with chemotherapy in the CPS of 20 or more population (median 14·9 months *vs* 10·7 months, hazard ratio [HR] 0·61 [95% CI 0·45–0·83], p=0·0007) and CPS of 1 or more population (12·3 *vs* 10·3, 0·78 [0·64–0·96], p=0·0086) and was non-inferior in the total population (11·6 *vs* 10·7, 0·85 [0·71–1·03]). Pembrolizumab with chemotherapy improved overall survival versus cetuximab with chemotherapy in the total population (13·0 months *vs* 10·7 months, HR 0·77 [95% CI 0·63–0·93], p=0·0034) at the second interim analysis and in the CPS of 20 or more population (14·7 *vs* 11·0, 0·60 [0·45–0·82], p=0·0004) and CPS of 1 or more population (13·6 *vs* 10·4, 0·65 [0·53–0·80], p<0·0001) at final analysis. Neither pembrolizumab alone nor pembrolizumab with chemotherapy improved progression-free survival at the second interim analysis. At final analysis, grade 3 or worse all-cause adverse events occurred in 164 (55%) of 300 treated participants in the pembrolizumab alone group, 235 (85%) of 276 in the pembrolizumab with chemotherapy group, and 239 (83%) of 287 in the cetuximab with chemotherapy group. Adverse events led to death in 25 (8%) participants in the pembrolizumab alone group, 32 (12%) in the pembrolizumab with chemotherapy group, and 28 (10%) in the cetuximab with chemotherapy group.

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

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*KEYNOTE-048 Investigators are listed in the appendix (pp 2–5)

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See Online for appendix

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 can be severe, and many patients succumb to recurrence or metastasis.[1,2] Standard first-line treatment for recurrent or metastatic disease that is not amenable to local therapy is cetuximab plus chemotherapy with platinum and 5-fluorouracil, which provides median overall survival of about 10 months and is associated with substantial toxicity.[3]

Immune checkpoint inhibitors have shown efficacy and manageable safety in HNSCC.[4–8] Monotherapy with the programmed cell death 1 (PD-1) inhibitors pembrolizumab and nivolumab improved overall survival 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]

Here, we aimed to determine whether pembrolizumab as monotherapy or in combination with chemotherapy

Research in context

Evidence before this study

We searched PubMed on May 28, 2019, using the search 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 of 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 versus investigator's choice of therapy for platinum-refractory recurrent or metastatic HNSCC which 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 versus 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 regimen is the standard for first-line treatment of recurrent or metastatic HNSCC. This regimen was used as the control group 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-programmed cell death 1 (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 programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of 20 or more or 1 or more and had non-inferior 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 of 20 or more population, PD-L1 CPS of 1 or more population, and total population compared with cetuximab, a platinum, and 5-fluorouracil. Compared with standard therapy, the incidence of adverse events of any grade and of grade 3 or worse 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 of 20 or more and of 1 or more 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 with recurrent or metastatic HNSCC.

improves overall survival compared with cetuximab plus chemotherapy in participants with previously untreated recurrent or metastatic HNSCC.

Methods

Study design and participants

The KEYNOTE-048 study was a randomised, open-label, phase 3 study done at 200 medical centres in 37 countries (appendix pp 2–5). Participants were eligible for enrolment if they were aged 18 years or older; 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 at least one 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 had progressive disease within 6 months of curatively intended systemic treatment given for locoregionally advanced disease, 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 pp 75–79).

The study protocol and all amendments were approved by the appropriate ethics committee at each centre. The study was done 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 and integrated web-response system (Almac Clinical Technologies, Souderton, PA, USA). Randomisation 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 randomly assigned (1:1:1) in blocks of three per stratum to receive pembrolizumab alone (pembrolizumab alone group), pembrolizumab plus platinum and 5-fluorouracil (pembrolizumab with chemotherapy group), or cetuximab plus platinum and 5-fluorouracil (cetuximab with chemotherapy group). Neither participants nor investigators were masked to treatment assignment.

Procedures

In the pembrolizumab alone and pembrolizumab with 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 with chemotherapy group received cetuximab (400 mg/m² loading dose, then 250 mg/m² per week) until disease progression, intolerable toxicity, or physician or participant decision, whichever occurred first. Participants in the pembrolizumab with chemotherapy and cetuximab with chemotherapy groups also received carboplatin (area under the curve 5 mg/m²) or cisplatin (100 mg/m²) and 5-fluorouracil (1000 mg/m² per day for 4 consecutive days) every 3 weeks for six cycles. All treatments were administered intravenously. Participants who experienced confirmed complete response and had received at least 24 weeks of therapy, including two 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 (done ≥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 characterised by the combined positive score (CPS), defined as the number of PD-L1-positive cells (tumour cells, lymphocytes, and 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 human papillomavirus association using the CINtec p16 Histology assay (Ventana Medical Systems, Tucson, AZ, USA) with strong and diffuse nuclear and cytoplasmic staining in at least 70% of cells used as the cutpoint for positivity.

Data on adverse events 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 done at baseline, week 9, every 6 weeks through year 1, and every 9 weeks thereafter. Participants were contacted to assess survival every 12 weeks during follow-up.

Outcomes

The primary endpoints were overall survival, defined as the time from randomisation to death from any cause, and progression-free survival, 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, proportion of participants with objective response

(defined as radiographically confirmed complete or partial response), proportion of participants who were progression-free at 6 and 12 months, change from baseline in global health status or quality of life (these data will be reported elsewhere), and time to deterioration in global health status or quality of life, pain, and swallowing (these data will be 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. The final protocol, which includes a full list of exploratory endpoints, and the original protocol are available in the appendix (pp 38–387), as is a summary of all endpoint changes (appendix pp 35–37). Notably, overall survival was a secondary endpoint in the original protocol, but in light of increasing evidence that progression-free survival is a poor surrogate of overall survival for immunotherapy,[11–14] overall survival was promoted to a primary endpoint. This change was made before any data analyses. Response and disease progression were assessed according to RECIST (version 1.1), by masked, independent central review. All endpoints, except safety, were evaluated for pembrolizumab alone versus cetuximab with chemotherapy and for pembrolizumab with chemotherapy versus cetuximab with chemotherapy in participants with PD-L1 CPS of 20 or more, in participants with PD-L1 CPS of 1 or more, and in the total population. Safety was evaluated in the total population.

Statistical analysis

Overall survival, progression-free survival, 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 a confirmed complete or partial response. Safety was assessed in the as-treated population, defined as all participants who received at least one dose of allocated study treatment.

