Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial

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Summary

Background Patients with advanced gastric or gastro-oesophageal junction cancer that progresses on chemotherapy have poor outcomes. We compared pembrolizumab with paclitaxel in patients with advanced gastric or gastro-oesophageal junction cancer that progressed on first-line chemotherapy with a platinum and fluoropyrimidine.

Methods This randomised, open-label, phase 3 study was done at 148 medical centres in 30 countries. Eligible patients were randomised (1:1) in blocks of four per stratum with an interactive voice-response and integrated web-response system to receive either pembrolizumab 200 mg every 3 weeks for up to 2 years or standard-dose paclitaxel. Primary endpoints were overall survival and progression-free survival in patients with a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of 1 or higher. Safety was assessed in all patients, irrespective of CPS. The significance threshold for overall survival was p=0·0135 (one-sided). This trial is registered at ClinicalTrials.gov, number NCT02370498.

Findings Between June 4, 2015, and July 26, 2016, 592 patients were enrolled. Of the 395 patients who had a PD-L1 CPS of 1 or higher, 196 patients were assigned to receive pembrolizumab and 199 patients were assigned to receive paclitaxel. As of Oct 26, 2017, 326 patients in the population with CPS of 1 or higher had died (151 [77%] of 196 patients in the pembrolizumab group and 175 [88%] of 199 patients in the paclitaxel group). Median overall survival was 9·1 months (95% CI 6·2–10·7) with pembrolizumab and 8·3 months (7·6–9·0) with paclitaxel (hazard ratio [HR] 0·82, 95% CI 0·66–1·03; one-sided p=0·0421). Median progression-free survival was 1·5 months (95% CI 1·4–2·0) with pembrolizumab and 4·1 months (3·1–4·2) with paclitaxel (HR 1·27, 95% CI 1·03–1·57). In the total population, grade 3–5 treatment-related adverse events occurred in 42 (14%) of the 294 patients treated with pembrolizumab and 96 (35%) of the 276 patients treated with paclitaxel.

Interpretation Pembrolizumab did not significantly improve overall survival compared with paclitaxel as second-line therapy for advanced gastric or gastro-oesophageal junction cancer with PD-L1 CPS of 1 or higher. Pembrolizumab had a better safety profile than paclitaxel. Additional trials of pembrolizumab in gastric and gastro-oesophageal cancer are ongoing.

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Introduction

Gastric cancer is the fifth most common cancer and is the third most common cause of cancer mortality worldwide.[1] Chemotherapy with a platinum and fluoropyrimidine is the recommended first-line therapy for patients with advanced or metastatic gastric or gastro-oesophageal junction cancer who have good performance status; patients who have human epidermal growth factor 2 (HER2)-positive tumours should also receive trastuzumab.[2–6] In the second-line setting, treatment options include cytotoxic chemotherapy with docetaxel, paclitaxel, or irinotecan and the vascular endothelial growth factor 2 (VEGFR2) monoclonal antibody ramucirumab given as either monotherapy or in combination with paclitaxel.

In recent years, immunotherapy with immune checkpoint inhibitors has revolutionised the treatment of advanced cancer. One such checkpoint is programmed death 1 (PD-1), which is a negative costimulatory receptor expressed mainly on activated T cells.[7] In tumour cells, inhibition of PD-1 prevents PD-1 from binding to its ligands, PD-1 ligand 1 (PD-L1) and PD-1 ligand 2 (PD-L2), thus restoring antitumour immunity. Overexpression of PD-L1 has been observed in gastric cancer,[8] making PD-1 pathway inhibition a rational target in patients with gastric or gastro-oesophageal junction cancer.

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Research in context

Evidence before this study

We searched PubMed on Feb 10, 2018, with the terms "PD-1 OR PD-L1 OR MK-3475 OR pembrolizumab OR Keytruda OR BMS-936558 OR nivolumab OR Opdivo OR MPDL3280A OR atezolizumab OR Tecentriq OR MEDI4736 OR durvalumab OR Imfinzi OR MSB0010718C OR avelumab OR Bavencio" AND "gastric cancer OR gastroesophageal junction cancer." No limits were applied to the search. We also searched the abstracts from the 2017 and 2018 American Society of Clinical Oncology Gastrointestinal Cancers Symposium, the 2016 and 2017 American Society of Clinical Oncology Annual Meeting, the 2016 and 2017 World Congress of Gastrointestinal Cancer, and the 2016 and 2017 European Society for Medical Oncology Congress using the same terms to identify results of any clinical trials that were not yet published in the peer-reviewed scientific literature. We identified one randomised phase 3 trial of anti-programmed death 1 (PD-1) or anti-programmed death ligand 1 (PD-L1) therapy for advanced gastric or gastro-oesophageal junction cancer, the ATTRACTION-2 study of nivolumab versus placebo as third-line or later therapy. We also identified phase 1 and phase 2 studies of anti-PD-1 or anti-PD-L1 monotherapy for advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-012 and KEYNOTE-059 studies of pembrolizumab and the JAVELIN study of avelumab). In three additional phase 1 and phase 2 studies of anti-PD-1 or anti-PD-L1 combination therapy, pembrolizumab was tested in combination with a platinum and fluoropyrimidine (KEYNOTE-059), ramucirumab (JVDF), or margetuximab, nivolumab was tested in combination with ipilimumab (CheckMate 032), and durvalumab was tested in combination with ramucirumab. We focused on the studies of anti-PD-1 or anti-PD-L1 monotherapy.

