Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study

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Summary

Background First-line therapy for advanced oesophageal cancer is currently limited to fluoropyrimidine plus platinum-based chemotherapy. We aimed to evaluate the antitumour activity of pembrolizumab plus chemotherapy versus chemotherapy alone as first-line treatment in advanced oesophageal cancer and Siewert type 1 gastro-oesophageal junction cancer.

Methods We did a randomised, placebo-controlled, double-blind, phase 3 study across 168 medical centres in 26 countries. Patients aged 18 years or older with previously untreated, histologically or cytologically confirmed, locally advanced, unresectable or metastatic oesophageal cancer or Siewert type 1 gastro-oesophageal junction cancer (regardless of PD-L1 status), measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1, and Eastern Cooperative Oncology Group performance status of 0–1, were randomly assigned (1:1) to intravenous pembrolizumab 200 mg or placebo, plus 5-fluorouracil and cisplatin (chemotherapy), once every 3 weeks for up to 35 cycles. Randomisation was stratified by geographical region, histology, and performance status. Patients, investigators, and site staff were masked to group assignment and PD-L1 biomarker status. Primary endpoints were overall survival in patients with oesophageal squamous cell carcinoma and PD-L1 combined positive score (CPS) of 10 or more, and overall survival and progression-free survival in patients with oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients. This trial is registered with ClinicalTrials.gov, NCT03189719, and is closed to recruitment.

Findings Between July 25, 2017, and June 3, 2019, 1020 patients were screened and 749 were enrolled and randomly assigned to pembrolizumab plus chemotherapy (n=373 [50%]) or placebo plus chemotherapy (n=376 [50%]). At the first interim analysis (median follow-up of 22·6 months), pembrolizumab plus chemotherapy was superior to placebo plus chemotherapy for overall survival in patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more (median 13·9 months *vs* 8·8 months; hazard ratio 0·57 [95% CI 0·43–0·75]; p<0·0001), oesophageal squamous cell carcinoma (12·6 months *vs* 9·8 months; 0·72 [0·60–0·88]; p=0·0006), PD-L1 CPS of 10 or more (13·5 months *vs* 9·4 months; 0·62 [0·49–0·78]; p<0·0001), and in all randomised patients (12·4 months *vs* 9·8 months; 0·73 [0·62–0·86]; p<0·0001). Pembrolizumab plus chemotherapy was superior to placebo plus chemotherapy for progression-free survival in patients with oesophageal squamous cell carcinoma (6·3 months *vs* 5·8 months; 0·65 [0·54–0·78]; p<0·0001), PD-L1 CPS of 10 or more (7·5 months *vs* 5·5 months; 0·51 [0·41–0·65]; p<0·0001), and in all randomised patients (6·3 months *vs* 5·8 months; 0·65 [0·55–0·76]; p<0·0001). Treatment-related adverse events of grade 3 or higher occurred in 266 (72%) patients in the pembrolizumab plus chemotherapy group versus 250 (68%) in the placebo plus chemotherapy group.

Interpretation Compared with placebo plus chemotherapy, pembrolizumab plus chemotherapy improved overall survival in patients with previously untreated, advanced oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, and overall survival and progression-free survival in patients with oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients regardless of histology, and had a manageable safety profile in the total as-treated population.

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Introduction

No single standard-of-care therapy has yet been approved for patients with treatment-naive advanced oesophageal cancer. Combination fluoropyrimidine plus platinum-based chemotherapy, most commonly oxaliplatin or cisplatin, is recommended as first-line treatment for

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed on Jan 20, 2021, with no date or language restrictions, using the terms "PD-1" OR "PD-L1" OR "MK-3475" OR "pembrolizumab" OR "Keytruda" OR "nivolumab" OR "Opdivo" OR "atezolizumab" OR "Tecentriq" OR "durvalumab" OR "Imfinzi" OR "avelumab" OR "Bravencio" AND "esophageal cancer". We also searched the 2019 and 2020 abstract records of the American Society of Clinical Oncology, American Society of Clinical Oncology Gastrointestinal Cancers Symposium, the World Congress on Gastrointestinal Cancer, and the European Society for Medical Oncology Congress using the same search terms to identify results of clinical studies that were not yet published in the peer-reviewed literature. We identified the phase 3 randomised studies CheckMate 649 of first-line nivolumab plus chemotherapy (capecitabine plus oxaliplatin once every 3 weeks or leucovorin, fluorouracil, and oxaliplatin once every 2 weeks) or nivolumab plus ipilimumab versus chemotherapy alone for advanced gastric cancer or gastro-oesophageal junction cancer or oesophageal adenocarcinoma; ATTRACTION-4 of first-line nivolumab plus chemotherapy (oxaliplatin plus S-1 or capecitabine) versus placebo plus chemotherapy in Asian patients with advanced or recurrent gastric cancer or gastro-oesophageal junction cancer; and CheckMate 648 of first-line nivolumab plus ipilimumab or nivolumab plus chemotherapy (fluorouracil plus cisplatin) versus chemotherapy alone for advanced oesophageal squamous cell carcinoma.

Added value of this study

To our knowledge, KEYNOTE-590 is the first randomised, phase 3 study to report a clinically meaningful and significant overall survival and progression-free survival benefit with an anti-PD-1 or anti-PD-L1 therapy plus chemotherapy versus chemotherapy alone as first-line therapy for advanced oesophageal cancer. The efficacy of pembrolizumab plus chemotherapy was greater in patients with PD-L1 combined positive score (CPS) of 10 or more than in patients with PD-L1 CPS of less than 10.

Implications of all the available evidence

According to hierarchical testing, pembrolizumab plus chemotherapy significantly improved overall survival in patients with oesophageal squamous cell carcinoma PD-L1 CPS of 10 or more, and overall survival and progression-free survival in patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, oesophageal squamous cell carcinoma, and PD-L1 CPS of 10 or more, and in all randomised patients with untreated, advanced oesophageal cancer or Siewert type 1 gastro-oesophageal junction cancer, compared with chemotherapy alone, with no new safety signals reported. Therefore, we expect that pembrolizumab plus chemotherapy could become a new standard therapy for these populations.

patients with advanced or metastatic oesophageal cancer (HER2-negative adenocarcinoma).[1–3] This combination has been a mainstay as first-line treatment for metastatic oesophageal cancer for approximately four decades, with minimal improvement in overall survival for patients with oesophageal cancer over that time. Multiple therapeutic strategies to improve overall survival in patients with advanced oesophageal cancer have been unsuccessful.[4] Therefore, metastatic oesophageal cancer remains a disease with high mortality, and effective first-line treatment remains an unmet need in this patient population.[3,5–7]

Immune checkpoint inhibitors have shown effective antitumour activity as second-line or later therapy in patients with unresectable, advanced or metastatic squamous cell carcinoma or adenocarcinoma of the oesophagus.[8–11] As monotherapy, pembrolizumab provided an overall response rate of 14% and median duration of response not reached in both oesophageal squamous cell carcinoma and PD-L1 combined positive score (CPS) of 10 or more tumours as third-line or later therapy in the phase 2 KEYNOTE-180 study in patients with advanced oesophageal cancer.[10] In the phase 3 KEYNOTE-181 study, pembrolizumab monotherapy provided a median overall survival of 10·3 months versus 6·7 months with chemotherapy (hazard ratio [HR] 0·64 [95% CI 0·46–0·90]) as second-line therapy in patients with oesophageal squamous cell carcinoma with PD-L1 CPS of 10 or more.[11]

The benefit of combining immune checkpoint inhibitor therapy with chemotherapy has been shown in several studies, and first-line treatment with combination chemotherapy and immune checkpoint inhibitors has gradually become the standard of care in several cancer types.[12–14] We aimed to evaluate the antitumour activity of pembrolizumab plus chemotherapy versus chemotherapy alone as first-line treatment in advanced oesophageal cancer and Siewert type 1 gastro-oesophageal junction cancer.