We used SAS version 9.4 for all statistical analyses. We estimated overall survival, progression-free survival, and duration of response using the Kaplan-Meier method and the censoring rules outlined in the protocol (appendix pp 152,154). We used the stratified log-rank test to assess between-group differences in overall survival and progression-free survival and used a stratified Cox proportional hazards model with Efron's method of tie handling[15] to estimate hazard ratios (HRs) and associated 95% CIs. The randomisation stratification factors were used for the stratified analyses. We assessed the consistency of the overall survival treatment effect in subgroups 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 with chemotherapy group during the pembrolizumab with chemotherapy enrolment hold were excluded from all efficacy comparisons between pembrolizumab with chemotherapy and cetuximab with chemotherapy.

The evolution of the statistical analysis plan is summarised in the appendix (pp 35–37). Notably, the addition of overall survival hypotheses and the delineation of the PD-L1–based hypotheses were completed before any data analyses. Overall, we tested 14 primary hypotheses: superiority of pembrolizumab alone and of pembrolizumab with chemotherapy, each versus cetuximab with chemotherapy, for overall survival and progression-free survival in the CPS of 20 or more population; non-inferiority of pembrolizumab with chemotherapy for overall survival and superiority of pembrolizumab with chemotherapy for progression-free survival, each versus cetuximab with chemotherapy, in the total population; non-inferiority of pembrolizumab alone versus cetuximab with chemotherapy for overall survival in the total population; superiority of pembrolizumab alone versus cetuximab with chemotherapy for overall survival and progression-free survival in the CPS of 1 or more population and total population; and superiority of pembrolizumab with chemotherapy versus cetuximab with chemotherapy for overall survival and progression-free survival in the CPS of 1 or more population and overall survival in the total population (appendix pp 59–60).

We used the graphical method of Maurer and Bretz[16] to control the family-wise type I error rate at α=0·025 (one-sided) across all primary hypotheses and interim analyses. The following six hypotheses were tested in parallel: superiority of pembrolizumab alone versus cetuximab with chemotherapy for progression-free survival and overall survival, superiority of pembrolizumab with chemotherapy versus cetuximab with chemotherapy for progression-free survival and overall survival in the PD-L1 CPS of 20 or more population, superiority of pembrolizumab with chemotherapy versus cetuximab with chemotherapy for progression-free survival in the total population, and the non-inferiority of pembrolizumab with chemotherapy versus cetuximab with chemotherapy for overall survival in the total population (appendix p 7). The remaining eight primary hypotheses were tested according to the prespecified multiplicity strategy if the hypotheses with initial alpha allocations were positive. Pembrolizumab alone and pembrolizumab with chemotherapy were considered effective if they had superior overall survival or progression-free survival compared with cetuximab with chemotherapy in any of the protocol-specified populations or if they had non-inferior overall survival in the total population.

The final protocol specified two interim analyses and a final analysis. The first interim analysis was planned to occur at least 9 months after the last participant was enrolled. The second interim analysis, which was the final analysis of progression-free survival, was planned

to occur about 17 months after the last participant was enrolled. The final analysis was planned to occur about 44 months after the first participant was enrolled. We planned to enrol 825 participants.

Assuming progression-free survival follows an exponential distribution with a median of 6 months for cetuximab with chemotherapy,[3] an enrolment period of 21 months, follow-up duration of at least 9 months at the first interim analysis and 17 months at the second interim analysis, and a yearly dropout rate of 5%, this study has the following power at the final progression-free survival analysis: 90% to detect a HR of 0·58 for pembrolizumab alone versus cetuximab with chemotherapy and for pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the PD-L1 CPS of 20 or more population at one-sided α=0·0019, with 237 events observed between one experimental group and the cetuximab with chemotherapy group; 98·6% to detect an HR of 0·59 for pembrolizumab alone versus cetuximab with chemotherapy and for pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the PD-L1 CPS of 1 or more population at one-sided α=0·0019, with 378 events observed between one experimental group and the cetuximab with chemotherapy group; 99·6% to detect an HR of 0·60 for pembrolizumab alone versus cetuximab with chemotherapy in the total population at one-sided α=0·0019, with 474 events observed between the pembrolizumab alone and cetuximab with chemotherapy groups; and 97·7% to detect an HR of 0·60 for pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the total population at one-sided α=0·0002 with 474 events observed between the pembrolizumab with chemotherapy and cetuximab with chemotherapy groups.

Assuming overall survival follows an exponential distribution with a median of 10 months for cetuximab with chemotherapy,[3] an enrolment period of 21 months, follow-up duration of at least 23 months at the final analysis, and a yearly dropout rate of 2%, this study has the following power at the final overall survival analysis: 90·5% to detect an HR of 0·60 for pembrolizumab alone versus cetuximab with chemotherapy and for pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the PD-L1 CPS of 20 or more population at one-sided α=0·007, with 222 events observed between one experimental group and the cetuximab with chemotherapy group; 94·3% to detect an HR of 0·65 for pembrolizumab alone versus cetuximab with chemotherapy and for pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the PD-L1 CPS of 1 or more population at one-sided α=0·007, with 359 events observed between one experimental group and the cetuximab with chemotherapy group; 87·85% to detect an HR of 0·85 and establish non-inferiority (non-inferiority margin, 1·2) for pembrolizumab alone versus cetuximab with chemotherapy and for pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the total population at one-sided α=0·007, with 455 events observed between one experimental group and the cetuximab with chemotherapy group; and 90·4% to detect an HR of 0·70 for pembrolizumab alone versus cetuximab with chemotherapy and for pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the total population at one-sided α=0·007, with 455 events observed between one experimental group and the cetuximab with chemotherapy group.

The data and safety monitoring committee recommended that the study continue as planned after reviewing the first interim analysis (data cutoff Oct 17, 2017). At the second interim analysis (data cutoff June 13, 2018), the one-sided p value boundaries for testing superiority of pembrolizumab alone versus cetuximab with chemotherapy were 0·0016 for progression-free survival in the CPS of 20 or more population, 0·0024 for overall survival in the CPS of 20 or more population, 0·0109 for overall survival in the CPS of 1 or more population, and 0·0117 for overall survival in the total population. The one-sided p value boundaries for testing superiority of pembrolizumab with chemotherapy versus cetuximab with chemotherapy at the second interim analysis were 0·0017 for progression-free survival in the PD-L1 CPS of 20 or more population, 0·0002 for progression-free survival in the total population, 0·0018 for overall survival in the CPS of 20 or more population, and 0·0041 for overall survival in the total population (appendix p 21). The non-inferiority margin for overall survival in the total population for both pembrolizumab alone and for pembrolizumab with chemotherapy versus cetuximab with chemotherapy was 1·2; the statistical criterion for the success of the non-inferiority hypothesis is met if the upper bound of the confidence interval, based on the alpha level allocated to the analysis, for the HR is less than 1·2. To complete statistical testing for the three remaining primary hypotheses, the study continued to the final analysis (data cutoff Feb 25, 2019). The one-sided p value boundaries for testing superiority of the three remaining primary hypotheses at the final analysis were 0·0023 for overall survival superiority of pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the PD-L1 CPS of 20 or more population, 0·0026 for overall survival superiority of pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the CPS of 1 or more population, and 0·0059 for overall survival superiority of pembrolizumab alone versus cetuximab with chemotherapy in the total population (appendix p 21). Results from the second interim analysis are given for the 11 primary hypotheses for which statistical testing was completed at the second interim analysis because they are the definitive results for these 11 hypotheses. Results from the final analysis are given for the three 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

