Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial

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Summary

Background PD-1 inhibitors combined with chemotherapy have shown efficacy in gastric or gastro-esophageal junction cancer. We compared the efficacy and safety of pembrolizumab plus chemotherapy with placebo plus chemotherapy in participants with locally advanced or metastatic HER2-negative gastric or gastro-esophageal junction adenocarcinoma.

Methods KEYNOTE-859 is a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial, done at 207 medical centres across 33 countries. Eligible participants were aged 18 years and older with previously untreated histologically or cytologically confirmed locally advanced or metastatic HER2-negative gastric or gastro-esophageal junction adenocarcinoma and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned (1:1) to receive pembrolizumab or placebo 200 mg, administered intravenously every 3 weeks for up to 35 cycles. All participants received investigator's choice of fluorouracil (intravenous, 800 mg/m² per day) administered continuously on days 1–5 of each 3-week cycle plus cisplatin (intravenous, 80 mg/m²) administered on day 1 of each 3-week cycle or capecitabine (oral, 1000 mg/m²) administered twice daily on days 1–14 of each 3-week cycle plus oxaliplatin (intravenous, 130 mg/m²) administered on day 1 of each 3-week cycle. Randomisation was done using a central interactive voice-response system and stratified by geographical region, PD-L1 status, and chemotherapy in permuted block sizes of four. The primary endpoint was overall survival, assessed in the intention-to-treat (ITT) population, and the populations with a PD-L1 combined positive score (CPS) of 1 or higher, and PD-L1 CPS of 10 or higher. Safety was assessed in the as-treated population, which included all randomly assigned participants who received at least one dose of study intervention. Here, we report the results of the interim analysis. This study is registered with ClinicalTrials.gov, NCT03675737, and recruitment is complete.

Findings Between Nov 8, 2018, and June 11, 2021, 1579 (66%) of 2409 screened participants were randomly assigned to receive pembrolizumab plus chemotherapy (pembrolizumab group; n=790) or placebo plus chemotherapy (placebo group; n=789). Most participants were male (527 [67%] of 790 participants in the pembrolizumab plus chemotherapy group; 544 [69%] of 789 participants in the placebo plus chemotherapy group) and White (426 [54%]; 435 [55%]). Median follow-up at the data cutoff was 31·0 months (IQR 23·0–38·3). Median overall survival was longer in the pembrolizumab group than in the placebo group in the ITT population (12·9 months [95% CI 11·9–14·0] *vs* 11·5 months [10·6–12·1]; hazard ratio [HR] 0·78 [95% CI 0·70–0·87]; p<0·0001), in participants with a PD-L1 CPS of 1 or higher (13·0 months [11·6–14·2] *vs* 11·4 months [10·5–12·0]; 0·74 [0·65–0·84]; p<0·0001), and in participants with a PD-L1 CPS of 10 or higher (15·7 months [13·8–19·3] *vs* 11·8 months [10·3–12·7]; 0·65 [0·53–0·79]; p<0·0001). The most common grade 3–5 adverse events of any cause were anaemia (95 [12%] of 785 participants in the pembrolizumab group *vs* 76 [10%] of 787 participants in the placebo group) and decreased neutrophil count (77 [10%] *vs* 64 [8%]). Serious treatment-related adverse events occurred in 184 (23%) participants in the pembrolizumab group and 146 (19%) participants in the placebo group. Treatment-related deaths occurred in eight (1%) participants in the pembrolizumab group and 16 (2%) participants in the placebo group. No new safety signals were identified.

Interpretation Participants in the pembrolizumab plus chemotherapy group had a significant and clinically meaningful improvement in overall survival with manageable toxicity compared with participants in the placebo plus chemotherapy group. Therefore, pembrolizumab with chemotherapy might be a first-line treatment option for patients with locally advanced or metastatic HER2-negative gastric or gastro-esophageal junction adenocarcinoma.

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed and Google Scholar from database inception to June 2, 2023, for randomised, controlled trials published in English, using the terms "PD-1 inhibitor" OR "PD-L1 inhibitor" OR "immune checkpoint inhibitor" AND "previously untreated" OR "treatment naïve" OR "first-line therapy" AND "unresectable" OR "metastatic" AND "gastric cancer" OR "gastroesophageal junction cancer."

Five randomised controlled trials relevant to the present study were identified. Results of the phase 3 KEYNOTE-062 trial found that among participants with untreated advanced HER2-negative gastric or gastro-esophageal junction cancer and PD-L1 combined positive score (CPS) of 1 or higher, pembrolizumab monotherapy was non-inferior to chemotherapy for overall survival, and both pembrolizumab and pembrolizumab plus chemotherapy were not superior to chemotherapy for the overall survival or progression free survival endpoints tested. In the phase 3 ATTRACTION-4 trial, nivolumab plus chemotherapy significantly improved progression-free survival, but not overall survival in Asian participants with untreated, HER2-negative, unresectable advanced or recurrent gastric or gastro-esophageal junction cancer. The phase 3 CheckMate 649 trial showed that nivolumab plus chemotherapy significantly improved overall survival and progression free survival compared with chemotherapy alone for participants with previously untreated advanced HER2-negative gastric, gastro-esophageal junction, or oesophageal adenocarcinoma and PD-L1 CPS of 5 or higher. The phase 3 ORIENT-16 trial showed that sintilimab plus chemotherapy significantly improved overall survival compared with placebo plus chemotherapy in participants with non-HER2-positive gastric or gastro-esophageal junction adenocarcinoma. Additionally, the phase 3 RATIONALE 305 trial showed that the PD-1 inhibitor tislelizumab plus chemotherapy provided significant and clinically meaningful improvement in overall survival versus chemotherapy alone, with acceptable safety in 546 participants with PD-L1–positive gastric or gastro-esophageal junction adenocarcinoma.

Added value of this study

The KEYNOTE-859 trial demonstrated the efficacy and manageable toxicity of pembrolizumab plus chemotherapy (capecitabine plus oxaliplatin or fluorouracil plus cisplatin) as first-line treatment for participants with locally advanced or metastatic HER2-negative gastric or gastro-esophageal junction adenocarcinoma. Participants in the pembrolizumab plus chemotherapy group had significantly improved overall survival, progression-free survival, and objective response rate compared with the placebo plus chemotherapy group.

Implications of all the available evidence

Data from the KEYNOTE-859 trial provide a novel treatment option to address a high unmet medical need for highly efficacious and safe therapies in the treatment of patients with previously untreated locally advanced unresectable or metastatic HER2-negative gastric or gastro-esophageal junction adenocarcinoma.

Introduction

Gastric and gastro-esophageal junction cancer are frequently asymptomatic in the early stages and, as a result, are often diagnosed at advanced disease stages.[1,2] The standard first-line palliative chemotherapy regimen is a combination of a platinum drug (cisplatin or oxaliplatin) and a fluoropyrimidine (fluorouracil, capecitabine, or S-1).[3] Despite improvements in available treatments, 5-year survival for advanced gastric or gastro-esophageal junction cancer is approximately 10%.[2] In contrast to cytotoxic chemotherapy, immune checkpoint inhibitors provide a different mechanism for antitumour activity: malignant cells promote an immunosuppressive tumour microenvironment by releasing cytokines that stimulate inhibitory immune checkpoints, and immune checkpoint inhibitors block these effects.[4] Preclinical models of other cancers have suggested that chemotherapy could potentially enhance the antitumour response elicited by immune checkpoint inhibitors by inducing immune-mediated cell death.[5,6]

In several trials done in the past 2 years,[7–11] combinations of immune checkpoint inhibitors and standard chemotherapy have improved survival versus chemotherapy alone for patients with advanced HER2-negative gastric or gastro-esophageal junction adenocarcinoma. Addition of the PD-1 inhibitor nivolumab to chemotherapy significantly improved overall survival and progression-free survival in the phase 3 CheckMate 649 trial[7,8] and significantly improved progression-free survival in Asian participants in the phase 3 ATTRACTION-4 trial.[9] Similarly, the PD-1 inhibitor sintilimab plus chemotherapy significantly improved overall survival versus chemotherapy alone in the phase 3 ORIENT-16 trial.[10,11]

Although the results of KEYNOTE-062 did not show superiority of pembrolizumab versus chemotherapy for overall survival or progression-free survival,[12] other evidence from the past 5 years has shown that the combination of the PD-1 inhibitor pembrolizumab with standard-of-care chemotherapy improves clinical outcomes in advanced unresectable or metastatic cancers,[13] and KEYNOTE-059 and KEYNOTE-061 showed the antitumour activity of pembrolizumab monotherapy in gastric or gastro-esophageal cancer.[14,15] We aimed to assess whether the addition of pembrolizumab to standard chemotherapy improved efficacy compared with chemotherapy alone in patients with previously untreated advanced HER2-negative gastric or gastro-esophageal junction adenocarcinoma.