Methods

Study design and participants

We did a randomised, placebo-controlled, double-blind, phase 3 study across 168 medical centres in 26 countries (KEYNOTE-590). Eligible patients were aged 18 years or older with previously untreated, histologically or cytologically confirmed, locally advanced, unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or Siewert type 1 gastro-oesophageal junction adenocarcinoma, with measurable disease per Response Criteria in Solid Tumors (RECIST) version 1.1 by investigator or radiology assessment, adequate organ function (appendix p 59), and Eastern Cooperative Oncology Group (ECOG) performance status of 0–1.

Patients also needed to have either a newly obtained or archival tissue sample for PD-L1 immunohistochemical analysis. Exclusion criteria were locally advanced oesophageal cancer that was resectable or potentially curable with radiation therapy as determined by local investigator, previous therapy for advanced or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or Siewert type 1 adenocarcinoma of the gastro-oesophageal junction, known human epidermal growth factor receptor-2-positive tumour, Siewert type 1 gastro-oesophageal junction adenocarcinoma with known active CNS metastases or carcinomatous meningitis or both, active autoimmune disease that had required systemic treatment, immunodeficiency or receiving chronic systemic steroid therapy, and history of non-infectious pneumonitis or current pneumonitis. Full eligibility criteria are listed in the study protocol (appendix pp 56–61). Patients were enrolled regardless of tumour PD-L1 status. The protocol and all amendments (appendix pp 14–171) were approved by the appropriate institutional review board or ethics committee at each participating study site. All patients provided written informed consent before study enrolment.

Randomisation and masking

Patients were enrolled by the study investigators and randomly assigned (1:1) using an interactive voice response system (IVRS) or integrated web response system (Almac Clinical Technologies, Souderton, PA, USA) with a block size of four to receive pembrolizumab plus chemotherapy or placebo plus chemotherapy. Randomisation was stratified by geographical region (Asia *vs* non-Asia), histology (oesophageal squamous cell carcinoma *vs* adenocarcinoma), and ECOG performance status (0 *vs* 1). The randomised allocation schedule was generated by the sponsor and implemented in the IVRS. Patients, investigators, and site staff were masked to group assignment and PD-L1 biomarker status.

Procedures

Patients received pembrolizumab 200 mg or saline placebo plus chemotherapy (5-fluorouracil 800 mg/m² on days 1–5 plus cisplatin 80 mg/m² on day 1 [for a maximum of six cycles]) once every 3 weeks for up to 35 cycles. All treatments were given intravenously. Treatment was continued until disease progression, unacceptable toxicity, illness, physician or patient decision to withdraw, non-compliance, completion of 35 cycles, complete response, or discontinuation for administrative reasons. No cross-over between treatment groups was allowed. Tumour response was assessed per RECIST version 1.1 by the investigators locally at week 9 and every 9 weeks thereafter. Disease progression was verified by central imaging review. During follow-up, survival was assessed every 12 weeks. Adverse events were evaluated throughout the study and at 30 days (90 days for serious adverse events and events of interest to pembrolizumab) after treatment discontinuation and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Additional study and treatment details are provided in the protocol.

PD-L1 expression was centrally assessed during screening using the US Food and Drug Administration approved PD-L1 IHC 22C3 assay (Agilent Technologies, Carpinteria, CA, USA). The PD-L1 CPS is defined as the number of PD-L1-positive cells (tumour cells, macrophages, and lymphocytes) divided by the total number of viable tumour cells. PD-L1-positive tumours had CPS of 10 or more in this study.

Outcomes

The dual primary endpoints were overall survival (time from randomisation to death from any cause) in patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients; and progression-free survival (time from randomisation to first disease progression or death from any cause) per RECIST version 1.1 by investigator assessment in patients with oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients. Secondary endpoints were objective response rate (proportion of patients with complete or partial response) per RECIST version 1.1 by investigator assessment in all randomised patients, and patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, oesophageal squamous cell carcinoma, and PD-L1 CPS of 10 or more; duration of response (time from first documented complete or partial response until disease progression per RECIST version 1.1 by investigator assessment) in all randomised patients, and patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, oesophageal squamous cell carcinoma, and PD-L1 CPS of 10 or more; health-related quality of life; and safety and tolerability. A full list of exploratory endpoints is provided in the protocol and the summary of its amendments (appendix p 44).

Statistical analysis

Primary efficacy analyses were done in the intention-to-treat population of all randomised patients. Safety was assessed in all randomised patients who received at least one dose of study treatment (the as-treated population). The Kaplan-Meier method was used to estimate overall survival, progression-free survival, and duration of response. Between-group differences in overall survival and progression-free survival were assessed using a stratified log-rank test. Differences in objective response rate were assessed with the stratified Miettinen and Nurminen method. Between-group treatment effect (with a nominal 95% CI) across prespecifed subgroups was estimated for the primary endpoints in patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, oesophageal

squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients. A stratified Cox proportional hazards model with Efron's method of tie handling was used to estimate HRs and associated 95% CIs. A prespecifed sensitivity analysis of progression-free survival per RECIST version 1.1 by masked independent central review was done to assess the robustness of the progression-free survival by investigator assessment endpoint. Exploratory analyses examined between-group treatment differences in patients by PD-L1 status, and in patients from Asian and non-Asian regions. A post-hoc analysis examined between-group treatment differences by histology and PD-L1 status.

The statistical analysis plan specified one interim analysis and a final analysis. The first interim analysis (final analysis of progression-free survival) was planned after at least 13 months of follow-up after enrolment (35 months after randomisation) and after approximately 460 investigator-assessed progression-free survival events and 391 deaths were observed in the oesophageal squamous cell carcinoma population. The independent data monitoring committee confirmed that the study met the specified efficacy and safety endpoints after reviewing the results of the interim analysis by an unmasked external statistician.

The protocol prespecified seven primary hypotheses and one secondary hypothesis (appendix pp 43–44): superiority of pembrolizumab plus chemotherapy versus placebo plus chemotherapy for overall survival in patients with oesophageal squamous cell carcinoma and PD-L1 CPS