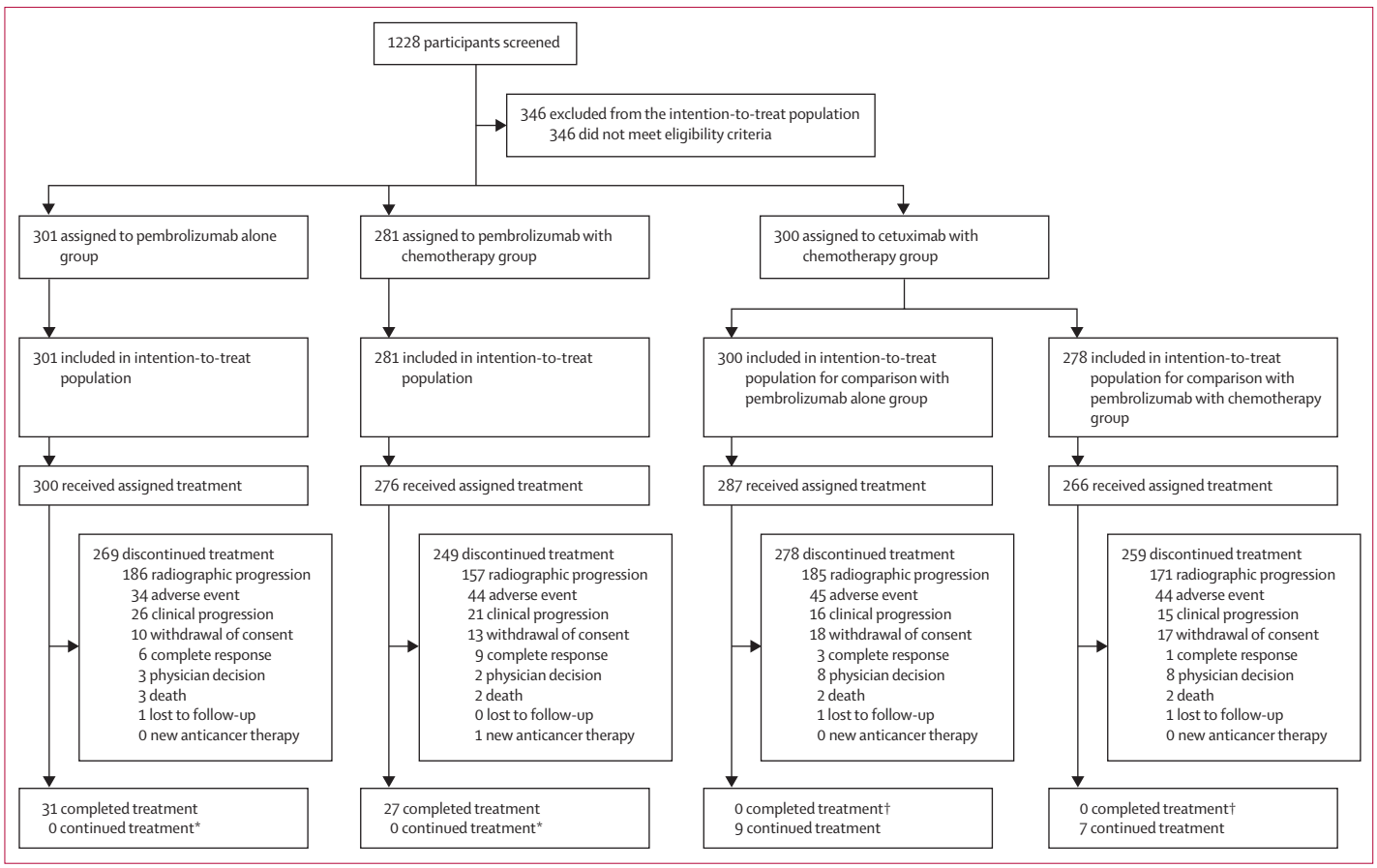


Figure 1: **Trial profile for the total population**
The profiles of the PD-L1 CPS of 20 or more and PD-L1 CPS of 1 or more populations are given in the appendix (pp 10–11). CPS=combined positive score. PD-L1=programmed death ligand 1. *No participants were eligible to continue treatment in the pembrolizumab alone or pembrolizumab with 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 with chemotherapy group because there is no maximum duration of cetuximab.

completed statistical testing at the second interim analysis, exploratory analyses of overall survival at the final analysis are also reported.

This trial is registered with ClinicalTrials.gov, number NCT02358031.

Role of the funding source

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

Results

Between April 20, 2015, and Jan 17, 2017, we screened 1228 individuals for eligibility, 882 of whom were randomly allocated to either pembrolizumab alone (n=301), pembrolizumab with chemotherapy (n=281), or cetuximab with chemotherapy (n=300; figure 1). Based on consultation between the sponsor and data and safety monitoring committee after three deaths (two from disease progression and one from an adverse event) occurred in the first 14 participants in the pembrolizumab with chemotherapy group, allocation to this group was temporarily stopped on Aug 13, 2015. After the data and safety monitoring committee reviewed safety data from 20 participants in the pembrolizumab with chemotherapy group who completed two cycles of study treatment, allocation to this group resumed on Oct 2, 2015. Among the 882 allocated participants, 381 (43%) had PD-L1 CPS of 20 or more and 754 (85%) had PD-L1 CPS of 1 or more. Carboplatin was the chosen platinum for 160 (57%) of 281 participants in the pembrolizumab with chemotherapy group and 170 (57%) of 300 participants in the cetuximab with chemotherapy group. Baseline demographics and disease characteristics were similar between groups and across the PD-L1 CPS and total populations (table 1, appendix pp 22–23).