Methods

Study design and participants

KEYNOTE-859 is a double-blind, randomised, phase 3 study done at 207 medical centres across 33 countries (appendix pp 2–7). Eligible individuals were aged 18 years or older, had histologically or cytologically confirmed adenocarcinoma of the stomach or gastro-esophageal junction that was locally advanced but unresectable or metastatic, had received no previous treatment for their cancer, had tumours that were HER2-negative, had measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) by investigator assessment, had provided tumour tissue adequate for PD-L1 assessment, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had adequate organ function. Individuals were excluded if they had squamous cell or undifferentiated gastric cancer, known history of hepatitis B infection, known history of active hepatitis C infection, diagnosis of immunodeficiency or history of receiving chronic systemic immuno-suppressant therapy, known history of HIV disease, active autoimmune disease requiring treatment, or active CNS metastases. Full eligibility criteria are available in the protocol (appendix).

The study protocol and amendments, including changes that affected study design (appendix), were approved by the appropriate local or national ethics committee at each participating centre. All participants provided written informed consent. The study was done in accordance with the Good Clinical Practice requirements outlined by the International Council on Harmonisation, the ethical principles of the Declaration of Helsinki, and all local regulations.

Randomisation and masking

Participants were randomly assigned (1:1) to receive pembrolizumab or placebo by study investigators using a central interactive voice-response system (Almac Clinical Technologies, Souderton, PA, USA) and a randomisation schedule generated by the study funder. Randomisation was stratified by geographical region (western Europe, Israel, North America, and Australia *vs* Asia *vs* rest of world), PD-L1 combined positive score (CPS; <1 *vs* ≥1), and investigator's choice of chemotherapy (fluorouracil plus cisplatin *vs* capecitabine plus oxaliplatin). Participants were randomly assigned in permuted block sizes of four per stratum, with a total of 12 strata. Participants, investigators, and individuals collecting or analysing the data, including representatives of the funder, were masked to treatment assignment. The final database was not unmasked until medical and scientific review was performed, protocol deviations were identified, and data were declared final and complete. In the event of medical emergency, treatment assignment could be unmasked by contacting an emergency unmasking call centre.

Procedures

HER2 status was determined locally during screening using immunohistochemistry or in-situ hybridisation. HER2 negativity was defined as an immunohistochemical score of 0 or 1+, and as a *HER2* to *CEP17* ratio of less than 2 with an average *HER2* copy number of less than 4·0 signals per cell if assessed by in-situ hybridisation. PD-L1 CPS was determined during screening at a central laboratory (Q² Solutions, Scotland, UK; Q² Solutions, Beijing, China; Q² Solutions, Singapore) in formalin-fixed paraffin-embedded tumour tissue using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA, USA). PD-L1 CPS was calculated as the number of PD-L1-staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100. Prespecified validated cutoffs for both PD-L1 CPS of 1 or higher and 10 or higher were used. Microsatellite instability status was assessed in tumour tissue at a central laboratory by PCR (Almac Diagnostics, Armagh, UK).

Pembrolizumab 200 mg or placebo was administered intravenously on day 1 of each 3-week cycle for up to 35 cycles (approximately 2 years of treatment). Chemotherapy regimens were investigator's choice of fluorouracil (intravenous, 800 mg/m² per day) administered continuously on days 1 to 5 of each 3-week cycle plus cisplatin (intravenous, 80 mg/m²) administered on day 1 of each 3-week cycle or capecitabine (oral, 1000 mg/m²) administered twice daily on days 1 to 14 of each 3-week cycle plus oxaliplatin (intravenous, 130 mg/m²) administered on day 1 of each 3-week cycle. Cisplatin and oxaliplatin could be limited to six cycles in accordance with local guidelines. All treatment was administered until disease progression, unacceptable toxicity, investigator decision, withdrawal of consent, completion of the maximum number of cycles, or other reasons (non-compliance with study treatment or procedure requirements, prohibited concomitant medication requiring withdrawal, interruption of pembrolizumab treatment lasting more than 12 consecutive weeks, confirmed positive serum pregnancy test, or recurrent grade 2 pneumonitis). Participants who discontinued one or more chemotherapy drugs because of toxicity could continue to receive pembrolizumab or placebo; participants who discontinued pembrolizumab or placebo because of toxicity could continue to receive chemotherapy. Crossover between groups was not permitted. Full details regarding treatment decisions, including guidelines for treatment interruption and discontinuation and dose reductions to manage adverse events (dose reductions of pembrolizumab and placebo were not permitted), are in the protocol (appendix).

CT (preferred) or contrast-enhanced MRI of the abdomen and pelvis was performed within 4 weeks before randomisation, 6 weeks after the date of randomisation, and every 6 weeks thereafter until confirmed disease progression (assessed according to RECIST [version 1.1]

by masked independent central review), or start of new anti-cancer treatment, or consent withdrawal. Following treatment discontinuation, survival was assessed every 12 weeks by telephone or scheduled visit until death, consent withdrawal, or study end.

Physical examination and laboratory, haematology, and chemistry analyses were done during screening, regularly during study treatment, and at the end of treatment according to the protocol (appendix). Adverse events and laboratory abnormalities were assessed regularly throughout treatment and up to 30 days after discontinuation (up to 90 days for serious events in the absence of new anticancer therapy) by telephone or scheduled visit and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Potentially immune-mediated adverse events were based on a list of terms prepared by the funder and were considered regardless of attribution to study treatment by the investigator. Patient-reported outcomes were completed before any procedures or assessments every 3 weeks until cycle 5, then every 6 weeks thereafter. Data on sex and race or ethnicity were self-reported by participants.

Outcomes

The primary endpoint was overall survival, defined as time from randomisation to death due to any cause. Secondary endpoints were progression-free survival, defined as time from randomisation to first documented progressive disease or death due to any cause, whichever occurred first; objective response rate, defined as the proportion of participants with a best overall response of complete or partial response; duration of response, defined as the time from first complete or partial response until disease progression or death due to any cause, whichever occurred first; and safety. All secondary efficacy endpoints were assessed according to RECIST (version 1.1) per masked independent central review. Change from baseline in health-related quality-of-life assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire (QLQ-C30) and EORTC QLQ-STO22 (gastric), and time to deterioration in EORTC QLQ-C30 subscales and QLQ-STO22 pain scale were prespecified exploratory endpoints. Additional prespecified exploratory endpoints were progression-free survival and objective response rate (assessed according to modified RECIST version 1.1 as per investigator), and characterisation of utilities using the EuroQol 5-dimension 5-level scores after treatment administration and will be reported separately elsewhere.

Statistical analysis

The graphical method of Maurer and Bretz[16] was used to control the family-wise type I error rate at a one-sided α of 0·025 across all hypotheses, a single interim analysis, and the final analysis. A one-sided α of 0·008 was allocated to test overall survival in the intention-to-treat (ITT) population and 0·017 was allocated to test overall survival in the population with a PD-L1 CPS of 10 or higher (appendix p 8). If the null hypothesis for overall survival was rejected for the PD-L1 CPS of 10 or higher population, overall survival could be tested for the PD-L1 CPS of 1 or higher population at an α of 0·017. If the null hypothesis for overall survival was rejected for both the population with a PD-L1 CPS of 10 or higher and the ITT population, overall survival could be tested in the population with a PD-L1 CPS of 1 or higher at an α of 0·025. For testing overall survival at the interim analysis, the α boundary was calculated based on the actual information fraction of the observed number of overall survival events at the interim analysis relative to the expected number of overall survival events at final analysis using the LanDeMets O'Brien-Fleming spending function. On rejection of the null hypothesis for overall survival in the ITT, PD-L1 CPS of 10 or higher, and PD-L1 CPS of 1 or higher populations, the secondary efficacy endpoints of progression-free survival and objective response rate were tested hierarchically using a sequential testing strategy at a one-sided α of 0·025 (appendix p 8).

Efficacy endpoints of overall survival, progression-free survival, and objective response rate were evaluated in the ITT population, which included all randomly assigned patients, and for participants with a PD-L1 CPS of 1 or higher and a PD-L1 CPS of 10 or higher, as prespecified in the protocol. Safety was assessed in the as-treated population, defined as all randomly assigned participants who received at least one dose of study intervention.

The planned overall sample size of the ITT population was increased from 780 to 1542 in a protocol amendment dated Dec 12, 2019, after reviewing the results of KEYNOTE-062. A later amendment dated Nov 30, 2022, increased the sample size to 1579 to merge the China mainland population into the global study due to the short interval between last patient randomisation date of the global study and the China mainland extension. The planned sample size of the PD-L1 CPS of 1 or higher population was approximately 1235 participants, based on a prevalence of approximately 78% of all participants with tumours expressing PD-L1 CPS of 1 or higher.[17] Similarly, the planned sample size of the PD-L1 CPS of 10 or higher population was approximately 551 participants, based on a prevalence of approximately 35% of all participants with tumours expressing PD-L1 CPS of 10 or higher.[17] To account for a potential delayed treatment effect, a piecewise hazard ratio (HR) was assumed for overall survival and for progression-free survival with an HR of 1 in the delayed period and an HR of less than 1 afterwards. It was estimated that approximately 1358 overall survival events would occur in the ITT population at final analysis, resulting in 84% power to detect an average HR of 0·83 at the one-sided α of 0·008

significance level. For the PD-L1 CPS of 1 or higher population at final analysis, it was estimated that approximately 1057 overall survival events would occur, resulting in 90% power to detect an average HR of 0·81 at a one-sided α of 0·017. For the PD-L1 CPS of 10 or higher population at final analysis, it was estimated that approximately 463 overall survival events would occur, resulting in 87% power to detect an average HR of 0·73 at the one-sided α of 0·017 significance level.