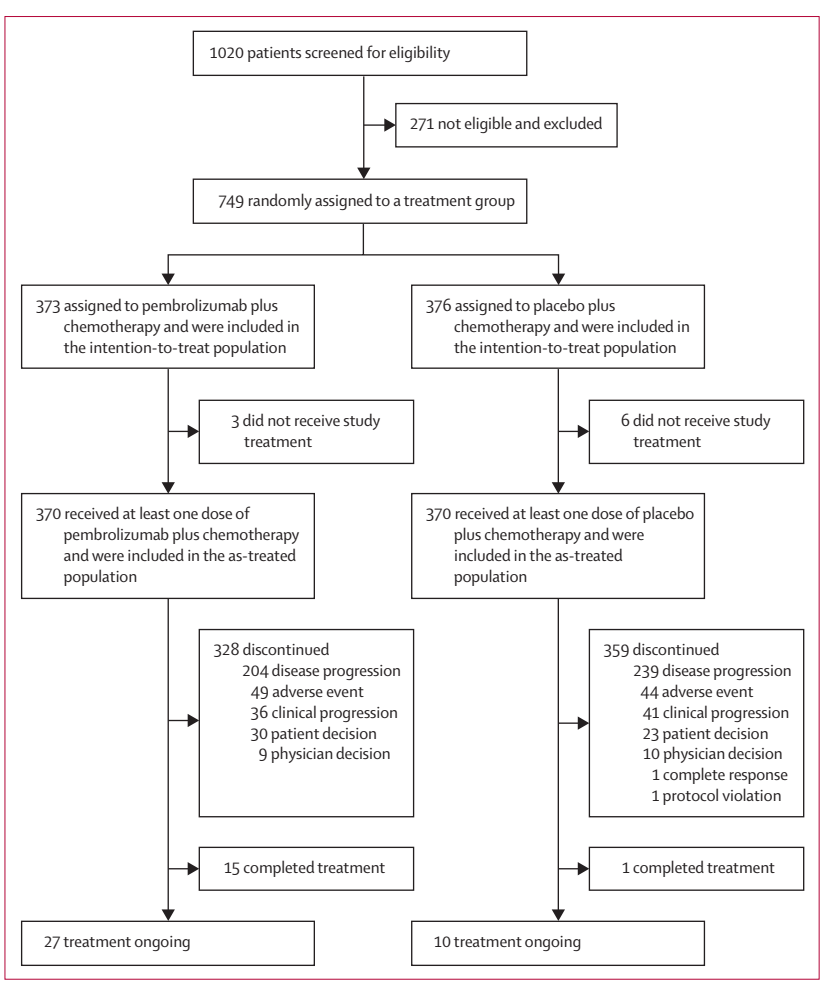

Figure 1: **Trial profile**

	Pembrolizumab plus chemotherapy group (n=373)	Placebo plus chemotherapy group (n=376)
Age, years		
Median (range)	64 (28–94)	62 (27–89)
≥65	172 (46%)	150 (40%)
Sex		
Female	67 (18%)	57 (15%)
Male	306 (82%)	319 (85%)
Asia region*	196 (53%)	197 (52%)
Race		
Asian	201 (54%)	199 (53%)
White	139 (37%)	139 (37%)
Missing	14 (4%)	15 (4%)
Native American	9 (2%)	12 (3%)
African American	5 (1%)	2 (1%)
Other†	5 (1%)	9 (2%)
ECOG performance status		
0	149 (40%)	150 (40%)
1	223 (60%)	225 (60%)
2	1 (<1%)	1 (<1%)
Oesophageal squamous cell carcinoma	274 (73%)	274 (73%)
Adenocarcinoma	99 (27%)	102 (27%)
Oesophageal adenocarcinoma	58 (16%)	52 (14%)
Siewert type 1 gastro-oesophageal junction adenocarcinoma‡	41 (11%)	50 (13%)
Disease status		
Metastatic	344 (92%)	339 (90%)
Unresectable locally advanced	29 (8%)	37 (10%)
PD-L1 CPS ≥10	186 (50%)	197 (52%)
Oesophageal squamous cell carcinoma	143 (38%)	143 (38%)
Adenocarcinoma	43 (12%)	54 (14%)
PD-L1 CPS <10	175 (47%)	172 (46%)
Oesophageal squamous cell carcinoma	121 (32%)	126 (34%)
Adenocarcinoma	54 (14%)	46 (12%)
PD-L1 status not evaluable or missing	12 (3%)	7 (2%)

Data are n (%) unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. CPS=combined positive score. *Countries in the Asia region include China, Hong Kong, Japan, South Korea, and Taiwan. †Other includes patients with multiple ethnicities. ‡58 patients were HER2-negative, 1 patient was HER2-positive, and 32 had unknown HER2 status.

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

of 10 or more; and superiority of pembrolizumab plus chemotherapy versus placebo plus chemotherapy for overall survival and progression-free survival in patients with oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients. Superiority of pembrolizumab plus chemotherapy versus placebo plus chemotherapy for objective response rate in all patients per investigator assessment was the secondary hypothesis.

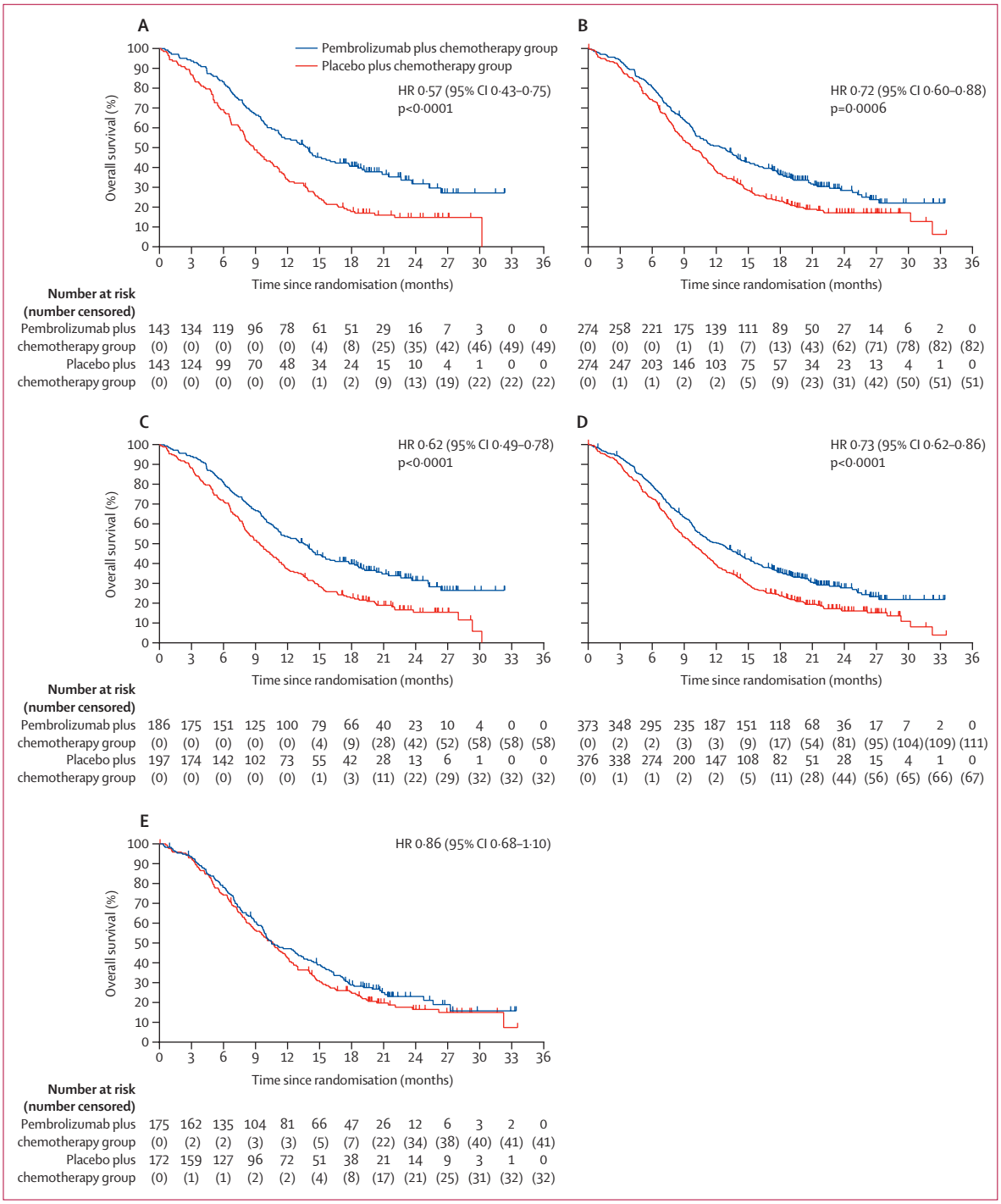

Figure 2: **Kaplan-Meier estimates of overall survival**
(A) Patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more. (B) Patients with oesophageal squamous cell carcinoma. (C) Patients with PD-L1 CPS of 10 or more. (D) All randomised patients. (E) Patients with PD-L1 CPS of less than 10 (post-hoc analysis). Tick marks represent data censored at the time of last imaging assessment. CPS=combined positive score. HR=hazard ratio.