The intention-to-treat population for the evaluation of pembrolizumab alone versus cetuximab with chemotherapy in the total population included all 301 participants allocated to pembrolizumab alone and all 300 participants allocated to cetuximab with chemotherapy (figure 1). The intention-to treat population for the evaluation

of pembrolizumab with chemotherapy versus cetuximab with chemotherapy included all 281 participants allocated to pembrolizumab with chemotherapy and the 278 participants allocated to cetuximab with chemotherapy while the pembrolizumab with chemotherapy group was available for allocation. Study treatment was received by 300 participants in the pembrolizumab alone group, 276 in the pembrolizumab with chemotherapy group, and 287 in the cetuximab with chemotherapy group. As of the final analysis (data cutoff Feb 25, 2019), no participants in the pembrolizumab alone or pembrolizumab with chemotherapy groups remained on pembrolizumab, with 31 (10%) of 300 treated participants in the pembrolizumab alone group and 27 (10%) of 276 treated participants in the pembrolizumab with chemotherapy group having completed all 35 cycles of pembrolizumab. In the cetuximab with chemotherapy group, nine (3%) of 287 treated participants remained on cetuximab. Trial profiles for the PD-L1 CPS of 20 or more and CPS of 1 or more populations are shown in the appendix (pp 10–11). In the intention-to-treat population at the final analysis, at least one subsequent anticancer therapy was received by 148 (49%) of 301 participants in the pembrolizumab alone group, 115 (41%) of 281 in the pembrolizumab with chemotherapy group, and 159 (53%) of 300 in the cetuximab with chemotherapy group, including 17 (6%) in the pembrolizumab alone group, 17 (6%) in the pembrolizumab with chemotherapy group, and 75 (25%) in the cetuximab with chemotherapy group who received a subsequent PD-1 or PD-L1 inhibitor (appendix p 24).

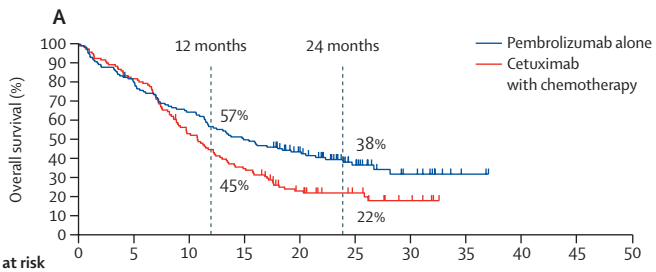
Median follow-up duration, defined as the time from randomisation to death or data cutoff, whichever occurred first, was 11·5 months (IQR 5·1–20·8) in the pembrolizumab alone group, 13·0 months (6·4–21·5) in the pembrolizumab with chemotherapy group, and 10·7 months (6·6–18·1) in the cetuximab with chemotherapy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

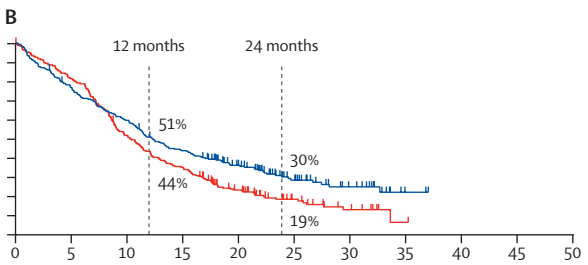
At the second interim analysis and compared with cetuximab with chemotherapy, pembrolizumab alone prolonged overall survival in the PD-L1 CPS of 20 or more population and CPS of 1 or more population (figure 2); the second interim analysis findings are therefore the definitive results for these two hypotheses. In the CPS of 20 or more population and with 177 (69%) of 255 participants having died, HR was 0·61 (95% CI 0·45–0·83, p=0·0007); median overall survival was 14·9 months (95% CI 11·6–21·5) in the pembrolizumab alone group versus 10·7 months (8·8–12·8) in the cetuximab with chemotherapy group. In the PD-L1 CPS of 1 or more population and with 383 (75%) of 512 participants having died, HR was 0·78 (95% CI 0·64–0·96, p=0·0086); median overall survival was 12·3 months (95% CI 10·8–14·9) versus 10·3 months (9·0–11·5). The benefit of pembrolizumab alone compared with cetuximab with chemotherapy in the CPS of 20 or more and CPS of 1 or more populations was maintained at the final analysis (appendix p 12). At the second interim analysis in the total population and with 453 (75%) of 601 participants having died,

	Pembrolizumab alone *vs* cetuximab with chemotherapy		Pembrolizumab with chemotherapy *vs* cetuximab with chemotherapy*	
	Pembrolizumab alone (n=301)	Cetuximab with chemotherapy (n=300)	Pembrolizumab with chemotherapy (n=281)	Cetuximab with 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)
Sex				
Female	51 (17%)	39 (13%)	57 (20%)	36 (13%)
Male	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, non-metastatic	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. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed death ligand 1. *Only includes participants randomly allocated to the cetuximab with chemotherapy group while the pembrolizumab with 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 randomly allocated to study treatment.

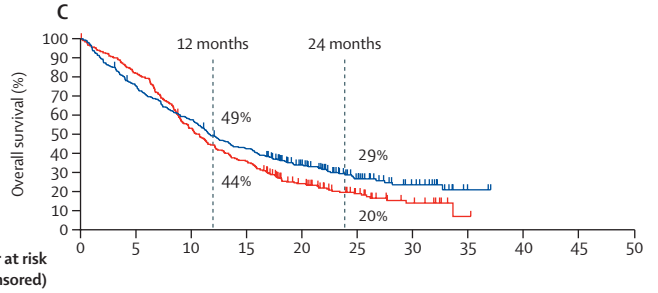
Table 1: **Baseline characteristics in the total intention-to-treat populations**

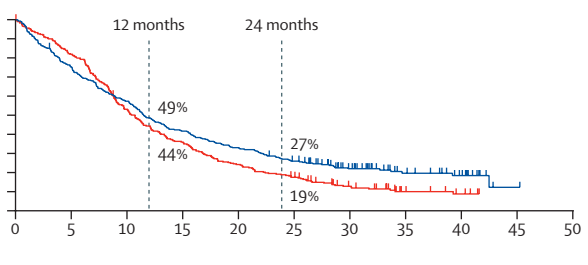




Number at risk (number censored)											
Pembrolizumab alone	133 (0)	106 (1)	85 (1)	65 (2)	47 (12)	24 (29)	11 (40)	2 (49)	0 (51)	0 (51)	0 (51)
Cetuximab with chemotherapy	122 (0)	100 (0)	64 (1)	42 (1)	22 (8)	12 (17)	5 (22)	0 (27)	0 (27)	0 (27)	0 (27)

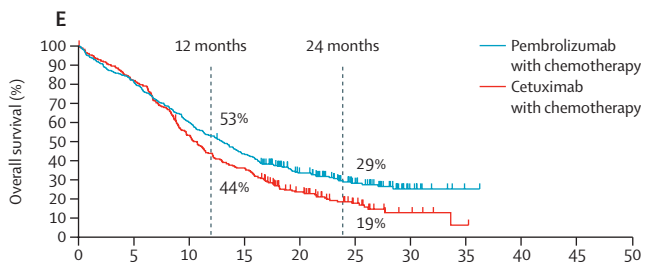
Pembrolizumab alone	257 (0)	196 (2)	152 (2)	110 (4)	74 (22)	34 (50)	17 (64)	2 (78)	0 (80)	0 (80)	0 (80)
Cetuximab with chemotherapy	255 (0)	207 (1)	131 (2)	89 (2)	47 (16)	21 (34)	9 (41)	1 (48)	0 (49)	0 (49)	0 (49)