Overall survival, progression-free survival, and duration of response were estimated using the non-parametric Kaplan-Meier method. Between-group differences in overall survival and progression-free survival were assessed using a stratified log-rank test. The HRs and associated 95% CIs for overall survival and progression-free survival were assessed using a stratified Cox proportional hazards model with the Efron method of handling ties. The proportional hazards assumption was evaluated using the Cox regression model with treatment and treatment by time interaction. The nominal p value for treatment by time interaction was 0·223 for overall survival and 0·785 for progression-free survival in the ITT population, suggesting that the proportional hazards assumption holds. Stratification factors used for randomisation were applied to both the stratified log-rank test and the stratified Cox model with small strata collapsed, as prespecified in the statistical analysis plan within the protocol (appendix). The difference in objective response rate (and corresponding 95% CI) between the two treatment groups was determined from the stratified Miettinen and Nurminen method[18] with strata weighting by sample size, with the same stratification factors used for overall survival. To assess consistency of treatment effect in prespecified subgroups for all α-controlled efficacy endpoints, an unstratified subgroup analysis of overall survival, progression-free survival, and objective response rate was also performed. Unstratified subgroup analyses by age (<65 years *vs* ≥65 years), sex (male *vs* female), race (Asian *vs* non-Asian), stratification factors, microsatellite instability status (high *vs* low or microsatellite stable), ECOG status (0 *vs* 1), disease status (locally advanced *vs* metastatic), primary location (stomach *vs* gastro-esophageal junction), histological subtype (diffuse *vs* intestinal *vs* indeterminate), liver metastases (yes *vs* no), previous gastrectomy or oesophagectomy (yes *vs* no), tumour burden (less than the median *vs* the median or higher), and number of metastases (≤2 *vs* ≥3) were prespecified for overall survival, progression-free survival, and objective response rate. Safety was assessed using descriptive statistics.

Patient-reported outcomes were assessed in the patient-reported outcomes full analysis set, defined as all randomly assigned participants who received at least one dose of study intervention and had at least one patient-reported outcomes assessment available for the specific endpoint. Mean change from baseline in patient-reported outcomes scores was assessed at the latest timepoint with a compliance rate of at least 80% for eligible participants who were expected to complete a patient-reported outcomes assessment and a completion rate of at least 60% for participants in the patient-reported outcomes full analysis set, selected at 18 weeks based on masked data review before the database lock. Treatment difference in terms of least-squares mean change from baseline was estimated from a constrained longitudinal data analysis model proposed by Liang and Zeger.[19] Time to true deterioration (first onset of 10-point or higher deterioration from baseline in a given scale or subscale with confirmation under right-censoring rule) was estimated using the Kaplan-Meier method, and the magnitude of treatment difference (HR) between treatment groups was determined using a stratified Cox proportional hazards model.

We did post-hoc sub-group analysis of overall survival, progression-free survival, and objective response rate in participants with a PD-L1 CPS of 1–9 and PD-L1 CPS of less than 10.

The protocol specified one interim analysis and a final analysis. The interim analysis was planned to occur when both approximately 403 overall survival events had occurred in the PD-L1 CPS of 10 or higher population and approximately 12 months had elapsed after the last participant was randomly assigned to treatment.

An independent data and safety monitoring committee oversaw the study and assessed efficacy and safety at the protocol-specified interim analysis. The data cutoff date for the interim analysis was Oct 3, 2022. Sample size and power and interim analysis calculations were performed using R software (version 4.2.1) packages gsDesign, gsDesign2, and gsdmvn. Statistical analyses were done using SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT03675737.

Role of the funding source

The study funder had a role in the study design, data collection, data analysis, data interpretation, and writing of the report. The funder maintained the study database and ensured that data were collected according to the protocol.

Results

Between Nov 8, 2018, and June 11, 2021, 2409 participants were screened for eligibility, of whom 1579 were randomly assigned to receive either pembrolizumab plus chemotherapy (n=790) or placebo plus chemotherapy (n=789; figure 1). In the ITT population, 1235 participants (78%) had tumours with a PD-L1 CPS of 1 or higher and 551 (35%) had PD-L1 CPS of 10 or higher. Capecitabine plus oxaliplatin was the choice of chemotherapy for 682 (86%) of 790 participants in the pembrolizumab group and 681 (86%) of 789 patients in the placebo group.

Baseline demographics and disease characteristics were generally balanced between treatment groups and

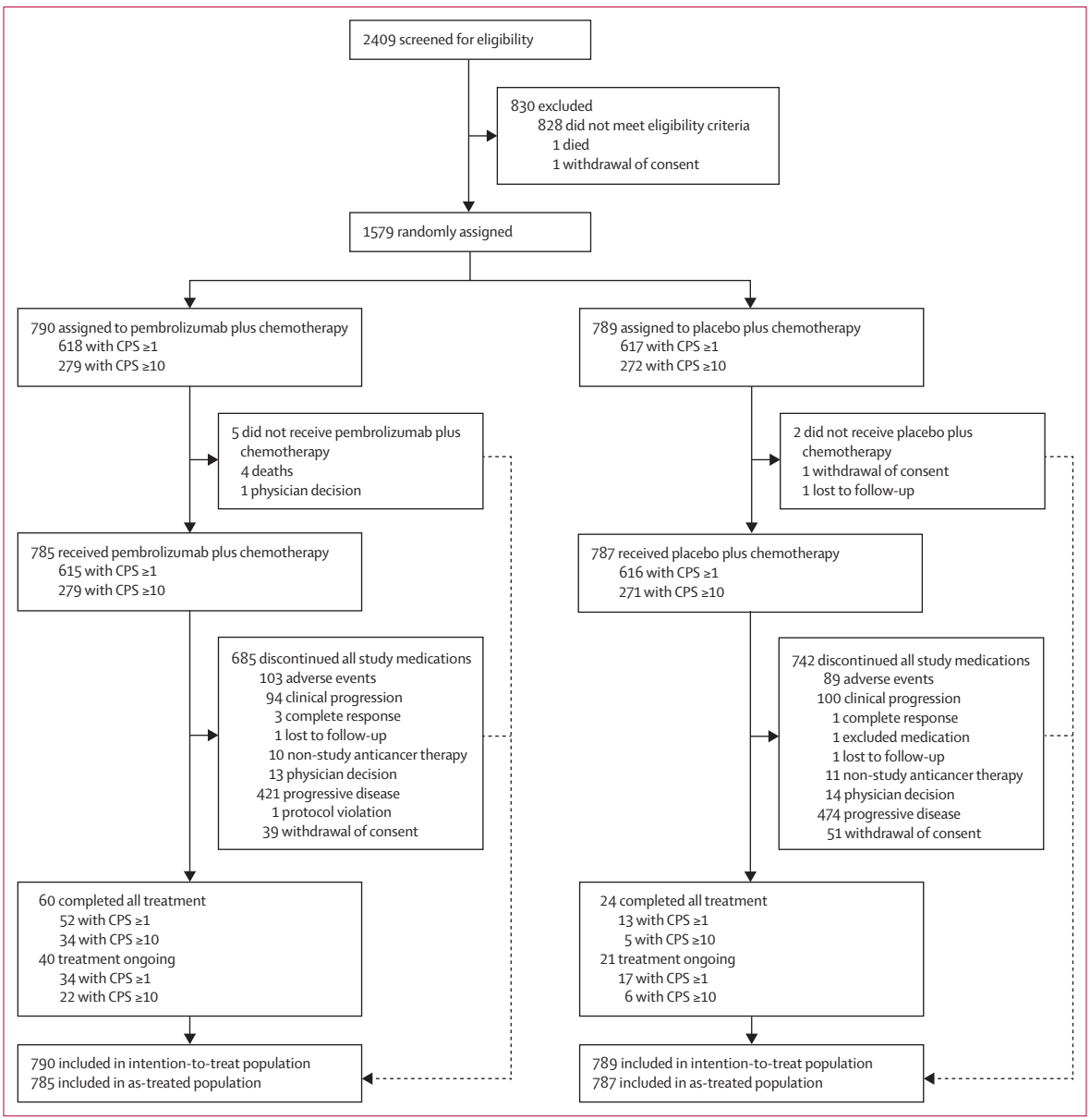


Figure 1: **Trial profile**
CPS=combined positive score. ITT=intention-to-treat.

between PD-L1 CPS subgroups (table 1). Most participants were male (527 [67%] of 790 participants in the pembrolizumab group and 544 [69%] of 789 participants in the placebo group), aged younger than 65 years (486 [62%] and 479 [61%]), non-Asian (520 [66%] and 520 [66%]), and had a ECOG performance status of 1 (509 [64%] and 488 [62%]). Most patients had not received previous gastrectomy or oesophagectomy (613 [78%] in the pembrolizumab group and 622 [79%] in the placebo group) and had adenocarcinoma of the stomach (640 [81%] and 603 [76%]). Clinically important protocol deviations occurred in two participants in the placebo group, both related to eligibility criteria (incorrect histology); there were no clinically important protocol deviations in the pembrolizumab group.