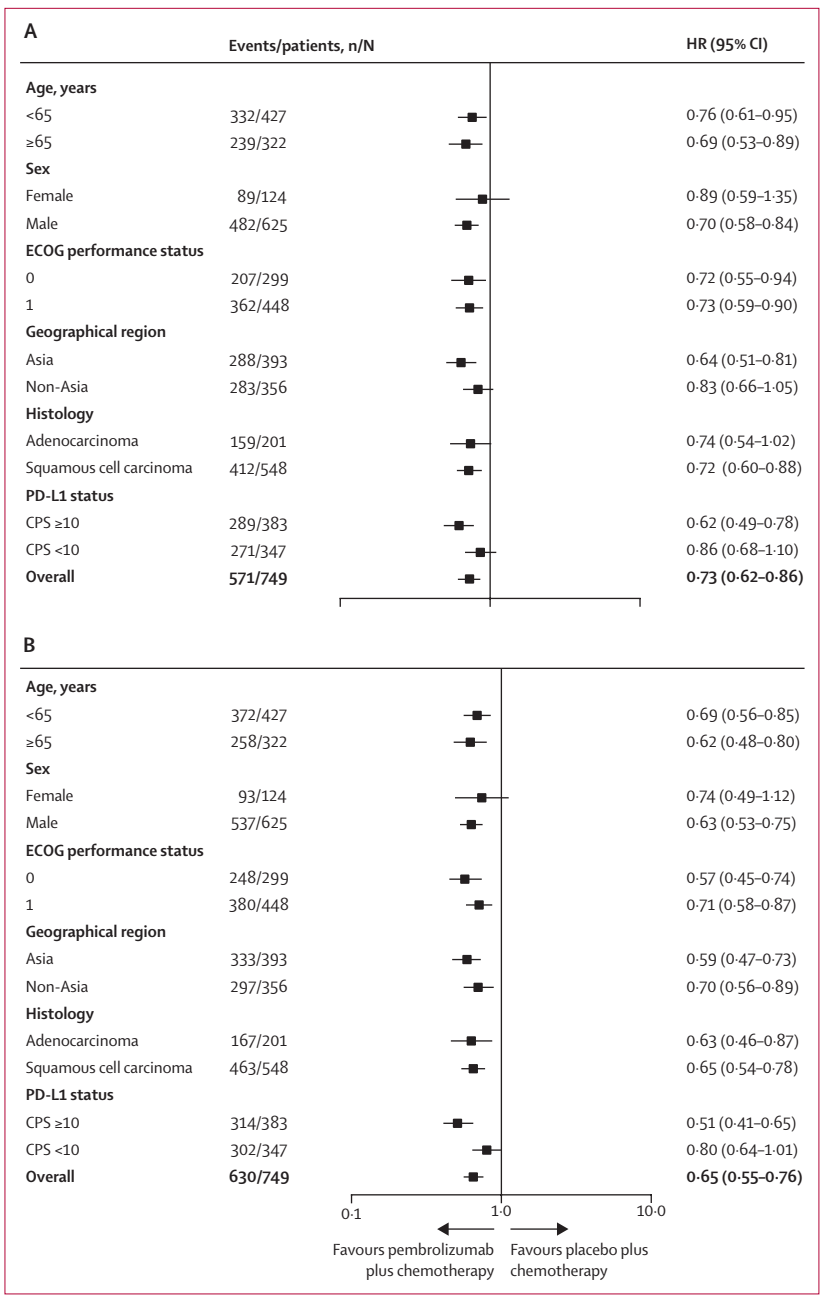

Figure 3: **Survival by patient subgroups**
Forest plot analysis of overall survival (A) and progression-free survival (B) in prespecified subgroups in the intention-to-treat population for pembrolizumab plus chemotherapy versus placebo plus chemotherapy. The Cox proportional hazards model with Efron's method of tie handling was used to assess the magnitude of the treatment difference between groups. These analyses were not adjusted for multiplicity and were not powered to show significant differences. HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. CPS=combined positive score.

Three hypotheses (superiority of pembrolizumab plus chemotherapy versus placebo plus chemotherapy for overall survival in patients with oesophageal squamous cell carcinoma and PD-1 CPS of 10 or more, and oesophageal squamous cell carcinoma, and progression-free survival in patients with oesophageal squamous cell carcinoma) were tested first and in parallel, with remaining hypotheses tested according to the prespecified multiplicity strategy only if the preceding hypothesis with allocated α was positive (appendix p 12). The study was considered successful if pembrolizumab plus chemotherapy was superior to placebo plus chemotherapy for any primary endpoint. The overall type I error was strongly controlled at a one-sided α of 2·5% with 1·2% initially allocated to overall survival in patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more (hypothesis one), 1·1% to patients with oesophageal squamous cell carcinoma (hypothesis two), and 0·2% to progression-free survival in patients with oesophageal squamous cell carcinoma (hypothesis five), which were tested first and in parallel. An initial α of 0 was allocated to the remaining hypotheses. Re-allocation of type I error was done using the graphical method of Maurer and Bretz (appendix p 12). All data reported are based on the interim analysis with a data cutoff date of July 2, 2020. Statistical analyses were done using SAS (version 9.4). This trial is registered with ClinicalTrials.gov, NCT03189719.

Role of the funding source

The funder of the study participated in study design, data interpretation, and the writing of this report, and maintained the study database.

Results

Between July 25, 2017, and June 3, 2019, 1020 patients were screened and 749 were randomly assigned to pembrolizumab plus chemotherapy (n=373 [50%]) or placebo plus chemotherapy (n=376 [50%]; figure 1). Baseline patient characteristics and demographics were generally well balanced between the two groups (table 1). 548 (73%) patients had oesophageal squamous cell carcinoma (286 [52%] of whom had PD-L1 CPS of 10 or more) and 201 (27%) had adenocarcinoma (91 [12%] of 749 had Siewert type 1 gastro-oesophageal junction adenocarcinoma). 383 (51%) of 749 patients had PD-L1 CPS of 10 or more (table 1). Evaluable microsatellite instability status was available only for 112 (40%) of 278 patients with a confirmed or unconfirmed response per RECIST; none had high microsatellite instability. At the data cutoff date of July 2, 2020, the median follow-up duration was 22·6 months (IQR 19·6–27·1). 15 (4%) of 373 patients in the pembrolizumab plus chemotherapy group and one (<1%) of 376 in the placebo plus chemotherapy group completed 35 treatment cycles, and 27 (7%) in the pembrolizumab plus chemotherapy group and ten (3%) in the placebo plus chemotherapy group remained on treatment at the data cutoff date (figure 1).