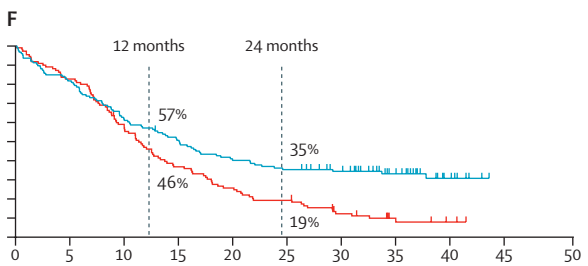




Number at risk (number censored)											
Pembrolizumab alone	301 (0)	225 (2)	172 (2)	125 (4)	81 (24)	37 (55)	18 (71)	2 (86)	0 (88)	0 (88)	0 (88)
Cetuximab with chemotherapy	300 (0)	245 (1)	158 (2)	107 (2)	57 (19)	26 (40)	10 (51)	1 (59)	0 (60)	0 (60)	0 (60)

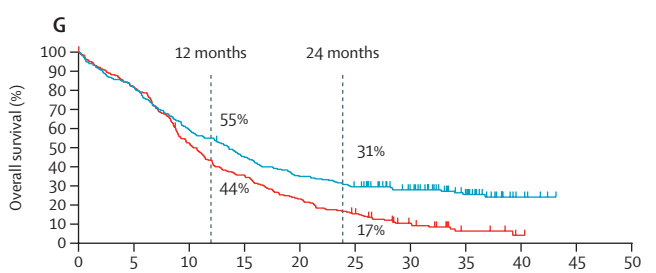
Pembrolizumab alone	301 (0)	226 (1)	172 (1)	125 (1)	99 (1)	75 (4)	46 (23)	22 (44)	13 (52)	1 (63)	0 (64)
Cetuximab with chemotherapy	300 (0)	245 (1)	158 (2)	107 (2)	72 (2)	51 (3)	28 (14)	11 (26)	6 (30)	0 (36)	0 (36)





Number at risk (number censored)											
Pembrolizumab with chemotherapy	281 (0)	227 (0)	169 (0)	122 (1)	75 (22)	40 (47)	10 (74)	1 (83)	0 (84)	0 (84)	0 (84)
Cetuximab with chemotherapy	278 (0)	227 (1)	147 (2)	100 (2)	51 (19)	20 (40)	5 (51)	1 (54)	0 (55)	0 (55)	0 (55)

Pembrolizumab with chemotherapy	126 (0)	102 (0)	77 (0)	60 (1)	50 (1)	44 (1)	36 (8)	21 (22)	4 (38)	0 (42)	0 (42)
Cetuximab with chemotherapy	110 (0)	91 (0)	60 (1)	40 (1)	26 (1)	19 (2)	11 (4)	4 (8)	1 (11)	0 (12)	0 (12)



Number at risk (number censored)											
Pembrolizumab with chemotherapy	242 (0)	197 (0)	144 (0)	109 (1)	84 (1)	70 (2)	52 (17)	29 (37)	5 (60)	0 (65)	0 (65)
Cetuximab with chemotherapy	235 (0)	191 (1)	122 (2)	83 (2)	54 (2)	35 (3)	17 (11)	5 (18)	1 (21)	0 (22)	0 (22)

pembrolizumab alone showed non-inferior, but not superior, overall survival compared with cetuximab with chemotherapy (HR 0·85 [95% CI 0·71–1·03], p=0·0456); this is the definitive result for the non-inferiority hypothesis. Median overall survival was 11·6 months (95% CI 10·5–13·6) in the pembrolizumab alone group versus 10·7 months (9·3–11·7) in the cetuximab with chemotherapy group. At the final analysis and with 501 (83%) of 601 participants having died, the threshold for superiority of overall survival for pembrolizumab alone versus cetuximab with chemotherapy in the total population was not met (HR 0·83 [95% CI 0·70–0·99], p=0·0199); median overall survival was 11·5 months (95% CI 10·3–13·4) versus 10·7 months (9·3–11·7; figure 2). In subgroup analyses, all HRs favoured pembrolizumab alone except for the recurrent disease subgroup of the total population and PD-L1 CPS of 1 or more population (appendix pp 13–15).

At the second interim analysis in the total population, 420 (75%) of 559 participants allocated to pembrolizumab with chemotherapy and cetuximab with chemotherapy had died, and pembrolizumab with chemotherapy prolonged overall survival (HR 0·77 [95% CI 0·63–0·93], p=0·0034; figure 2); the second interim analysis findings are therefore the definitive results for this hypothesis. Median overall survival was 13·0 months (95% CI 10·9–14·7) in the pembrolizumab with chemotherapy group versus 10·7 months (9·3–11·7) in the cetuximab with chemotherapy group. The survival benefit was maintained at the final analysis (appendix p 12). The superiority threshold for an overall survival benefit of pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the CPS of 20 or more population was not met at the second interim analysis and, per the analysis plan, formal statistical testing in the CPS of 1 or more population was not done. At the final analysis, pembrolizumab with chemotherapy improved overall survival versus cetuximab with chemotherapy in the CPS of 20 or more and CPS of 1 or more populations (figure 2). With 182 (77%) of 236 participants having died in the CPS of 20 or more population, HR was 0·60 (95% CI 0·45–0·82, p=0·0004), and median overall survival was 14·7 months (95% CI 10·3–19·3) in the pembrolizumab with chemotherapy group versus 11·0 months (9·2–13·0) in the cetuximab with chemotherapy group. With 390 (82%) of 477 participants having died in the CPS of 1 or more population, HR was 0·65 (95% CI 0·53–0·80, p<0·0001), and median overall survival was 13·6 months (95% CI 10·7–15·5) versus 10·4 months (9·1–11·7). In subgroup analyses, all HRs favoured pembrolizumab with chemotherapy (appendix pp 16–17).

At the second interim analysis (final, definitive analysis of progression-free survival) and compared with cetuximab with chemotherapy, pembrolizumab alone did not improve progression-free survival in the PD-L1 CPS of 20 or more population (HR 0·99 [95% CI 0·75–1·29], p=0·4562), and pembrolizumab with chemotherapy did not improve progression-free survival in the CPS of 20 or more population (HR 0·73 [95% CI 0·55–0·97], p=0·0162) or total population (HR 0·92 [95% CI 0·77–1·10], p=0·1697; figure 3). Because superiority was not met for these comparisons, no formal statistical testing was done for pembrolizumab alone versus cetuximab with chemotherapy in the PD-L1 CPS of 1 or more population (HR 1·16 [95% CI 0·96–1·39]) or total population (1·34 [1·13–1·59]) or for pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the CPS of 1 or more population (0·82 [0·67–1·00]; figure 3).