Median duration of follow-up, defined as the time from randomisation to data cutoff (Oct 3, 2022), was 31·0 months (IQR 23·0–38·3). Overall, 785 (99%) of 790 participants randomly assigned to the pembrolizumab group and 787 (>99%) of 789 participants randomly assigned to the placebo group received at least one dose of study treatment (figure 1). Among participants who received at least one dose of study treatment, 40 (5%) participants in the pembrolizumab group and 21 (3%) participants in the placebo group remained on study treatment at the data cutoff. Treatment was

	Pembrolizumab plus chemotherapy (n=790)			Placebo plus chemotherapy (n=789)		
	ITT (n=790)	PD-L1 CPS ≥1 (n=618)	PD-L1 CPS ≥10 (n=279)	ITT (n=789)	PD-L1 CPS ≥1 (n=617)	PD-L1 CPS ≥10 (n=272)
Age, years	61 (52–67)	62 (53–68)	63 (54–69)	62 (52–69)	63 (53–69)	63 (54–69)
<65	486 (62%)	377 (61%)	161 (58%)	479 (61%)	364 (59%)	159 (58%)
≥65	304 (38%)	241 (39%)	118 (42%)	310 (39%)	253 (41%)	113 (42%)
Sex*						
Female	263 (33%)	196 (32%)	86 (31%)	245 (31%)	169 (27%)	67 (25%)
Male	527 (67%)	422 (68%)	193 (69%)	544 (69%)	448 (73%)	205 (75%)
Race*						
American Indian or Alaskan Native	31 (4%)	24 (4%)	7 (3%)	36 (5%)	29 (5%)	11 (4%)
Asian	270 (34%)	206 (33%)	98 (35%)	269 (34%)	203 (33%)	89 (33%)
Black or African American	12 (2%)	7 (1%)	2 (1%)	9 (1%)	9 (1%)	5 (2%)
Multiple	43 (5%)	32 (5%)	16 (6%)	30 (4%)	25 (4%)	8 (3%)
Native Hawaiian or other Pacific Islander	1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0
White	426 (54%)	342 (55%)	155 (56%)	435 (55%)	343 (56%)	157 (58%)
Missing	7 (1%)	6 (1%)	0	8 (1%)	7 (1%)	2 (1%)
Geographical region						
Asia	263 (33%)	201 (33%)	96 (34%)	262 (33%)	200 (32%)	88 (32%)
Rest of world	326 (41%)	251 (41%)	105 (38%)	325 (41%)	251 (41%)	120 (44%)
Western Europe, Israel, North America, and Australia	201 (25%)	166 (27%)	78 (28%)	202 (26%)	166 (27%)	64 (24%)
ECOG performance status						
0	281 (36%)	223 (36%)	99 (35%)	301 (38%)	228 (37%)	103 (38%)
1	509 (64%)	395 (64%)	180 (65%)	488 (62%)	389 (63%)	169 (62%)
Primary tumour location						
Gastro-esophageal junction	149 (19%)	123 (20%)	65 (23%)	185 (23%)	164 (27%)	73 (27%)
Stomach	640 (81%)	494 (80%)	214 (77%)	603 (76%)	453 (73%)	199 (73%)
Other	0	0	0	1 (<1%)	0	0
Missing	1 (<1%)	1 (<1%)	0	0	0	0
Disease status						
Locally advanced	28 (4%)	26 (4%)	14 (5%)	30 (4%)	24 (4%)	11 (4%)
Metastatic	761 (96%)	591 (96%)	265 (95%)	759 (96%)	593 (96%)	261 (96%)
Missing	1 (<1%)	1 (<1%)	0	0	0	0
Histological subtype (Lauren classification[20])						
Diffuse	318 (40%)	236 (38%)	102 (37%)	301 (38%)	220 (36%)	89 (33%)
Intestinal	284 (36%)	239 (39%)	111 (40%)	273 (35%)	215 (35%)	99 (36%)
Indeterminate	186 (24%)	141 (23%)	65 (23%)	215 (27%)	182 (29%)	84 (31%)
Unknown	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0
Missing	1 (<1%)	1 (<1%)	0	0	0	0
Liver metastases						
No	475 (60%)	359 (58%)	160 (57%)	478 (61%)	364 (59%)	162 (60%)
Yes	314 (40%)	258 (42%)	119 (43%)	311 (39%)	253 (41%)	110 (40%)
Missing	1 (<1%)	1 (<1%)	0	0	0	0
Prior gastrectomy or oesophagectomy						
No	613 (78%)	506 (82%)	231 (83%)	622 (79%)	508 (82%)	231 (85%)
Yes	172 (22%)	109 (18%)	48 (17%)	162 (21%)	105 (17%)	40 (15%)
Missing	5 (1%)	3 (<1%)	0	5 (1%)	4 (1%)	1 (<1%)
Microsatellite instability status						
High	39 (5%)	35 (6%)	20 (7%)	35 (4%)	31 (5%)	16 (6%)
Low or microsatellite stable	641 (81%)	503 (81%)	227 (81%)	639 (81%)	500 (81%)	224 (82%)
Unknown	0	0	0	1 (<1%)	1 (<1%)	1 (<1%)
Missing	110 (14%)	80 (13%)	32 (11%)	114 (14%)	85 (14%)	31 (11%)

(Table 1 continues on next page)

	Pembrolizumab plus chemotherapy (n=790)			Placebo plus chemotherapy (n=789)		
	ITT (n=790)	PD-L1 CPS ≥1 (n=618)	PD-L1 CPS ≥10 (n=279)	ITT (n=789)	PD-L1 CPS ≥1 (n=617)	PD-L1 CPS ≥10 (n=272)
(Continued from previous page)						
PD-L1 CPS						
≥1	618 (78%)	618 (100%)	279 (100%)	617 (78%)	617 (100%)	272 (100%)
<1	172 (22%)	0	0	172 (22%)	0	0
≥10	279 (35%)	279 (45%)	279 (100%)	272 (34%)	272 (44%)	272 (100%)
<10	509 (64%)	337 (55%)	0	517 (66%)	345 (56%)	0
Missing	2 (<1%)	2 (<1%)	0	0	0	0
Choice of chemotherapy						
Capecitabine and oxaliplatin	682 (86%)	528 (85%)	242 (87%)	681 (86%)	528 (86%)	235 (86%)
Flurouracil and cisplatin	108 (14%)	90 (15%)	37 (13%)	108 (14%)	89 (14%)	37 (14%)

Data are median (IQR) or n (%). CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. ITT=intention-to-treat. *Self-reported by participants.

Table 1: **Baseline demographic and clinical characteristics**

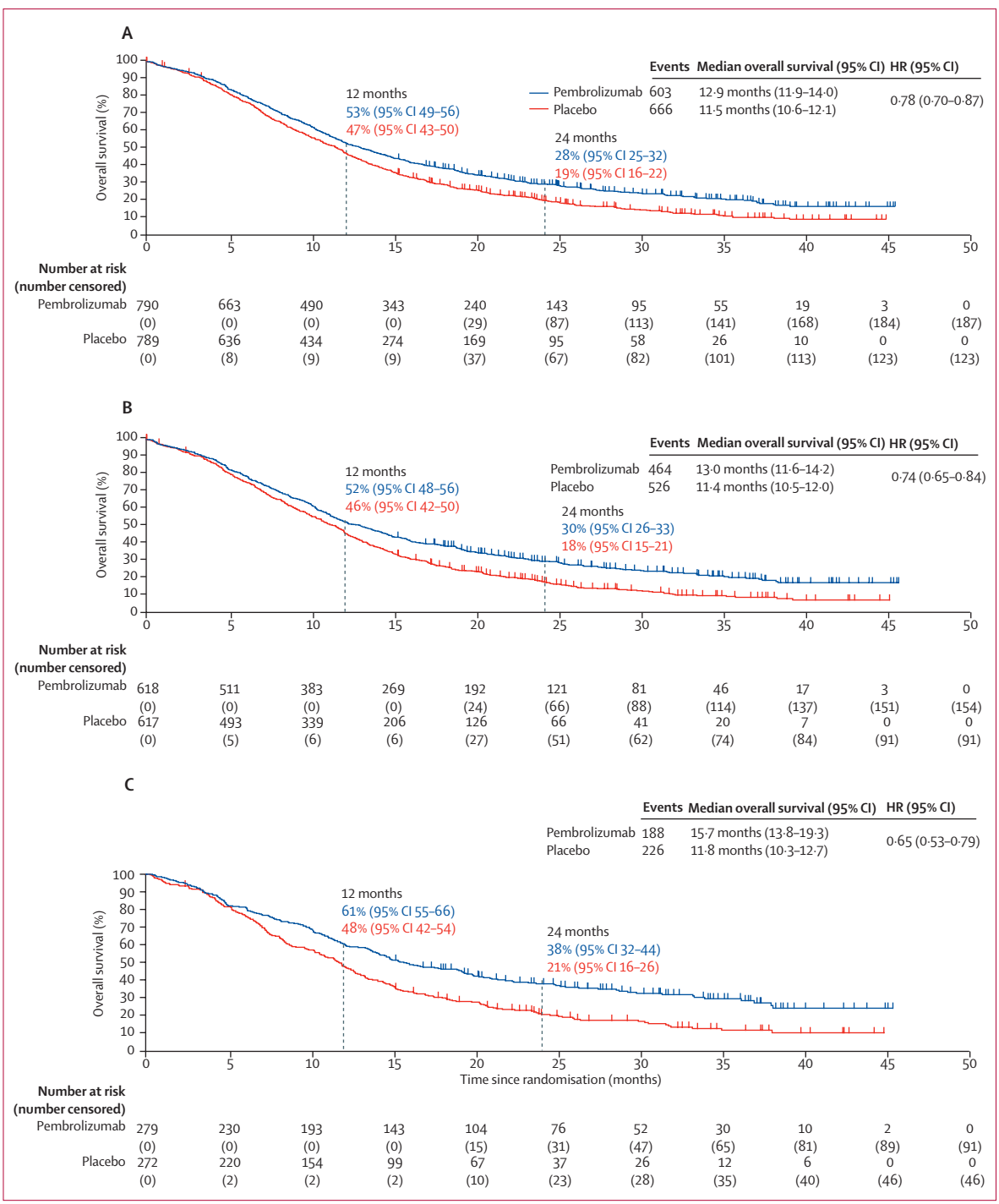
discontinued in 685 (87%) of 790 participants in the pembrolizumab group and 742 (94%) of 789 participants in the placebo group; the most common reason for discontinuation was progressive disease (421 [53%] and 474 [60%], respectively). In the ITT population, 355 (45%) of 790 participants in the pembrolizumab group and 369 (47%) of 789 participants in the placebo group received subsequent anticancer therapy (appendix p 9); chemotherapy was the most common subsequent therapy (339 [43%] and 346, respectively). 66 (8%) of 790 participants in the pembrolizumab group and 72 (9%) of 789 participants in the placebo group received a PD-1 or PD-L1 checkpoint inhibitor; 137 participants (17%) in the pembrolizumab group and 138 (17%) participants in the placebo group received a VEGF or VEGF receptor inhibitor.