740 patients received at least one dose of study treatment (n=370 in each treatment group). The mean duration of treatment exposure was 7·7 months (SD 6·84) in the pembrolizumab plus chemotherapy group and 5·8 months (4·76) in the placebo plus chemotherapy

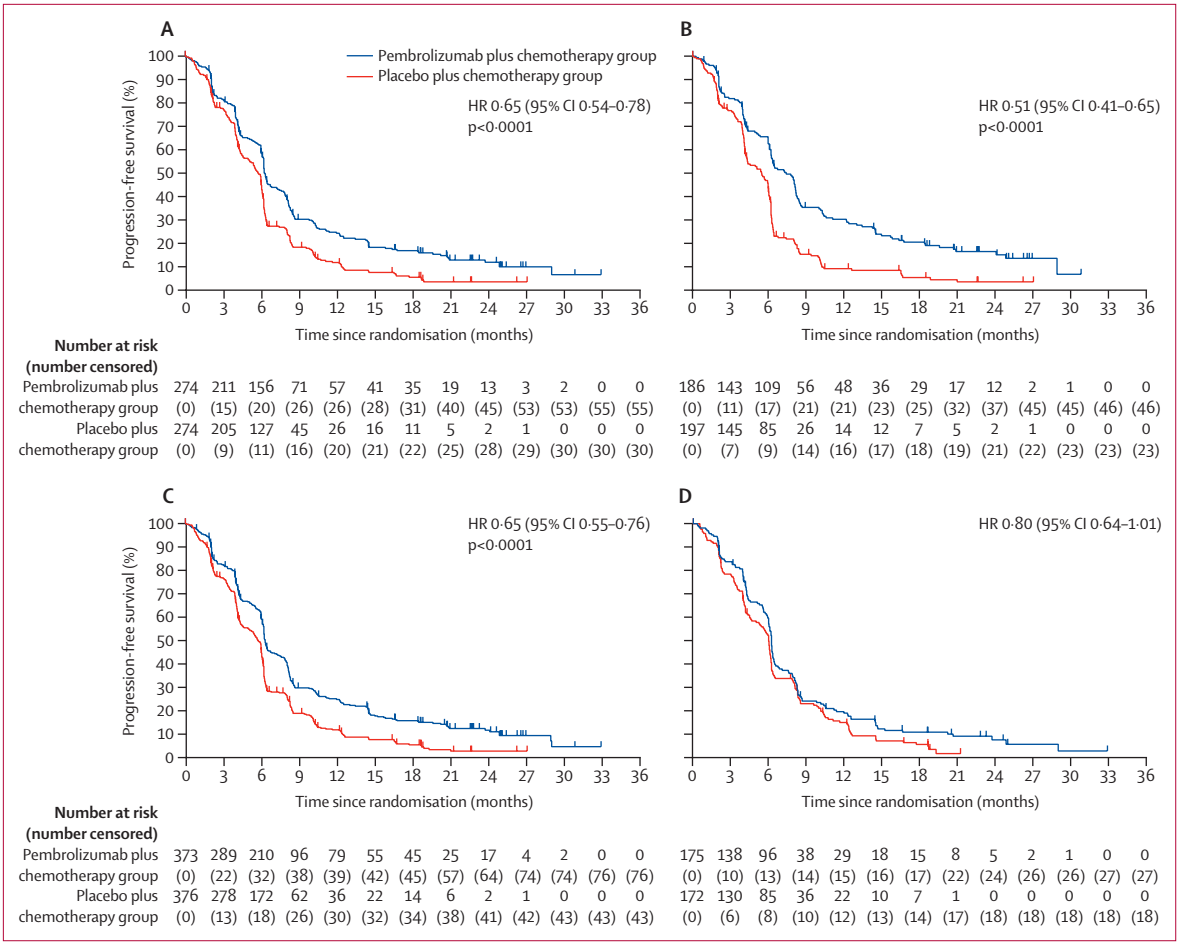

Figure 4: **Kaplan-Meier estimates of progression-free survival**
(A) Patients with oesophageal squamous cell carcinoma. (B) Patients with PD-L1 CPS of 10 or more. (C) All randomised patients. (D) Patients with PD-L1 CPS of less than 10 (post-hoc analysis). Tick marks represent data censored at the time of last imaging assessment. Progression-free survival was assessed per the Response Evaluation Criteria in Solid Tumors version 1.1 by investigators. CPS=combined positive score. HR=hazard ratio.

group. 161 (43%) patients in the pembrolizumab plus chemotherapy group versus 177 (47%) in the placebo plus chemotherapy group received subsequent anticancer therapy; 22 (6%) in the pembrolizumab plus chemotherapy group versus 35 (9%) in the placebo plus chemotherapy group received subsequent immunotherapy (appendix p 6).

At this first interim analysis, pembrolizumab plus chemotherapy met the criteria for superiority versus placebo plus chemotherapy for overall survival in patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 more (median 13·9 months [95% CI 11·1–17·7] *vs* 8·8 months [7·8–10·5]; HR 0·57 [95% CI 0·43–0·75]; p<0·0001; figure 2A). Pembrolizumab plus chemotherapy was also superior to placebo plus chemotherapy for overall survival in patients with oesophageal squamous cell carcinoma (12·6 months [10·2–14·3] *vs* 9·8 months [8·6–11·1]; 0·72 [0·60–0·88]; p=0·0006; figure 2B); PD-L1 CPS of 10 or more (13·5 months [11·1–15·6] *vs* 9·4 months [8·0–10·7]; 0·62 [0·49–0·78]; p<0·0001; figure 2C); and in all randomised patients (12·4 months [10·5–14·0] *vs* 9·8 months [8·8–10·8]; 0·73 [0·62–0·86]; p<0·0001; figure 2D). The 24-month overall survival rates for the pembrolizumab plus chemotherapy group versus placebo plus chemotherapy group were 31% versus 15% in patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, 29% versus 17% in patients with oesophageal squamous cell carcinoma, 31% versus 15% in patients with PD-L1 CPS of 10 or more, and 28% versus 16% in all randomised patients. Overall survival was generally consistent across prespecified subgroups (figure 3A). In a subgroup of patients with adenocarcinoma, including oesophageal and Siewert type 1 gastro-oesophageal junction adenocarcinoma, overall survival was longer in the pembrolizumab plus chemotherapy group than in the placebo plus chemotherapy group (median 11·6 months [95% CI 9·7–15·2] *vs* 9·9 months [7·8–12·3]; HR 0·74 [95% CI 0·54–1·02]; appendix pp 7, 13).

Pembrolizumab plus chemotherapy met the criteria for superiority versus placebo plus chemotherapy for progression-free survival in patients with oesophageal squamous cell carcinoma (median 6·3 months [95% CI 6·2–6·9] *vs* 5·8 months [5·0–6·1]; HR 0·65 [95% CI 0·54–0·78]; p<0·0001; figure 4A). Pembrolizumab plus chemotherapy was also superior to placebo plus chemotherapy for progression-free survival in patients with PD-L1 CPS of 10 or more (7·5 months [6·2–8·2] *vs* 5·5 months [4·3–6·0]; 0·51 [0·41–0·65]; p<0·0001; figure 4B); and in all randomised patients (6·3 months [6·2–6·9] *vs* 5·8 months [5·0–6·0]; 0·65 [0·55–0·76]; p<0·0001; figure 4C). In a sensitivity analysis, investigator-assessed progression-free survival was similar to that of progression-free survival by blinded independent central review in patients with oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients (appendix p 8). Progression-free survival was generally consistent across prespecified subgroups (figure 3B). In a subgroup of patients with adenocarcinoma, including oesophageal and Siewert type 1 gastro-oesophageal adenocarcinoma, progression-free survival was longer in the pembrolizumab plus chemotherapy group than in the placebo plus chemotherapy group (median 6·3 months *vs* 5·7 months; HR 0·63 [95% CI 0·46–0·87]; appendix pp 7, 13).