Across populations, median progression-free survival was 2·3–3·4 months for pembrolizumab alone, 4·9–5·8 months for pembrolizumab with chemotherapy, and 5·0–5·2 months for cetuximab with chemotherapy (table 2). For pembrolizumab alone versus cetuximab with chemotherapy, the estimated proportion of participants who were alive and without progression was greater for cetuximab with chemotherapy at 6 months; however, by 12 months, the proportion was greater or similar with pembrolizumab alone (table 2). For pembrolizumab with chemotherapy versus cetuximab with chemotherapy, the estimated proportion of participants who were alive and without progression was similar at 6 months and, at 12 months, was greater for pembrolizumab with chemotherapy.

At the final analysis, 31 (23%) of 133 participants in the pembrolizumab alone group and 44 (36%) of 122 in the cetuximab with chemotherapy group had an objective response in the PD-L1 CPS of 20 or more population; 49 (19%) of 257 and 89 (35%) of 255, respectively, in the CPS of 1 or more population, and 51 (17%) of 301 and 108 (36%) of 300, respectively, in the total population had an objective response (appendix p 25). Median response duration was 22·6 months in the pembrolizumab alone group and 4·2 months in the cetuximab with chemotherapy group in the CPS of 20 or more population; median duration was 23·4 months and 4·5 months, respectively, in the CPS of 1 or more population, and 22·6 months and 4·5 months, respectively, in the total population (appendix p 18). At final analysis, the number of participants with an objective response in the pembrolizumab with chemotherapy and cetuximab with

Figure 2: **Kaplan-Meier estimates of overall survival**
Tick marks show censoring of the data at the last time the patient was known to be alive. Pembrolizumab alone versus cetuximab with chemotherapy in the PD-L1 CPS of 20 or more population (A), PD-L1 CPS of 1 or more population (B), and total population (C) at the second interim analysis. (D) Pembrolizumab alone versus cetuximab with chemotherapy in the total population at the final analysis. (E) Pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the total population at the second interim analysis. Pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the PD-L1 CPS of 20 or more population (F) and the PD-L1 CPS of 1 or more population (G) at the final analysis. CPS=combined positive score. PD-L1=programmed death ligand 1.

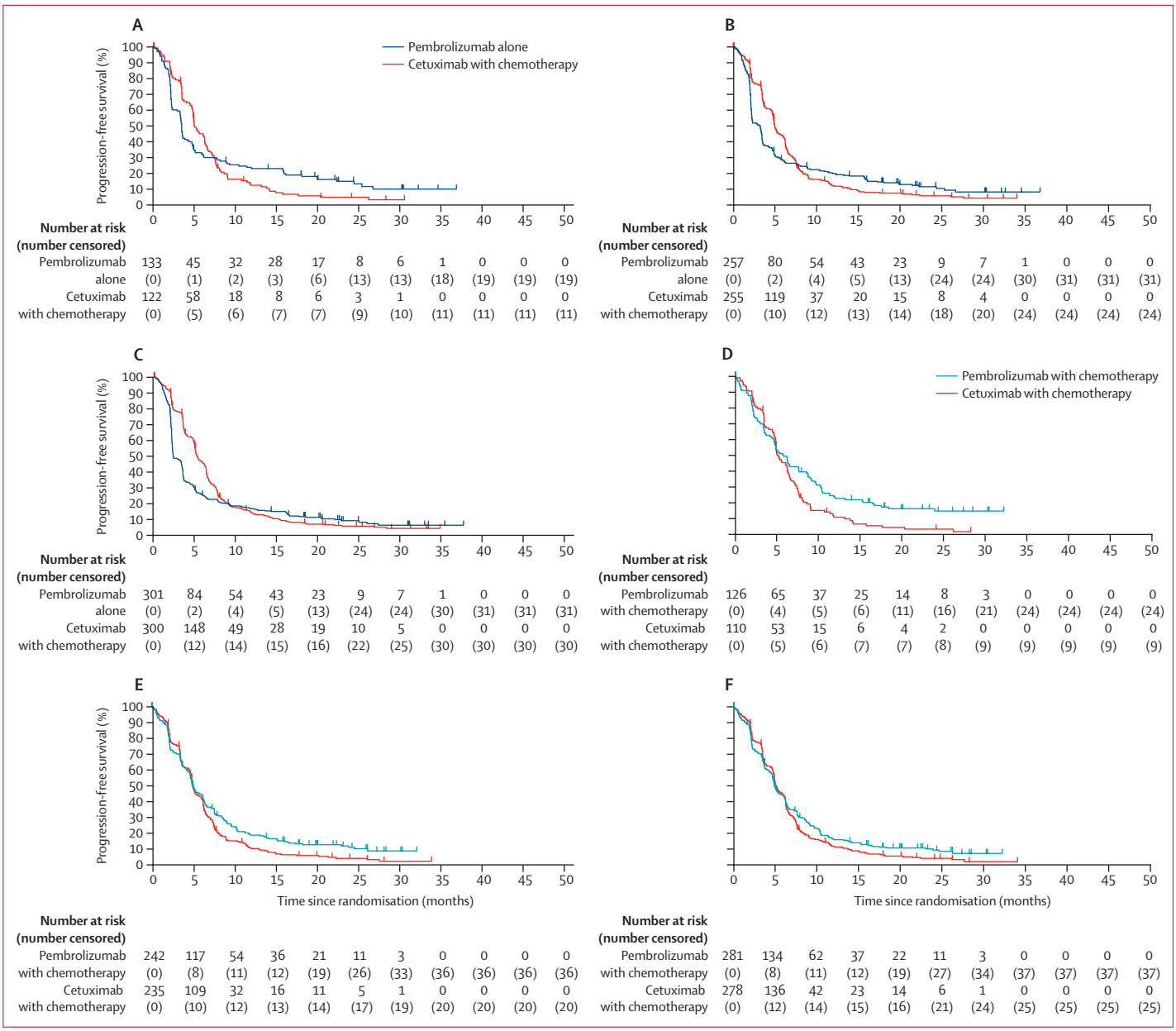


***Figure 3*: Kaplan-Meier estimates of progression-free survival at the second interim analysis**

Tick marks show censoring of the data at the time of the last imaging assessment. Pembrolizumab alone versus cetuximab with chemotherapy in the PD-L1 CPS of 20 or more population (A), PD-L1 CPS of 1 or more population (B), and total population (C). Pembrolizumab with chemotherapy versus cetuximab with chemotherapy in the PD-L1 CPS of 20 or more population (D), PD-L1 CPS of 1 or more population (E), and total population (F). CPS=combined positive score. PD-L1=programmed death ligand 1.

chemotherapy groups was 54 (43%) of 126 and 42 (38%) of 110, respectively, in the CPS of 20 or more population, 88 (36%) of 242 and 84 (36%) of 235, respectively, in the CPS of 1 or more population, and 100 (36%) of 281 and 101 (36%) of 278, respectively, in the total population (appendix p 26). Median response duration in the pembrolizumab with chemotherapy and cetuximab with chemotherapy groups was 7·1 months and 4·2 months, respectively, in the CPS of 20 or more population, 6·7 months and 4·3 months, respectively, in the CPS of 1 or more population, and 6·7 months and 4·3 months, respectively, in the total population (appendix p 19).