At data cut-off, in the ITT population, 603 (76%) of 790 participants in the pembrolizumab group and 666 (84%) of 789 participants in the placebo group had died. Median overall survival was 12·9 months (95% CI 11·9–14·0) in the pembrolizumab group compared with 11·5 months (10·6–12·1) in the placebo group (HR 0·78 [95% CI 0·70–0·87; p<0·0001]; figure 2A). In the population with a PD-L1 CPS of 1 or higher, 464 (75%) of 618 participants in the pembrolizumab group and 526 (85%) of 617 participants in the placebo group had died at data cutoff. Median overall survival was 13·0 months (95% CI 11·6–14·2) in the pembrolizumab group compared with 11·4 months (10·5–12·0) in the placebo group (HR 0·74 [95% CI 0·65–0·84]; p<0·0001; figure 2B). In the population with a PD-L1 CPS of 10 or higher, 188 (67%) of 279 participants in the pembrolizumab group and 226 (83%) of 272 in the placebo group had died at data cutoff. Median overall survival was 15·7 months (95% CI 13·8–19·3) in the pembrolizumab group compared with 11·8 months (10·3–12·7) in the placebo group (HR 0·65 [95% CI 0·53–0·79]; p<0·0001; figure 2C). In the prespecified subgroup analysis of overall survival for the ITT population, all HRs favoured pembrolizumab plus chemotherapy over placebo plus chemotherapy (figure 2D; appendix pp 10–11).

At data cutoff, in the ITT population, 572 (72%) of 790 participants in the pembrolizumab group and 608 (77%) of 789 in the placebo group had died or had disease progression. Median progression-free survival was 6·9 months (95% CI 6·3–7·2) in the pembrolizumab group compared with 5·6 months (5·5–5·7) in the placebo group (HR 0·76 [95% CI 0·67–0·85]; p<0·0001; figure 3A). In the population with a PD-L1 CPS of 1 or higher, median progression-free survival was 6·9 months (95% CI 6·0–7·2) for the pembrolizumab group compared with 5·6 months (5·4–5·7) in the placebo group (HR 0·72 [95% CI 0·63–0·82]; p<0·0001; figure 3B). In the population with a PD-L1 CPS of 10 or higher, median progression-free survival was 8·1 months (95% CI 6·8–8·5) in the pembrolizumab group compared with 5·6 months (5·4–6·7) in the placebo group (HR 0·62 [95% CI 0·51–0·76]; p<0·0001; figure 3C). In a prespecified subgroup analysis of progression-free survival for the ITT population, all HRs favoured pembrolizumab plus chemotherapy versus placebo (appendix pp 12–13).

Best overall response in each population is summarised in the appendix (pp 14, 18, 19). In the ITT population, 405 (51%) of 790 participants in the pembrolizumab group had an objective response (75 [9%] participants with a complete response; 330 [42%] with a partial response) compared with 331 (42%) of 789 participants in the placebo group (49 [6%] participants with a complete response; 282 [36%] with a partial response; between-group difference 9·3% [95% CI 4·4–14·1]; p<0·0001). In the population with a PD-L1 CPS of 1 or higher, 322 (52%) of 618 participants in the pembrolizumab group had an objective response (61 [10%] participants had a complete response; 261 [42%] had a partial response) compared with 263 (43%) of 617 participants in the placebo group (36 [6%] had a complete response; 227 [37%] had a partial response; between-group difference 9·5% [95% CI

3·9–15·0]; p=0·0004). In the PD-L1 CPS of 10 or higher population, 169 (61%) of 279 participants in the pembrolizumab group had an objective response (36 [13%] complete responses; 133 [48%] partial responses) versus 117 (43%) of 272 participants in the placebo group (14 [5%] complete responses; 103 [38%] partial responses), for a between-group difference of 17·5% (95% CI 9·3–25·5; p<0·0001). In the ITT population, median duration of response was 8·0 months (95% CI 7·0–9·7) in the pembrolizumab group compared with 5·7 months (5·5–6·9) in the placebo group (appendix p 15). In the population with a PD-L1 CPS of 1 or higher, median duration of response was 8·3 months (95% CI 7·0–10·9) in the pembrolizumab group compared with 5·6 months



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	Pembrolizumab group, n/N	Placebo group, n/N	HR (95% CI)
Overall	603/790	666/789	0·78 (0·70–0·87)
Age, years			
<65	383/486	416/479	0·76 (0·66–0·88)
≥65	220/304	250/310	0·77 (0·64–0·92)
Sex			
Female	208/263	218/245	0·76 (0·63–0·92)
Male	395/527	448/544	0·77 (0·67–0·88)
Race			
Asian	190/270	212/269	0·72 (0·59–0·88)
Non–Asian	408/513	447/512	0·80 (0·70–0·92)
Geographical location			
Asia	184/263	206/262	0·71 (0·58–0·87)
Western Europe, Israel, North America, and Australia	160/201	172/202	0·80 (0·65–1·00)
Rest of the world	259/326	288/325	0·80 (0·68–0·95)
ECOG performance status			
0	193/281	246/301	0·73 (0·60–0·88)
1	410/509	420/488	0·77 (0·68–0·89)
Primary tumour location			
Gastro-esophageal junction	117/149	159/185	0·74 (0·58–0·94)
Stomach	485/640	507/603	0·77 (0·68–0·87)
Histological subtype			
Diffuse	259/318	269/301	0·76 (0·64–0·90)
Indeterminate	132/186	177/215	0·69 (0·55–0·87)
Intestinal	210/284	220/273	0·81 (0·67–0·98)
Disease status			
Metastatic	582/761	643/759	0·77 (0·69–0·86)
Liver metastases			
No	355/475	401/478	0·73 (0·63–0·84)
Yes	247/314	265/311	0·83 (0·70–0·99)
Previous gastrectomy or oesophagectomy			
No	487/613	535/622	0·79 (0·70–0·90)
Yes	112/172	126/162	0·69 (0·54–0·90)
Microsatellite instability status			
High	14/39	25/35	0·34 (0·18–0·66)
Low or microsatellite stable	497/641	540/639	0·79 (0·70–0·89)
PD–L1 CPS at baseline			
<1	139/172	140/172	0·92 (0·73–1·17)
≥1	464/618	526/617	0·73 (0·65–0·83)
1–9	274/337	300/345	0·83 (0·70–0·98)
<10	413/509	440/517	0·86 (0·75–0·98)
≥10	188/279	226/272	0·64 (0·52–0·77)
Chemotherapy choice at randomisation			
Capecitabine and oxaliplatin	509/682	567/681	0·76 (0·68–0·86)
Fluorouracil and cisplatin	94/108	99/108	0·82 (0·62–1·09)