Added value of this study

This is the first report of data from a randomised trial of anti-PD-1 or anti-PD-L1 therapy as second-line therapy for advanced gastric cancer and the first report of data from a randomised trial of anti-PD-1 or anti-PD-L1 therapy to include an active comparator. Although the prespecified boundary for detecting a statistically significant improvement in overall survival with pembrolizumab versus paclitaxel in patients with PD-L1-expressing tumours was not reached, the results of the protocol-specified exploratory subgroup analysis suggest that pembrolizumab might have antitumour activity in patients with a good Eastern Cooperative Oncology Group performance status. Data from post-hoc analyses suggest that pembrolizumab also has antitumour activity in patients whose tumours had higher levels of PD-L1 expression or high levels of microsatellite instability. The findings show that pembrolizumab has a favourable safety profile compared with paclitaxel, with patients treated with pembrolizumab having fewer adverse events attributed to study treatment that were high-grade or led to treatment discontinuation.

Implications of all the available evidence

Anti-PD-1 and anti-PD-L1 therapies appear to have antitumour activity in select patients with advanced gastric or gastro-oesophageal cancer, as well as a favourable safety profile. The greatest relative benefit for these therapies, when given as monotherapy, might be in the setting of third-line therapy and beyond in patients with a PD-L1 combined positive score of 1 or higher (approved by the US Food and Drug Administration) and as second-line therapy in patients with good performance status or patients whose tumours show high levels of microsatellite instability or higher levels of PD-L1 expression. These hypothesis-generating results suggest that prospective, controlled assessments of these subgroups are of value. Data from phase 1 and phase 2 studies suggest that combination regimens that include anti-PD-1 and anti-PD-L1 therapies are worthy of further assessment, particularly in early lines of therapy for advanced disease or earlier stages of disease.

Pembrolizumab is a humanised, high-affinity, IgG4-κ monoclonal antibody that binds to PD-1, preventing the interaction of PD-1 with PD-L1 and PD-L2. In the phase 2 KEYNOTE-059 study,[9] pembrolizumab had antitumour activity and a manageable safety profile in patients with previously treated gastric cancer who received pembrolizumab monotherapy at a fixed dose of 200 mg on day 1 of each 3-week cycle. Patients with advanced gastric cancer that progressed on two or more lines of previous therapy had a response rate of 11·6%; the response rate in patients with a PD-L1 combined positive score (CPS) of 1 or more was 15·5% in those who received pembrolizumab as third-line or later therapy and 22·7% in those who received pembrolizumab as third-line therapy. On the basis of the observed response rate and the durability of response, the US Food and Drug Administration (FDA) granted accelerated approval of pembrolizumab for the treatment of recurrent locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma that expresses PD-L1 (CPS ≥1) and progressed on or after two or more previous lines of therapy including platinum-containing and fluoropyrimidine-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy.

Here we present results of the KEYNOTE-061 study of pembrolizumab compared with paclitaxel as second-line therapy in patients with advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma.

Methods

Study design and participants

This randomised, open-label, phase 3 study was done at 148 medical centres in 30 countries (Argentina, Australia, Belgium, Canada, Chile, Colombia, Denmark, Estonia,

Finland, Germany, Guatemala, Hong Kong, Ireland, Israel, Italy, Japan, Malaysia, Mexico, New Zealand, Norway, Poland, Russia, Singapore, South Africa, South Korea, Spain, Taiwan, Turkey, UK, and USA). An open-label design was chosen because the different pembrolizumab and paclitaxel administration schedules would make it difficult to do a masked study. Eligible patients were aged 18 years or older, had histologically or cytologically confirmed adenocarcinoma of the stomach or gastro-oesophageal junction that was metastatic or locally advanced but unresectable, had progression as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)[10] after first-line therapy with a platinum and fluoropyrimidine, as well as with trastuzumab in patients with HER2-positive tumours, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had provided a tumour sample for PD-L1 assessment. Initially, patients were enrolled irrespective of PD-L1 expression status. After 489 patients were enrolled, the independent data monitoring committee recommended that enrolment be restricted to patients with a PD-L1 CPS of 1 or higher on the basis of outcomes in patients with a CPS less than 1. Exclusion criteria included squamous-cell or undifferentiated histology, previous therapy with any PD-1, PD-L1, or PD-L2 inhibitor, and active autoimmune disease that necessitated systemic treatment. A complete list of inclusion and exclusion criteria is included in the appendix.