At final analysis in the as-treated population, the median duration of any study therapy was 3·5 months (IQR 1·4–7·6) in the pembrolizumab alone group, 5·8 months (2·8–9·7) in the pembrolizumab with chemotherapy group, and 4·9 months (2·5–7·4) in the cetuximab with chemotherapy group. In the as-treated population, grade 3 or worse adverse events of any cause occurred in 164 (55%) of 300 participants in

the pembrolizumab alone group, 235 (85%) of 276 in the pembrolizumab with chemotherapy group, and 239 (83%) of 287 in the cetuximab with chemotherapy group (appendix p 27); these adverse events were attributed to study treatment by the investigator in 51 (17%), 198 (72%), and 199 (69%) participants, respectively (appendix p 32). Grade 3 or worse adverse events of any cause that occurred in at least five participants in any group are summarised in the appendix (pp 27–28); there were 13 such events in the pembrolizumab alone group, 36 in the pembrolizumab with chemotherapy group, and 34 in the cetuximab with chemotherapy group. Adverse events of any cause led to discontinuation of any treatment in 36 (12%) of 300 participants in the pembrolizumab alone group, 90 (33%) of 276 participants in the pembrolizumab with chemotherapy group, and 79 (28%) of 287 participants in the cetuximab with chemotherapy group. In the pembrolizumab with chemotherapy and cetuximab with chemotherapy groups, 23 (8%) and 26 (9%) participants, respectively, had an adverse event that led to discontinuation of all treatment. 25 (8%) participants in the pembrolizumab alone group, 32 (12%) in the pembrolizumab with chemotherapy group, and 28 (10%) in the cetuximab with chemotherapy group died from adverse events, including three (1%), 11 (4%), and eight (3%), respectively, who died from treatment-related adverse events (appendix pp 29–30).

The most common adverse events with pembrolizumab alone were fatigue and anaemia (table 3); the most common treatment-related adverse events were fatigue and hypothyroidism (appendix p 32). Anaemia and nausea were the most common adverse events of any cause and those attributed to study treatment with pembrolizumab with chemotherapy and cetuximab with chemotherapy (table 3, appendix p 32). Pembrolizumab alone was associated with a greater risk of hypothyroidism than was cetuximab with chemotherapy, whereas cetuximab with chemotherapy was associated with a greater risk of 20 adverse events (appendix p 20). Pembrolizumab with chemotherapy was associated with a greater risk of anaemia, hypothyroidism, and cough than was cetuximab with chemotherapy, whereas risks of hypokalaemia, hypomagnesaemia, rash, and acneiform dermatitis were greater with cetuximab with chemotherapy (appendix p 20). Exposure-adjusted all-cause adverse events are in the appendix (p 31). Adverse events of interest, which were based on a list of terms specified by the sponsor and were included regardless of treatment attribution by the investigator, occurred in 93 (31%) of 300 participants in the pembrolizumab alone group, 73 (26%) of 276 participants in the pembrolizumab with chemotherapy group, and 68 (24%) of 287 participants in the cetuximab with chemotherapy group; these were of grade 3 or worse in 21 (7%) participants, 15 (5%) participants, and 30 (10%) participants, respectively (appendix p 33). One participant each in the pembrolizumab alone group and pembrolizumab with chemotherapy group died from pneumonitis. Bleeding from the tumour site occurred in 20 (7%) of 300 participants in the pembrolizumab alone group, 24 (9%) of 276 participants in the pembrolizumab with chemotherapy group, and 15 (5%) of 287 participants in the cetuximab with chemotherapy group (appendix p 34).

	Pembrolizumab alone *vs* cetuximab with chemotherapy		Pembrolizumab with chemotherapy *vs* cetuximab with chemotherapy*	
	Pembrolizumab alone	Cetuximab with chemotherapy	Pembrolizumab with chemotherapy	Cetuximab with chemotherapy
PD-L1 CPS ≥20 population	133	122	126	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	257	255	242	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	301	300	281	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)

Data are n, median (95% CI), or estimated % (95% CI). CPS=combined positive score. PD-L1=programmed death ligand 1. *Only includes participants randomly allocated to the cetuximab with chemotherapy group while the pembrolizumab with chemotherapy group was open for enrolment.

Table 2: **Kaplan-Meier estimates of median progression-free survival at the second interim analysis**

Discussion

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

Neither pembrolizumab alone nor pembrolizumab with chemotherapy improved progression-free survival or objective response compared with cetuximab with chemotherapy, and the proportion of participants with progressive disease as best response was greater with pembrolizumab alone than with cetuximab with chemotherapy. Progression-free survival and objective response were similar for pembrolizumab with chemotherapy and cetuximab with chemotherapy. Our statistical analysis plan specified one-sided testing only

	Pembrolizumab alone (n=300)		Pembrolizumab with chemotherapy (n=276)		Cetuximab with chemotherapy (n=287)	
	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5
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%)

Data are n (%). Adverse events are presented according to the Medical Dictionary for Regulatory Affairs system organ class.

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

but, numerically, progression-free survival and objective response favoured the cetuximab with chemotherapy group in the CPS of 1 or more and total populations. Although there were no progression-free survival or objective response benefits, pembrolizumab alone and pembrolizumab with chemotherapy were associated with more complete responses and a longer duration of response. Pembrolizumab alone improved median response duration by more than 16 months versus cetuximab with chemotherapy. The improvement in median response duration in the pembrolizumab with chemotherapy group was 2·5 months, which probably reflects a mix of shorter chemotherapy-driven and longer pembrolizumab-driven responses.

As seen for immune checkpoint inhibition,[5,6,11,17,18] we report profound overall survival benefits for pembrolizumab monotherapy in participants with PD-L1-positive tumours and for pembrolizumab with chemotherapy in all participants without improvements in progression-free survival or objective response. Substantial survival advantages were seen for pembrolizumab monotherapy in the PD-L1 CPS of 20 or more and CPS of 1 or more populations and for pembrolizumab with chemotherapy in the CPS of 20 or more, CPS of 1 or more, and total populations despite the fact that the overall survival benefit emerged only after about 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. The 3-year overall survival benefit in the pembrolizumab alone and pembrolizumab with chemotherapy groups is greater than can be explained by the proportion of patients with a long-term response. This observation raises the possibility that early exposure to pembrolizumab might induce durable alterations in the tumour microenvironment, altering the natural history of the cancer and sensitising it to subsequent therapy.[19] Support for this hypothesis comes from retrospective analyses[20–25] 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. Further clinical and translational analyses and prospective studies are needed to explore this hypothesis.