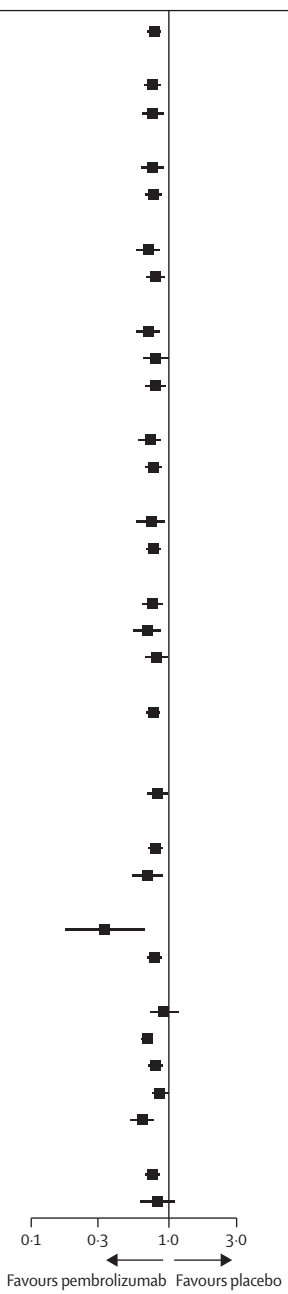

Figure 2: **Overall survival**
Kaplan-Meier estimates of overall survival in the ITT population (A), in participants with PD-L1 CPS of 1 or higher (B) and in participants with PD-L1 CPS of 10 or higher (C), and overall survival in subgroups of the ITT population (D). In part D, stratified HRs and 95% CIs are shown for the overall population; unstratified HRs and 95% CIs are depicted for all subgroups. If any level of a subgroup variable contained <5% of the ITT population, the analysis was not performed for that level of the subgroup variable. If a subgroup variable had two levels and one level of the subgroup variable contained <5% of the ITT population, then that subgroup was not shown in the forest plot. HR=hazard ratio. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. ITT=intention-to-treat. n=events. N=participants.

(5·4–6·9) in the placebo group (appendix p 16). In the population with a PD-L1 CPS of 10 or higher, median duration of response was 10·9 months (95% CI 8·0–13·8) in the pembrolizumab group compared with 5·8 months (5·3–7·0) in the placebo group (appendix p 17). Since the primary and secondary endpoints all met the prespecified

criteria for superiority of pembrolizumab plus chemotherapy compared with placebo plus chemotherapy, the null hypotheses were rejected and no further hypothesis testing will be performed.

Post-hoc analysis of overall survival in participants with a PD-L1 CPS of 1–9and a PD-L1 CPS of less than 10, is shown in figure 2D, and the similar analyses for progression-free survival are shown in the appendix (pp 12–13).

The median duration of therapy for the as-treated population was 6·7 months (IQR 3·6–12·5) in the pembrolizumab group and 5·6 months (3·1–9·1) in the placebo group. 386 (24%) of 1572 participants who received capecitabine plus oxaliplatin as chemotherapy and 104 (7%) who received fluorouracil plus cisplatin continued either pembrolizumab or placebo after stopping platinum chemotherapy by the sixth chemotherapy cycle. Adverse events of any cause occurred in 776 (99%) of 785 participants in the pembrolizumab group and 771 (98%) of 787 participants in the placebo group (appendix p 20). The most common grade 3–5 adverse events of any cause were anaemia (95 [12%] of 785 participants in the pembrolizumab group *vs* 76 [10%] of 787 participants in the placebo group) and decreased neutrophil count (77 [10%] participants *vs* 64 [8%] participants). Treatment-related adverse events occurred in 751 (96%) of 785 participants in the pembrolizumab group and 736 (94%) of 787 participants in the placebo group (table 2). The most common treatment-related adverse events were nausea (325 [41%] of 785 participants in the pembrolizumab group; 326 [41%] of 787 participants in the placebo group), diarrhoea (252 [32%]; 214 [27%]), and anaemia (243 [31%]; 212 [27%]). 466 (59%) of 785 participants in the pembrolizumab group and 402 (51%) of 787 participants in the placebo group had treatment-related adverse events of grade 3 or worse. Treatment-related adverse events led to treatment discontinuation in 207 (26%) of 785 participants in the pembrolizumab group and 158 (20%) of 787 participants in the placebo group (appendix p 21). Treatment-related adverse events led to interruption of any treatment for 518 (66%) of 785 participants in the pembrolizumab group and 444 (56%) of 787 participants in the placebo group. Treatment-related adverse events led to dose reductions of chemotherapy in 292 (37%) of 785 participants in the pembrolizumab group and 304 (39%) of 787 participants in the placebo group. Serious treatment-related adverse events occurred in 184 (23%) of 785 participants in the pembrolizumab group and 146 (19%) of 787 participants in the placebo group. Adverse events led to death in 64 (8%) of 785 participants in the pembrolizumab group and 58 (7%) of 787 participants in the placebo group (appendix pp 22–23). Eight (1%) of 785 participants in the pembrolizumab group and 16 (2%) of 787 participants in the placebo group died of treatment-related adverse events (table 2).

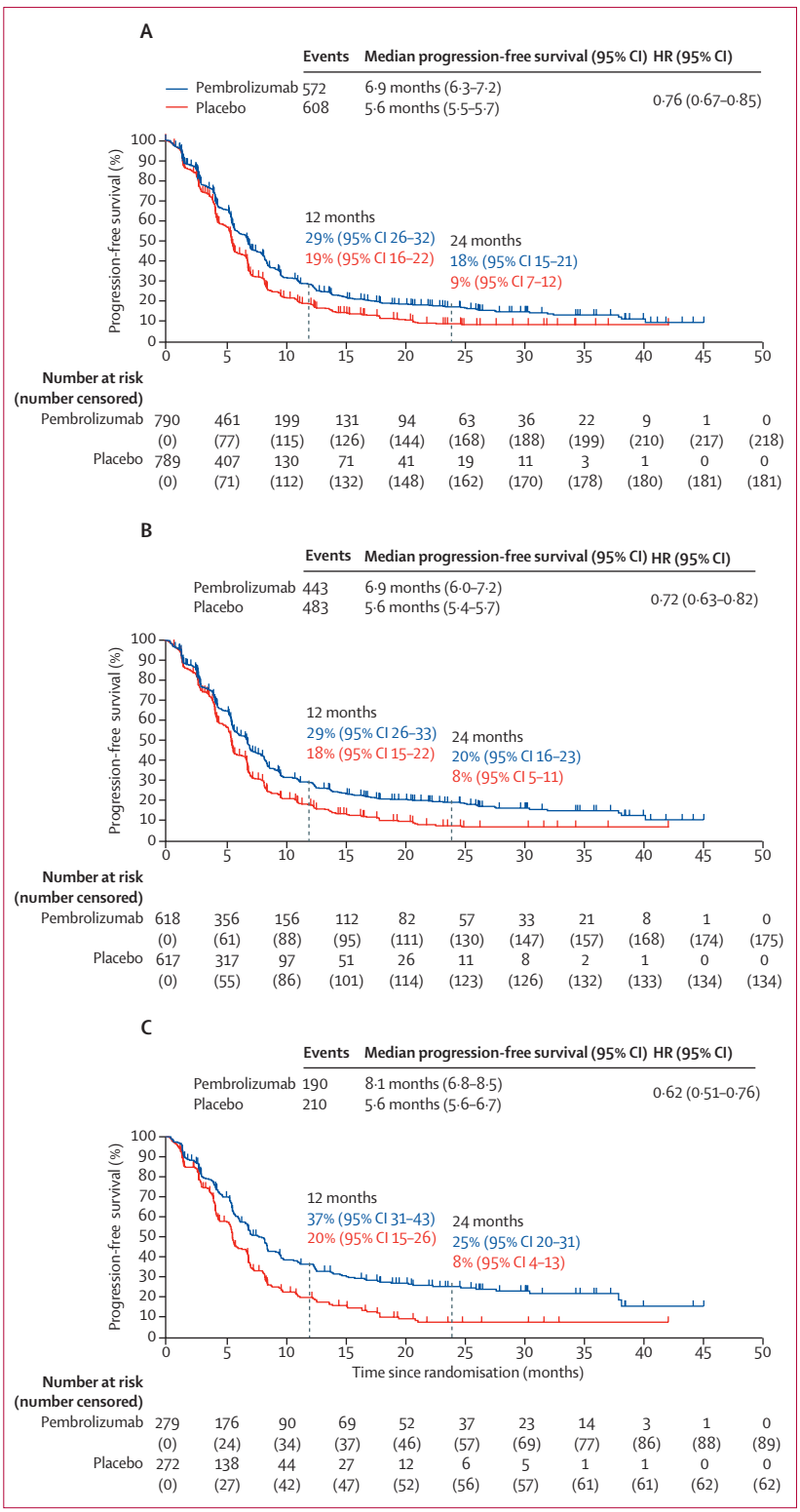

***Figure 3*: Progression-free survival**
Kaplan-Meier estimates of progression-free survival in the ITT population (A), in participants with PD-L1 CPS of 1 or higher (B), and in participants with PD-L1 CPS of 10 or higher (C). ITT=intention-to-treat.