The study protocol and all amendments were approved by the institutional review board or ethics committee at each institution. The study was done in accordance with the protocol and its amendments and Good Clinical Practice guidelines. All patients provided written informed consent before enrolment.

Randomisation and masking

Patients were randomly allocated (1:1) using a central interactive voice-response and integrated web-response system to receive pembrolizumab 200 mg intravenously every 3 weeks or paclitaxel 80 mg/m² intravenously on days 1, 8, and 15 of 4-week cycles. The allocation schedule was generated by the system vendor using a computerised random list generator. Enrolment of the first 125 patients was stratified by geographical region (Europe, Israel, North America, and Australia *vs* Asia *vs* rest of world) and ECOG performance status (0 *vs* 1). Following a protocol amendment, enrolment of the remaining 467 patients was stratified by geographical region (Europe, Israel, North America, and Australia *vs* Asia *vs* rest of the world), time to progression on first-line therapy (<6 months *vs* ≥6 months), and PD-L1 CPS (<1 *vs* ≥1). The stratification factors were changed because time to progression on first-line therapy and PD-L1 expression status are predictive of response in second-line gastric cancer treatment and therefore might affect overall survival. Treatment was allocated in blocks of four in each stratum. Patients, treating doctors, the external data monitoring committee, and sponsor representatives were not masked to treatment assignment. The central radiological reviewers were masked to treatment assignment.

Procedures

Premedication with an oral corticosteroid, an antihistamine, cimetidine, and an antiemetic according to local guidelines was recommended in the paclitaxel group. Treatment was continued for 35 cycles (roughly 2 years; pembrolizumab only) or until disease progression, intolerable toxicity, doctor decision, or patient withdrawal of consent. Patients with radiological disease progression who were clinically stable could continue study treatment until progression was confirmed on a scan obtained at least 4 weeks later. Patients who achieved confirmed complete response could discontinue treatment if they received treatment for at least 24 weeks and received at least two doses of treatment beyond the time complete response was initially declared. Patients in the paclitaxel group were not permitted to cross over to receive pembrolizumab.

Radiographic imaging was done every 6 weeks. Response was assessed per RECIST v1.1[10] by masked and independent central review. Adverse events were collected throughout treatment and for 30 days thereafter (90 days for serious adverse events and events of special interest to pembrolizumab) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. PD-L1 expression was assessed in archival or newly collected tumour samples at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies; Carpinteria, CA, USA) and measured using the CPS, defined as the number of PD-L1–positive cells (tumour cells, lymphocytes, macrophages) as a proportion of the total number of tumour cells multiplied by 100. DNA mismatch repair in five mononucleotide repeat markers (*NR21*, *NR24*, *BAT25*, *BAT26*, *MONO27*) was assessed using DNA extracted from formalin-fixed, paraffin-embedded tumour samples and blood (normal control) using the MSI Analysis System version 1.2 (Promega; Madison, WI, USA). Tumours with high levels of microsatellite instability were those for which two or more markers were changed compared with normal controls.

See Online for appendix

Outcomes

Primary endpoints were overall survival, defined as the time from randomisation to death from any cause, and progression-free survival, defined as the time from randomisation to radiological disease progression (assessed per RECIST v1.1 by masked and independent central review) or death from any cause, in patients with a PD-L1 CPS of 1 or higher. Secondary efficacy endpoints included: response rate, defined as the proportion of patients with complete or partial response, and duration of response, defined as the time from first documented