The observed adverse events were as expected based on the known toxicity profiles of the individual treatment components. Pembrolizumab monotherapy had a favourable safety profile compared with cetuximab with chemotherapy. The incidences of grade 3 or worse adverse events and those leading to treatment discontinuation were lower with pembrolizumab alone than with cetuximab with chemotherapy, as was the incidence of treatment-related death. The incidence of grade 3 or worse adverse events and those leading to discontinuation and death were similar in the pembrolizumab with chemotherapy and cetuximab with chemotherapy groups. Pembrolizumab did not exacerbate adverse events associated with chemotherapy or vice versa. Tumour bleeding was not substantially increased with pembrolizumab alone or with pembrolizumab with chemotherapy.

This study was powered to compare pembrolizumab monotherapy with cetuximab with chemotherapy and to compare pembrolizumab with chemotherapy with cetuximab with chemotherapy and had 14 primary hypotheses. Per protocol, once a primary hypothesis completed statistical testing, the result was considered definitive. Therefore, the second interim analysis results

are the definitive study findings for 11 of 14 primary hypotheses and the final analysis results are the definitive findings for the remaining three hypotheses. Notably, this study was not powered to compare pembrolizumab monotherapy with pembrolizumab with 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 might direct the choice of pembrolizumab monotherapy or pembrolizumab with chemotherapy. For example, although pembrolizumab monotherapy had a favourable toxicity profile compared with cetuximab with chemotherapy, fewer participants had an objective response and progression-free survival was shorter. Conversely, the proportion of participants with objective response and progression-free survival were similar for pembrolizumab with chemotherapy and cetuximab with chemotherapy. For pembrolizumab monotherapy, greater PD-L1 expression was associated with greater response. Overall, pembrolizumab monotherapy might be preferred for PD-L1-positive cancers that are associated with a lesser symptom burden, whereas pembrolizumab with chemotherapy might 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 with 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 could have resulted in the higher proportion of participants in the cetuximab with chemotherapy group than in the pembrolizumab alone and pembrolizumab with chemotherapy groups who did not receive the assigned therapy. Other limitations are the inconsistent access to second-line PD-1 and PD-L1 inhibitors across the countries that enrolled participants and the lack of statistical power to compare outcomes in the pembrolizumab alone and pembrolizumab with chemotherapy groups.

In summary, first-line therapy with pembrolizumab monotherapy significantly improved overall survival in the PD-L1 CPS of 20 or more and CPS of 1 or more populations, had non-inferior overall survival 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 with 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 overall survival in the PD-L1 CPS of 20 or more, CPS of 1 or more, and total populations, was associated with a longer duration of response, and had a comparable safety profile versus cetuximab with chemotherapy. Based on the observed efficacy and safety, pembrolizumab combined with platinum and 5-fluorouracil is an appropriate first-line treatment for recurrent or metastatic HNSCC and pembrolizumab monotherapy is an appropriate first-line treatment for PD-L1-positive recurrent or metastatic HNSCC.

Contributors

BB, KJH, JDC, and FJ conceived, designed, and planned the study. BB, KJH, RG, DS, MT, GdC, 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 manuscript. 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 reports honoraria and travel support for steering committee activities from Boehringer-Ingelheim, Merck Sharp & Dohme (MSD), a subsidiary of Merck & Co; 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; travel support for advisory activities from Celgene, Debiopharm, Maverick Therapeutics, and Genentech/Roche; honoraria and travel support for data safety monitoring committee activities from IDDI for AstraZeneca/MedImmune; and funding to their institution to support study conduct from Boehringer-Ingelheim and MSD. KJH reports personal fees for serving as an advisory board member from MSD, AstraZeneca, Amgen, Boehringer-Ingelheim, Merck Serono, Mersana, Oncolys, Pfizer, Replimmune, and Vyriad; personal fees for serving as a speaker from MSD, AstraZeneca, Amgen, Merck Serono; and honoraria from MSD, AstraZeneca, Amgen, Boehringer-Ingelheim, Merck Serono, Pfizer, Replimmune, and Vyriad. RG reports honoraria and travel support for serving in a consultant or advisory role from MSD. DS reports personal fees for serving as an advisor and a speaker from MSD. MT reports personal fees from Merck Serono, Bristol-Myers Squibb, Eisai, Ono Pharmaceutical, AstraZeneca, Pfizer, Rakuten Aspyrian Therapeutics, Celgene, Amgen, and Bayer, and grants from Bristol-Myers Squibb, Ono Pharmaceutical, AstraZeneca, Pfizer, Rakuten Aspyrian Therapeutics, Bayer, LOXO, and Novartis. GdC reports personal fees for serving as a speaker from MSD, AstraZeneca, Bristol-Myers Squibb, and Merck Serono; personal fees for presentations from AstraZeneca and Teva; travel and accommodation support from MSD, Bristol-Myers Squibb, and Merck Serono; and funding to their institution to support study conduct from MSD, Bristol-Myers Squibb, and Merck Serono. AP reports personal fees for advisory boards from MSD, Bristol-Myers Squibb, Roche, and Genesis; travel support from MSD, Bristol-Myers Squibb, Roche, and Merck Serono; honoraria from MSD, Bristol-Myers Squibb, and Roche; and grants from Bristol-Myers Squibb, Roche, Boehringer-Ingelheim, Pfizer, Merck Serono, Genesis, and KURA. NB reports personal fees from Bristol-Myers Squibb, Nanobiotix, and Merck Serono, and non-financial support from Bristol-Myers Squibb, Nanobiotix, AstraZeneca, Merck Serono, Boehringer Ingelheim, Novartis, MSD, ISA Therapeutics, Debiopharm, and Roche. TF reports honoraria and travel support to support advisory activities from MSD, Merck KGaA, Roche, Bristol-Myers Squibb, and Boehringer-Ingelheim; honoraria for lectures from Accord, AstraZeneca, Novartis, Sanofi, and Boehringer-Ingelheim; research grants from MSD and Merck KGaA; and funding to their institution to support study conduct from MSD, Bristol-Myers Squibb, Merck KGaA, AstraZeneca, Novartis, Sanofi, Roche, Amgen, and Pfizer. BGMH reports personal fees for serving as an advisory board member for MSD, Bristol-Myers Squibb, Pfizer, Roche, AstraZeneca, Eisai, and Boehringer-Ingelheim. RM reports personal fees for serving in an advisory role for AstraZeneca, MSD, Merck, Bristol-Myers Squibb, Roche, and Nanobiotix, and honoraria for conferences from MSD and Bristol-Myers Squibb. NN reports personal

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Data sharing

For the **data sharing policy** see http://engagezone.msd.com/ds_documentation.php

Data will be available according to Merck Sharp & Dohme's data sharing policy, which, including restrictions, is available online at EngageZone. Requests for access to the clinical study data can be submitted through EngageZone or via email to dataacess@merck.com.

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