	Pembrolizumab plus chemotherapy (n=785)				Placebo plus chemotherapy (n=787)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	285 (36%)	405 (52%)	53 (7%)	8 (1%)*	334 (42%)	352 (45%)	34 (4%)	16 (2%)†
Nausea	299 (38%)	25 (3%)	1 (<1%)	0	297 (38%)	29 (4%)	0	0
Diarrhoea	206 (26%)	42 (5%)	3 (<1%)	1 (<1%)	177 (22%)	35 (4%)	1 (<1%)	1 (<1%)
Anaemia	179 (23%)	62 (8%)	2 (<1%)	0	161 (20%)	48 (6%)	3 (<1%)	0
Vomiting	180 (23%)	35 (4%)	0	0	143 (18%)	32 (4%)	0	0
Decreased platelet count	141 (18%)	47 (6%)	8 (1%)	0	141 (18%)	32 (4%)	4 (1%)	0
Decreased neutrophil count	121 (15%)	63 (8%)	9 (1%)	0	112 (14%)	54 (7%)	4 (1%)	0
Palmar-plantar erythrodysaesthesia syndrome	165 (21%)	24 (3%)	0	0	152 (19%)	14 (2%)	0	0
Decreased appetite	153 (19%)	15 (2%)	0	0	154 (20%)	14 (2%)	0	0
Fatigue	130 (17%)	27 (3%)	0	0	132 (17%)	32 (4%)	0	0
Peripheral neuropathy	140 (18%)	10 (1%)	0	0	139 (18%)	24 (3%)	1 (<1%)	0
Neutropenia	87 (11%)	50 (6%)	5 (1%)	0	75 (10%)	52 (7%)	8 (1%)	0
Increased aspartate aminotransferase	128 (16%)	11 (1%)	0	0	94 (12%)	7 (1%)	1 (<1%)	0
Peripheral sensory neuropathy	115 (15%)	22 (3%)	0	0	123 (16%)	8 (1%)	0	0
Hypothyroidism	106 (14%)	1 (<1%)	0	0	32 (4%)	0	0	0
Increased alanine aminotransferase	91 (12%)	10 (1%)	0	0	61 (8%)	7 (1%)	0	0
Decreased white blood cell count	89 (11%)	9 (1%)	3 (<1%)	0	78 (10%)	7 (1%)	2 (<1%)	0
Asthenia	81 (10%)	12 (2%)	1 (<1%)	0	63 (8%)	16 (2%)	0	0
Thrombocytopenia	71 (9%)	10 (1%)	2 (<1%)	0	59 (7%)	18 (2%)	0	0
Increased blood bilirubin	69 (9%)	8 (1%)	1 (<1%)	0	48 (6%)	3 (<1%)	0	0

Data are n (%). *The treatment-related adverse events that led to death were diarrhoea (n=1), peripheral embolism (n=1), pneumonitis (n=1), pulmonary haemorrhage (n=1), sepsis (n=1), septic shock (n=1), thrombotic thrombocytopenia purpura (n=1), and unknown cause (n=1). †The treatment-related adverse events that led to death were septic shock (n=3), acute myocardial infarction (n=2), abnormal hepatic function (n=1), cerebral haemorrhage (n=1), cerebrovascular accident (n=1), diarrhoea (n=1), gastric perforation (n=1), neurotoxicity (n=1), pneumonitis (n=1), pulmonary embolism (n=1), sepsis (n=1), sudden death (n=1), and urosepsis (n=1).

Table 2: **Treatment-related adverse events that occurred in at least 10% of participants in the as-treated population**

	Pembrolizumab plus chemotherapy (n=785)				Placebo plus chemotherapy (n=787)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	151 (19%)	57 (4%)	4 (1%)	1 (<1%)	60 (8%)	11 (1%)	1 (<1%)	1 (<1%)
Hypothyroidism	119 (15%)	1 (<1%)	0	0	34 (4%)	0	0	0
Hyperthyroidism	44 (6%)	0	0	0	13 (2%)	0	0	0
Colitis	7 (1%)	18 (2%)	1 (<1%)	0	10 (1%)	4 (1%)	0	0
Pneumonitis	15 (2%)	8 (1%)	1 (<1%)	1 (<1%)	4 (1%)	2 (<1%)	0	1 (<1%)
Thyroiditis	9 (1%)	0	0	0	1 (<1%)	0	0	0
Adrenal insufficiency	6 (1%)	3 (<1%)	1 (<1%)	0	1 (<1%)	0	0	0
Hepatitis	6 (1%)	3 (<1%)	0	0	1 (<1%)	2 (<1%)	1 (<1%)	0
Severe skin reactions	4 (1%)	12 (2%)	0	0	0	1 (<1%)	0	0
Hypophysitis	2 (<1%)	1 (<1%)	0	0	0	0	0	0
Vasculitis	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Hypoparathyroidism	1 (<1%)	0	0	0	0	0	0	0
Uveitis	1 (<1%)	0	0	0	0	0	0	0
Myositis	0	1 (<1%)	0	0	0	0	0	0
Myasthenic syndrome	0	1 (<1%)	0	0	0	0	0	0
Myocarditis	0	0	0	0	0	1 (<1%)	0	0
Nephritis	0	4 (1%)	0	0	0	0	0	0
Pancreatitis	0	3 (<1%)	0	0	2 (<1%)	1 (<1%)	0	0
Type 1 diabetes	0	4 (1%)	1 (<1%)	0	1 (<1%)	0	0	0

Data are n (%). Potentially immune-mediated adverse events were based on a list of terms prepared by the funder and were considered regardless of attribution to trial treatment by the investigator. In addition to the specific preferred terms listed, related terms were included.

Table 3: **Potentially immune-mediated adverse events in the as-treated population**

Potentially immune-mediated adverse events occurred in 213 (27%) of 785 participants in the pembrolizumab group and 73 (9%) of 787 participants in the placebo group (table 3). Grade 3–5 events occurred in 62 (8%) of 785 participants in the pembrolizumab group and 13 (2%) of 787 participants in the placebo group. The most common potentially immune-mediated adverse events in either group were hypothyroidism (120 [15%] of 785 participants in the pembrolizumab group; 34 [4%] of 787 participants in the placebo group), hyperthyroidism (44 [6%]; 13 [2%]), and colitis (26 [3%]; 14 [2%]). Potentially immune-mediated adverse events led to discontinuation of any drug in 27 (3%) of 785 participants in the pembrolizumab group and six (1%) of 787 participants in the placebo group. One participant in each group (<1% both groups) died of a potentially immune-mediated adverse event (pneumonitis).

In a prespecified exploratory analysis in the full analysis set population, the compliance rates for the EORTC QLQ-C30 and EORTC QLQ-STO22 were comparable and higher than 95% in both pembrolizumab and placebo groups at baseline. From baseline to week 18, least-squares mean changes were similar between arms in QLQ-C30 global health status/quality of life (appendix p 24) and favoured pembrolizumab versus placebo in the QLQ-STO22 pain scale (appendix p 24). Similarly, time to true deterioration was similar between groups in QLQ-C30 global health status/quality of life and favoured pembrolizumab versus placebo in the QLQ-STO22 pain scale (appendix p 25).

Discussion

Among all participants and participants with a PD-L1 CPS of 1 or higher and CPS of 10 or higher, with previously untreated, locally advanced, unresectable or metastatic HER2-negative gastric or gastro-esophageal junction adenocarcinoma, overall survival, progression-free survival, and objective response rate outcomes were significantly improved in the pembrolizumab plus chemotherapy group compared with the placebo group, with a manageable safety profile. KEYNOTE-859 met all prespecified primary endpoints and statistically tested secondary endpoints for all participants, including those with PD-L1 CPS scores of higher than 1, and higher than 10; no further hypothesis testing will be performed. The safety profile of pembrolizumab plus chemotherapy was generally consistent with the known safety profiles of pembrolizumab monotherapy or chemotherapy alone.[12] These results address an important unmet medical need and provide a new treatment option for first-line treatment of advanced gastric cancer with improved median overall survival of more than 1 year, irrespective of PD-L1 CPS expression. The Kaplan-Meier curves for overall survival and progression-free survival separated early and remained separated throughout the evaluation period, and the 24-month estimates of overall survival and progression-free survival were higher for the pembrolizumab plus chemotherapy group. More complete and durable responses were observed with pembrolizumab plus chemotherapy than with chemotherapy alone. The overall survival and progression-free survival benefit were generally consistent across all prespecified subgroups.

Enrichment of PD-L1 expression is known to result in comparatively more benefit for immunotherapies across a variety of tumour types,[21,22] and a similar effect was observed in KEYNOTE-859, whereby the magnitude of benefit was greater with increasing PD-L1 CPS values. KEYNOTE-859 enrolled 1579 participants with advanced HER2-negative gastric cancer regardless of PD-L1 CPS expression. The prevalence of participants with PD-L1 CPS of 1 or higher (78%) and CPS of 10 or higher (35%) in KEYNOTE-859 were consistent with the literature.[15,17,23]

Additionally, prespecified and post-hoc subgroup analyses showed that unstratified HRs for overall survival and progression-free survival in participants with PD-L1 CPS of 1–9 and less than 10 favoured the pembrolizumab plus chemotherapy group over the placebo plus chemotherapy group, consistent with the results observed in the overall study participants. However, these are post-hoc exploratory analyses, and were not statistically powered, and thus should be interpreted with caution.