	Pembrolizumab plus chemotherapy group (n=370)		Placebo plus chemotherapy group (n=370)	
	Any	Grade ≥3	Any	Grade ≥3
Any adverse event	370 (100%)	318 (86%)	368 (99%)	308 (83%)
Treatment-related adverse events*				
Nausea	233 (63%)	26 (7%)	220 (59%)	24 (6%)
Decreased appetite	145 (39%)	13 (4%)	119 (32%)	16 (4%)
Anaemia	143 (39%)	46 (12%)	162 (44%)	54 (15%)
Fatigue	135 (36%)	23 (6%)	107 (29%)	20 (5%)
Decreased neutrophil count	135 (36%)	84 (23%)	109 (29%)	62 (17%)
Vomiting	110 (30%)	23 (6%)	99 (27%)	18 (5%)
Diarrhoea	97 (26%)	12 (3%)	85 (23%)	7 (2%)
Neutropenia	96 (26%)	53 (14%)	88 (24%)	60 (16%)
Stomatitis	96 (26%)	21 (6%)	93 (25%)	14 (4%)
Decreased white blood cells	89 (24%)	32 (9%)	69 (19%)	18 (5%)
Increased blood creatinine	67 (18%)	5 (1%)	70 (19%)	1 (<1%)
Decreased platelet count	61 (16%)	7 (2%)	56 (15%)	17 (5%)
Mucosal inflammation	59 (16%)	12 (3%)	65 (18%)	13 (4%)
Leukopenia	24 (6%)	6 (2%)	28 (8%)	11 (3%)
Thrombocytopenia	25 (7%)	5 (1%)	33 (9%)	10 (3%)
Tinnitus	33 (9%)	2 (1%)	25 (7%)	0
Hyperthyroidism	19 (5%)	0	2 (1%)	0
Hypothyroidism	38 (10%)	0	22 (6%)	0
Constipation	50 (14%)	0	63 (17%)	0
Asthenia	45 (12%)	12 (3%)	35 (9%)	4 (1%)
Malaise	43 (12%)	2 (1%)	39 (11%)	4 (1%)
Increased aspartate aminotransferase	18 (5%)	3 (1%)	19 (5%)	2 (1%)
Decreased lymphocyte count	21 (6%)	7 (2%)	20 (5%)	5 (1%)
Decreased weight	43 (12%)	4 (1%)	47 (13%)	8 (2%)
Dehydration	20 (5%)	8 (2%)	16 (4%)	8 (2%)
Hypokalaemia	34 (9%)	17 (5%)	41 (11%)	19 (5%)
Hypomagnesaemia	21 (6%)	2 (1%)	14 (4%)	3 (1%)
Hyponatraemia	32 (9%)	20 (5%)	40 (11%)	20 (5%)
Dysgeusia	34 (9%)	0	32 (9%)	0
Peripheral neuropathy	32 (9%)	1 (<1%)	32 (9%)	0
Peripheral sensory neuropathy	34 (9%)	1 (<1%)	29 (8%)	1 (<1%)
Hiccups	40 (11%)	0	33 (9%)	0
Pneumonitis	20 (5%)	7 (2%)	0	0
Alopecia	51 (14%)	0	39 (11%)	0
Pruritus	23 (6%)	1 (<1%)	8 (2%)	0
Rash	29 (8%)	0	18 (5%)	1 (<1%)

(Table 2 continues on next page)

Among all randomised patients, the objective response rate was 45·0% (95% CI 39·9–50·2; 168 of 373) in the pembrolizumab plus chemotherapy group versus 29·3% (24·7–34·1; 110 of 376) in the placebo plus chemotherapy group; estimated percentage difference (15·8% [95% CI 9·0–22·5]; p<0·0001). The median duration of response was 8·3 months (range 1·2+ to 31·0+ [+ indicates that there was no progressive disease at the time of the last disease assessment]) in the pembrolizumab plus chemotherapy group and 6·0 months (range 1·5+ to 25·0+) in the placebo plus chemotherapy group (appendix p 9). Response durations of 24 months or longer occurred in 18% of patients in the pembrolizumab plus chemotherapy group and 6% of patients in the placebo plus chemotherapy group (appendix p 9). The antitumour response was higher in the pembrolizumab plus chemotherapy group than in the placebo plus chemotherapy group (48% *vs* 25%; estimated percentage difference 24·3% [95% CI 11·1–36·7]) in patients with adenocarcinoma, including Siewert type 1 gastro-oesophageal adenocarcinoma (appendix p 7).

In an exploratory analysis in patients with PD-L1 CPS of less than 10, median overall survival was 10·5 months in the pembrolizumab plus chemotherapy group versus 10·6 months in the placebo plus chemotherapy group (HR 0·86 [95% CI 0·68–1·10]; figure 2E), and median progression-free survival was 6·2 months versus 6·0 months (0·80 [0·64–1·01]; figure 4D). In a post-hoc analysis, median overall survival and progression-free survival outcomes by histology and PD-L1 status (appendix p 10) in the pembrolizumab plus chemotherapy group versus the placebo plus chemotherapy group were consistent with survival outcomes in the overall population. Similarly, survival outcomes in patients from Asian and non-Asian regions (appendix p 11) were also consistent with survival outcomes observed in the overall population.

Adverse events occurred in 370 (100%) patients in the pembrolizumab plus chemotherapy group versus 368 (99%) in the placebo plus chemotherapy group (table 2). Adverse events of grade 3 or higher occurred in 318 (86%) patients in the pembrolizumab plus

chemotherapy group versus 308 (83%) in the placebo plus chemotherapy group; decreased neutrophil count (89 [24%] patients *vs* 64 [17%]), anaemia (63 [17%] *vs* 81 [22%]), and neutropenia (54 [15%] *vs* 61 [16%]) were the most common. Treatment discontinuation due to adverse events occurred in 90 (24%) patients in the pembrolizumab plus chemotherapy group versus 74 (20%) in the placebo plus chemotherapy group. Death due to adverse events occurred in 28 (8%) patients in the pembrolizumab plus chemotherapy group versus 38 (10%) in the placebo plus chemotherapy group. Treatment-related adverse events occurred in 364 (98%) patients in the pembrolizumab plus chemotherapy group versus 360 (97%) in the placebo plus chemotherapy group. Grade 3 or higher treatment-related adverse events occurred in 266 (72%) patients in the pembrolizumab plus chemotherapy group versus 250 (68%) in the placebo plus chemotherapy group, with deaths due to treatment-related events occurring in nine (2%) versus five (1%) patients respectively.

Immune-mediated adverse events and infusion reactions occurred in 95 (26%) patients in the pembrolizumab plus chemotherapy group versus 43 (12%) in the placebo plus chemotherapy group; hypothyroidism (40 [11%] *vs* 24 [7%]), pneumonitis (23 [6%] *vs* 2 [1%]), and hyperthyroidism (21 [6%] *vs* 3 [1%]) were the most common (table 2). Grade 3 or higher immune-mediated adverse events and infusion reactions occurred in 26 (7%) patients in the pembrolizumab plus chemotherapy group versus eight (2%) in the placebo plus chemotherapy group, with death due to pneumonitis occurring in two (1%) versus one (<1%) patients respectively.

	Pembrolizumab plus chemotherapy group (n=370)		Placebo plus chemotherapy group (n=370)	
	Any	Grade ≥3	Any	Grade ≥3
(Continued from previous page)				
Adverse events of special interest†				
Hypothyroidism	40 (11%)	0	24 (6%)	0
Pneumonitis	23 (6%)	2 (1%)	2 (1%)	1 (<1%)
Hyperthyroidism	21 (6%)	1 (<1%)	3 (1%)	0
Colitis	8 (2%)	4 (1%)	6 (2%)	3 (1%)
Infusion reactions	6 (2%)	1 (<1%)	4 (1%)	0
Hepatitis	5 (1%)	5 (1%)	0	0
Adrenal insufficiency	4 (1%)	2 (1%)	2 (1%)	0
Severe skin reactions	4 (1%)	4 (1%)	2 (1%)	2 (1%)
Hypophysitis	3 (1%)	1 (<1%)	0	0
Pancreatitis	2 (1%)	0	1 (<1%)	1 (<1%)
Myositis	1 (<1%)	1 (<1%)	0	0
Nephritis	1 (<1%)	0	2 (1%)	1 (<1%)
Thyroiditis	1 (<1%)	0	0	0
Type 1 diabetes	1 (<1%)	1 (<1%)	0	0

Data are n (%). The as-treated population included all patients who were randomly assigned to a treatment group and received at least one dose of study treatment. *Treatment-related adverse events with incidence of 5% or higher in any group are shown; treatment-related grade 5 events included febrile neutropenia, diarrhoea, multiple organ dysfunction, hepatic failure, pneumonia, acute kidney injury, interstitial lung disease, pneumonitis, and pulmonary embolism, which each occurred in one patient in the pembrolizumab plus chemotherapy group, and febrile neutropenia, death, multiple organ dysfunction syndrome, sepsis, and interstitial lung disease, which each occurred in one patient in the placebo plus chemotherapy group. †Immune-mediated adverse events and infusion reactions were based on a list of terms specified by the sponsor, regardless of attribution to any study treatment by investigators.