Similar to KEYNOTE-859, the phase 3 CheckMate 649 study showed that nivolumab plus chemotherapy improved overall survival and progression-free survival, with manageable safety, compared with chemotherapy alone in 1581 randomly assigned participants with previously untreated advanced non-HER2-positive gastric or gastro-esophageal junction or oesophageal cancer.[7] The HR for overall survival was 0·71 (98% CI 0·59–0·86; p<0·0001), and the HR for progression-free survival was 0·68 (98% CI 0·56–0·81; p<0·0001) in participants with PD-L1 CPS of 5 or higher after approximately 1 year of follow-up. Progression-free survival in all randomly assigned participants and in those with PD-L1 of CPS of 1 or higher also suggested a benefit from combination therapy but was not formally tested in CheckMate 649. Additionally, KEYNOTE-859 was a double-blind study, whereas CheckMate 649 was an open-label study.

Neither pembrolizumab nor nivolumab plus chemotherapy resulted in a significant improvement in overall survival versus chemotherapy alone in participants with advanced or recurrent gastric or gastro-esophageal junction adenocarcinoma in the KEYNOTE-062 and ATTRACTION-4 trials, respectively.[9,12] Several factors are likely to be responsible for the differences in the results of CheckMate 649, ORIENT-16, RATIONALE-305, KEYNOTE-062, ATTRACTION-4, and KEYNOTE-859, including study population, statistical design, biomarker testing, chemotherapy regimen, regional variations, and subsequent therapy use. More participants received subsequent therapy after discontinuation in

ATTRACTION-4 (72% in ATTRACTION-4 *vs* 45% in KEYNOTE-859 combination groups), which might have had a confounding effect on overall survival. At the time of KEYNOTE-062 study design, little information was available that could be used as a reference for the HR assumption to predict the effect of pembrolizumab in gastric cancers. The KEYNOTE-062 results were obtained after the start of KEYNOTE-859. In view of the results of KEYNOTE-062, the assumed efficacy HRs and target sample size in KEYNOTE-859 was increased from 780 to 1579 participants accordingly in a protocol amendment to maintain sufficient power to demonstrate clinically meaningful and statistically significant benefits of pembrolizumab plus chemotherapy versus chemotherapy alone. However, differences in primary endpoints, number of treatment groups, sample size, strategy for significance level allocation, and strategy for the assumption of overall survival HR between KEYNOTE-062 and KEYNOTE-859 preclude direct comparison of results.

The subgroup and post-hoc analyses showed results consistent with the overall population. Limitations of the study include the small sample size in some subgroups, such as participants with PD-L1 CPS of less than 1 and participants with gastro-esophageal junction adenocarcinoma, which were consistent with lower prevalence in the population. Additionally, the post-hoc analyses in participants with a PD-L1 CPS of 1–9 were not powered for any hypothesis testing. The overall ratio of men to women enrolled in KEYNOTE-859 was consistent with the global incidence of gastric or gastro-esophageal junction adenocarcinoma.[24]

Taken together with the results from KEYNOTE-811 in HER2-positive disease,[25] results from KEYNOTE-859 indicate a broad utility of pembrolizumab in the first-line treatment of patients with advanced gastric cancer.

Contributors

SYR, LY, SB, and PB were involved in conceptualisation of the study. TC and M-HR were involved in data curation. Formal analysis was done by LY and SB. SYR, K-KS, SB, TC, JLi, D-YO, FR, YB, GVA, JLee, ZAW, and M-HR were involved in the investigation process. SB developed the methodology. SB, TC, D-YO, and FR were involved with the project administration. SYR, K-KS, TC, JLee, D-YO, FR, ZAW, and M-HR provided study resources. SYR, K-KS, SB, JLi, D-YO, FR, and PB provided supervision. SYR, K-KS, SYR, LY, SB, FR, and M-HR provided validation. SYR, K-KS, SB, FR, and ZAW provided data visualisation. SYR, LY, SB, ZAW, and M-HR were involved with drafting the manuscript. K-KS, SYR, LY, SB, PB, JLee, D-YO, FR, GVA, ZAW, and M-HR critically reviewed and edited the manuscript. All authors reviewed the final version of the manuscript to be submitted and agree with its content and submission. All authors had access to all the relevant study data and related analyses and vouch for the completeness and accuracy of the data presented. SYR, LY, SB, and PB had full access to and verified all study data. SYR had final responsibility for the decision to submit this manuscript for publication.

Declaration of interests

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Data sharing

Merck Sharp and Dohme, 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. Merck Sharp and Dohme 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 Merck Sharp and Dohme data sharing website outlines the process and requirements for submitting a data request. Feasible requests will be reviewed by a committee of Merck Sharp and Dohme subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation,

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submitters of approved requests must enter into a standard data-sharing agreement with Merck Sharp and Dohme before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent Merck Sharp and Dohme 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 statistical analysis plan that is collaboratively developed by the requestor and Merck Sharp and Dohme subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, Merck Sharp and Dohme 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 a SAS portal so that the requestor can perform the proposed analyses.

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References

1 National Cancer Institute, Surveillance, Epidemiology, and End Results Program. Cancer stat facts: stomach cancer. https://seer.cancer.gov/statfacts/html/stomach.html (accessed Oct 21, 2022).
2 Li Y, Feng A, Zheng S, Chen C, Lyu J. Recent estimates and predictions of 5-year survival in patients with gastric cancer: a model-based period analysis. *Cancer Control* 2022; **29:** 10732748221099227.
3 Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2022; **33:** 1005–20.
4 Marin-Acevedo JA, Kimbrough EO, Lou Y. Next generation of immune checkpoint inhibitors and beyond. *J Hematol Oncol* 2021; **14:** 45.
5 Park SJ, Ye W, Xiao R, et al. Cisplatin and oxaliplatin induce similar immunogenic changes in preclinical models of head and neck cancer. *Oral Oncol* 2019; **95:** 127–35.
6 Zhai J, Gu X, Liu Y, Hu Y, Jiang Y, Zhang Z. Chemotherapeutic and targeted drugs-induced immunogenic cell death in cancer models and antitumor therapy: an update review. *Front Pharmacol* 2023; **14:** 1152934.
7 Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021; **398:** 27–40.
8 Janjigian YY, Shitara K, Moehler MH, et al. Nivolumab (NIVO) plus chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 3-year follow-up from CheckMate 649. *J Clin Oncol* 2023; **41:** 291–91.
9 Kang YK, Chen LT, Ryu MH, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2022; **23:** 234–47.
10 Xu J, Jiang H, Pan Y, et al. Sintilimab plus chemotherapy (chemo) versus chemo as first-line treatment for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (ORIENT-16): first results of a randomized, double-blind, phase III study. *Ann Oncol* 2021; **32:** S1283–346.
11 Xu J, Jiang H, Pan Y, et al. Abstract CT078: First-line treatment with sintilimab (sin) vs placebo in combination with chemotherapy (chemo) in patients (pts) with unresectable gastric or gastroesophageal junction (G/GEJ) cancer: final overall survival (OS) results from the randomized, phase III ORIENT-16 trial. *Cancer Res* 2023; **83:** CT078–78.
12 Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy *vs* chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. *JAMA Oncol* 2020; **6:** 1571–80.
13 Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; **378:** 2078–92.
14 Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 Trial. *JAMA Oncol* 2018; **4:** e180013.
15 Shitara K, Özgüroğlu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2018; **392:** 123–33.
16 Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. *Stat Med* 2009; **28:** 586–604.
17 Huang RSP, Haberberger J, Severson E, et al. A pan-cancer analysis of PD-L1 immunohistochemistry and gene amplification, tumor mutation burden and microsatellite instability in 48,782 cases. *Mod Pathol* 2021; **34:** 252–63.
18 Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med* 1985; **4:** 213–26.
19 Liang KY, Zeger SL. Longitudinal data analysis of continuous and discrete responses for pre-post designs. *Indian J Stat* 2017; **62:** 134.
20 Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64:** 31–49.
21 Xu Y, Wan B, Chen X, et al. The association of PD-L1 expression with the efficacy of anti-PD-1/PD-L1 immunotherapy and survival of non-small cell lung cancer patients: a meta-analysis of randomized controlled trials. *Transl Lung Cancer Res* 2019; **8:** 413–28.
22 Yang Y, Chen D, Zhao B, et al. The predictive value of PD-L1 expression in patients with advanced hepatocellular carcinoma treated with PD-1/PD-L1 inhibitors: a systematic review and meta-analysis. *Cancer Med* 2023; **12:** 9282–92.
23 Kulangara K, Guerrero L, Posch A, et al. Investigation of PD-L1 expression and response to pembrolizumab (pembro) in gastric cancer (GC) and cervical cancer (CC) using combined positive score (CPS) and tumor proportion score (TPS). *J Clin Oncol* 2018; **36:** 4065–65.
24 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71:** 209–49.
25 Janjigian YY, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature* 2021; **600:** 727–30.