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

Discussion

In this phase 3 study, pembrolizumab plus chemotherapy provided significant and clinically meaningful improvements in overall survival, progression-free survival, and objective response rates compared with placebo plus chemotherapy in patients with unresectable, locally advanced or metastatic, oesophageal cancer or Siewert type 1 gastro-oesophageal junction cancer in the first-line setting. To our knowledge, this is the first study to show a significant survival benefit with immunotherapy plus chemotherapy in the first-line setting for oesophageal cancer. These data support the recent US Food and Drug Administration approval of pembrolizumab plus chemotherapy in first-line therapy for advanced or metastatic oesophageal or gastro-oesophageal junction cancer.[15]

According to hierarchical testing, overall survival was significantly improved with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more (HR 0·57), oesophageal squamous cell carcinoma (0·72), PD-L1 CPS of 10 or more (0·62), and in all randomised patients (0·73). There was early divergence, without overlap, of the overall survival Kaplan-Meier curves in favour of pembrolizumab plus chemotherapy. This separation and subsequent plateau were sustained over time, indicating a long-term overall survival benefit with pembrolizumab plus chemotherapy in patients with advanced oesophageal cancer. The estimated 24-month overall survival rates were higher with pembrolizumab plus chemotherapy than with placebo plus chemotherapy in each patient population, with a two-fold increase observed with pembrolizumab plus chemotherapy versus placebo plus chemotherapy in patients with PD-L1 CPS of 10 or more, and patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more (31% *vs* 15% in both populations).

The overall survival benefit observed with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy was supported by significant improvement in progression-free survival in patients with oesophageal squamous cell carcinoma (HR 0·65), PD-L1 CPS of 10 or more (0·51), and in all randomised patients (0·65), and by 12-month and 18-month progression-free survival rates that were consistently higher in the pembrolizumab plus chemotherapy group than in the placebo plus chemotherapy group. A similar proportion of patients in each study group (45% *vs* 48%) received subsequent anticancer therapy of a similar type, suggesting that the overall survival benefit observed with pembrolizumab plus chemotherapy was not confounded by subsequent anticancer treatment. The

higher objective response rate with pembrolizumab plus chemotherapy than with placebo plus chemotherapy (45·0% *vs* 29·3%) in all randomised patients, longer duration of response (median 8·3 months *vs* 6·0 months), and almost three-fold increase in patients with response duration of 24 months or longer (18% *vs* 6%), all suggest durability of the overall survival benefit observed with pembrolizumab plus chemotherapy.

The overall survival benefit observed in patients with adenocarcinoma including gastro-oesophageal adenocarcinoma (HR 0·74 [95% CI 0·54–1·02]) was consistent with that observed in all randomised patients (0·73 [0·62–0·86]). This overall survival benefit in patients with adenocarcinoma, who constituted 27% of the study population in KEYNOTE-590, was similar to that observed with nivolumab plus chemotherapy in patients with adenocarcinoma in CheckMate 649.[16] Patients with PD-L1 CPS of less than 10 experienced a modest survival benefit with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy (HR 0·86 [95% CI 0·68–1·10]), but the risk of death was lower in patients with PD-L1 CPS of 10 or more (0·62 [0·43–0·75]). In CheckMate 649, overall survival was improved with nivolumab plus chemotherapy versus chemotherapy alone in patients with CPS of 5 or more (HR 0·71 [98·4% CI 0·59–0·86]) compared with in all randomised patients (0·80 [99·3% CI 0·68–0·94]).[16] Interestingly, the survival benefit with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy appeared to be enhanced in patients from Asian regions (HR 0·64 [95% CI 0·51–0·81]) compared with patients from non-Asian regions (0·83 [0·66–1·05]). This finding is consistent with data from previous studies where patients with oesophageal cancer from Asian regions, typically with squamous cell carcinoma histology, experienced greater treatment benefit than those from non-Asian regions in response to treatment with immune checkpoint inhibitors.[10,11]

Multiple studies have examined the efficacy of the immune checkpoint inhibitor plus chemotherapy combination in gastric or oesophageal cancers but the results have varied. Although between-study comparisons are difficult, and KEYNOTE-590 was predominantly a study in oesophageal cancer whereas CheckMate 649 predominantly enrolled patients with gastric cancer, there was some overlap between the two studies. CheckMate 649 included a subgroup of patients with oesophageal (12%) or gastro-oesophageal junction (18%) adenocarcinoma, compared with KEYNOTE-590 where approximately 15% had oesophageal adenocarcinoma and 12% had Siewert type 1 gastro-oesophageal adenocarcinoma. In a subgroup analysis in CheckMate 649, overall survival with nivolumab plus chemotherapy versus chemotherapy alone in patients with oesophageal adenocarcinoma (CPS ≥5) was median 11·2 months versus 11·3 months (HR 0·78 [95% CI 0·51–1·21]) and in patients with gastro-oesophageal adenocarcinoma was median 14·2 months versus 13·1 months (HR 0·84 [0·57–1·22]).[16]

In the phase 3 KEYNOTE-062 and ATTRACTION-4 studies, overall survival was numerically longer but not significantly different with pembrolizumab plus chemotherapy (HR 0·85 [95% CI 0·70–1·03]) or nivolumab plus chemotherapy (0·90 [0·75–1·08]) compared with chemotherapy alone in patients with advanced gastric or gastro-oesophageal cancer, including in patients with PD-L1-expressing tumours.[17,18] A potential contributing factor for the absence of a significant overall survival benefit observed in these studies might be the study population size differences among these studies, and contribution of post-study treatment with anticancer agents. How the differences between these studies, alone or in combination, might have influenced the disparate results observed remains to be determined.[16–19]

The significant benefit observed with first-line pembrolizumab plus chemotherapy in all randomised patients in KEYNOTE-590 was also contrasted by the more modest benefit observed with third-line and second-line pembrolizumab monotherapy versus chemotherapy in the phase 2 KEYNOTE-180 and phase 3 KEYNOTE-181 studies of pembrolizumab in advanced oesophageal cancer.[10,11] An explanation, beyond the combination with chemotherapy, is that patients who have been previously treated with fewer lines of therapy (ie, in the first-line setting) might have less refractory and immunosuppressive tumour microenvironments than patients who have progressed on therapy.[20] Moreover, previous studies have shown that efficacy of immune checkpoint inhibitors is increased in earlier lines of therapy across multiple tumour types compared with in later lines of therapy.[21–25]

Of note, although the submission of a viable tumour specimen for evaluation of PD-L1 expression was mandatory for enrolment in KEYNOTE-590, the study was not enriched for patients with high PD-L1 expression as PD-L1 status was not required for stratification or randomisation. The proportion of patients with PD-L1 CPS of 10 or more were similar between the study groups (50% *vs* 52%). Interestingly, the proportion of patients with tumours expressing high levels of PD-L1 in the first-line studies KEYNOTE-590 (51% with PD-L1 CPS ≥10) and CheckMate 649 (60% with PD-L1 CPS ≥5), although detected by different anti-PD-1 antibody clones (22C3 and 28-8, respectively), were higher than observed in the previous second-line study of pembrolizumab in patients with advanced oesophageal cancer (KEYNOTE-181) and the third-line study of nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer (ATTRACTION-2).[11,26,27]

Specifically, 222 (35%) of 628 patients in KEYNOTE-181 had PD-L1 CPS of 10 or more and 26 (13%) of 193 patients in ATTRACTION-2 had PD-L1-positive tumours.[11,26] Although the reason for this phenomenon is unclear,

a potential explanation could be change in PD-L1 expression after previous chemotherapy.[28]

A limitation of this study is the inclusion of both adenocarcinoma and squamous cell carcinoma histologies, as responses to the immune checkpoint inhibitor and chemotherapy combination might differ between these groups, and the study was not powered to address differences adequately in the small subgroup of patients with adenocarcinoma. However, we believe that inclusion of both histologies is representative of the global epidemiology of oesophageal cancer.[29] Additional limitations are that we did not stratify based on PD-L1 status, and that 34% of patients with gastro-oesophageal junction adenocarcinoma had unknown HER2/neu status as testing was not mandated if not required locally.

A similar proportion of treatment-related (98% *vs* 97%) and grade 3 or higher treatment-related (72% *vs* 68%) adverse events were reported in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups. Most immune-mediated adverse events and infusion reactions reported in the pembrolizumab plus chemotherapy group were grade 1–2 and were consistent with the known safety profile of pembrolizumab. The safety profile reported for pembrolizumab plus chemotherapy compared with placebo plus chemotherapy was similar to that which has been previously reported, with no new safety signals observed.[12,18,24] Details on health-related outcomes with first-line pembrolizumab plus chemotherapy versus chemotherapy alone in patients with advanced oesophageal cancer is the subject of a separate publication.[30]

Fluoropyrimidine plus platinum-based chemotherapy has been a mainstay of the treatment landscape for patients with untreated, advanced oesophageal cancer for about four decades, without any significant improvements in patient overall survival during that time. KEYNOTE 590 is, to our knowledge, the first global phase 3 study to show that the combination of an immune checkpoint inhibitor with chemotherapy in patients with previously untreated, advanced or metastatic, oesophageal or Siewert type 1 gastro-oesophageal cancer results in a significant and clinically meaningfully improvement in overall and progression-free survival, and objective response, compared with chemotherapy alone. These data show that, compared with placebo plus chemotherapy, pembrolizumab plus chemotherapy significantly improved overall survival and progression-free survival in patients with untreated, advanced oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, or PD-L1 CPS of 10 or more, and in all randomised patients regardless of histology, with a manageable safety profile in the total as-treated population. Pembrolizumab plus chemotherapy should be considered for patients with unresectable, metastatic oesophageal cancer in the first-line setting.

Contributors

J-MS, MAS, TD, TK, J-PM, S-BK, QL, SS, PB, and KK contributed to the conception, design, and planning of the study. J-MS, LS, MAS, PE, TK, ZL, BCC, WM, S-HL, PS, EG, HH, LA, CF, and VCO contributed to the acquisition of data. J-MS, MAS, TD, J-PM, S-BK, BCC, WM, and QL contributed to the analysis of data. QL, SS, and PB accessed and verified the data. J-MS, LS, MAS, PE, AA, TD, J-PM, S-BK, BCC, WM, MAM, EG, LA, CF, AT, SS, PB, and KK contributed to the interpretation of results. All authors contributed to the drafting or critical review and revision of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

J-MS reports research funding to the institution by Merck Sharp & Dohme (MSD; a subsidiary of Merck), AstraZeneca, and Ono Pharmaceuticals, during the conduct of the study. LS reports research funding to the institution by MSD, grants from Beijing Xiantong Biomedical Technology, Qily Pharmaceutical, Zaiding Pharmaceutical, Jacobio Pharmaceuticals, and Beihai Kangcheng Medical Technology, and consulting fees from HARBOUR and Merck, during the conduct of the study. MAS reports funding to the institution from MSD, Bristol Myers Squibb (BMS), and Oncolys BioPharma, during the conduct of the study. PE reports funding to the institution from MSD, during the conduct of the study, and personal fees from MSD, AstraZeneca, Celgene, Daiichi Sankyo, Five Prime, Lilly, Loxo, Taiho, Takeda, and Zymeworks, outside of the submitted work. AA reports funding to the institution from MSD, BMS, and Bayer Pharmaceuticals, during the conduct of the study, and personal fees from MSD and BMS, and personal fees for advisory role from Merck Serono and Servier, outside of the submitted work. TD reports funding to the institution from MSD, Daiichi Sankyo, Sumitomo Dainippon, AbbVie, Novartis, Boehringer Ingelheim, Taiho Pharmaceutical, Merck Serono, BMS, Pfizer, Lilly, Kyowa Hakko, Kirin, and IQVIA, during the conduct of the study, and personal fees for consulting or advisory role from MSD, Daiichi Sankyo, Amgen, Sumitomo Dainippon, Taiho Pharmaceutical, Takeda, AbbVie, Novartis, Bayer, Boehringer Ingelheim, Rakuten Medical, and BMS, and honoraria from Ono Pharmaceutical, Astellas Pharma, Oncolys BioPharma, Taiho Pharmaceutical, and Otsuka, outside of the submitted work. TK reports funding to the institution from MSD, Ono Pharmaceutical, Shionogi, Astellas Amgen Bio Pharma, and Taiho Pharmaceutical, during the conduct of the study, and personal fees from MSD, Ono Pharmaceutical, Merck, Astellas Pharma, BMS, and Oncolys BioPharma, outside of the submitted work. J-PM reports funding to the institution from MSD, during the conduct of the study, and honoraria from MSD, Bayer, and BMS, outside of the submitted work. ZL reports funding to the institution from MSD, during the conduct of the study. S-BK reports funding to the institution from MSD, Novartis, and Sanofi-Genzyme, during the conduct of the study, and personal fees for consulting or advisory role from Dae Hwa Pharmaceutical, ISU Abxis, and Daiichi-Sankyo, outside of the submitted work. BCC reports funding to the institution from MSD, Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, AbbVie, Medpacto, G Innovation, Eli Lilly, Blueprint Medicines, and Interpark Bio Convergence, fees for consulting or advisory role from Novartis, AstraZeneca, Boehringer Ingelheim, Roche, BMS, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, MSD, Janssen, Medpacto, Blueprint Medicines, KANAPH Therapeutic, Brigebio Therapeutics, Cyrus Therapeutics, and Guardant Health, stock ownership in TheraCanVac, Gencurix, Bridgebio Therapeutics, KANAPH Therapeutic, Cyrus Therapeutics, and Interpark Bio Convergence, personal fees for Board of Directorship from Gencurix and Interpark Bio Convergence, royalties from Champions Oncology, and is the founder of DAAN Biotherapeutics, outside of the submitted work. MAM reports funding to the institution from MSD, during the conduct of the study, and consultancy for MSD, BMS, Servier, and Lilly, and honoraria from BMS, Servier, and Amgen, outside of the submitted work. EG reports funding to the institution from MSD, during the conduct of the study, and personal fees from MSD, BMS, Servier, and Roche, outside of the submitted work. HH reports funding to the institution from MSD, during the conduct of the study, and grants from AstraZeneca, Daiichi Sankyo, Dainippon Sumitomo Pharma, Merck Biopharma, MSD, Taiho, Chugai, Eisai, LSK BioPharma, Incyte, Pfizer, Boehringer Ingelheim, Beigene, Ono, BMS, and Astellas, and

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Data sharing

MSD, a subsidiary of Merck, is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the USA and the EU or after product development is discontinued. There are circumstances that might prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal, so that the requestor can perform the proposed analyses.

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