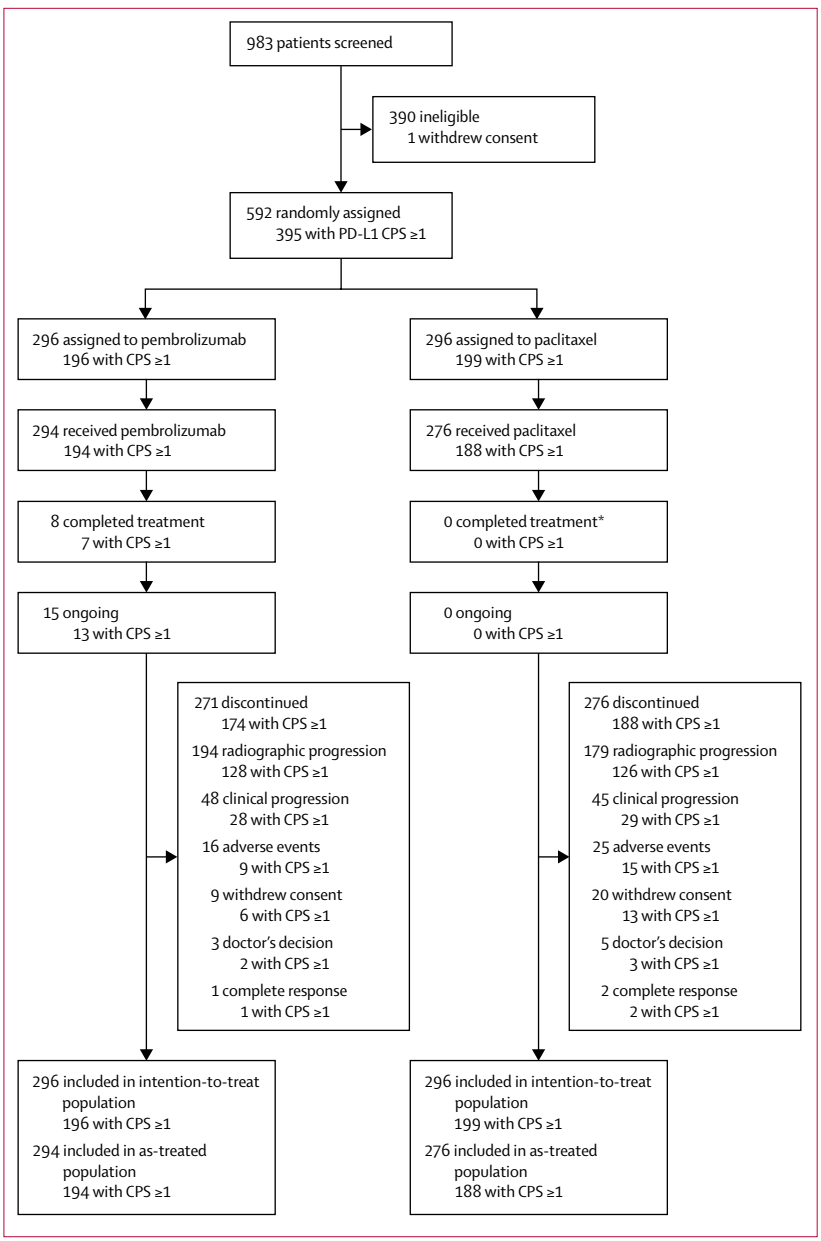


Figure 1: **Trial profile**
PD-L1=programmed death ligand 1. CPS=combined proportion score. *There was no maximum number of doses of paclitaxel.

complete or partial response to radiological disease progression or death due to any cause (both assessed per RECIST v1.1 by masked and independent central review and by investigator assessment) in patients with a PD-L1 CPS of 1 or higher and in the total population; progression-free survival (assessed per RECIST v1.1 by masked and independent central review) and overall survival in the total population; progression-free survival (assessed per RECIST v1.1 by investigator assessment and per irRECIST by masked and independent central review) in the population with CPS of 1 or higher and in the total population; and time to progression, defined as the time from randomisation to radiological disease progression (assessed per RECIST v1.1 by masked and independent central review and by investigator assessment) in the population with CPS of 1 or higher and in the total population. Safety in all patients, irrespective of CPS, was also a secondary endpoint and was assessed by clinical review of all relevant parameters, including adverse events, laboratory tests, and vital signs.

Statistical analysis

Overall survival, progression-free survival, and response rate were analysed in the intention-to-treat population, defined as all patients who were randomly allocated to treatment, irrespective of whether they received the treatment. Duration of response was analysed in all patients who had a best response of complete or partial response. Safety was assessed in all patients who received at least one dose of study treatment.

The protocol specified one interim analysis and a final analysis. After reviewing the results of the interim analysis of overall survival, which was done by an unmasked statistician and was the primary analysis of progression-free survival, the external data monitoring committee recommended the study continue as planned. From inception, the study was designed to show a difference in overall survival or progression-free survival in patients with a PD-L1 CPS of 1 or higher. The final analysis was planned for when at least 290 deaths occurred in patients with a CPS of 1 or higher or about 15 months after the last patient was randomised, whichever occurred later. Assuming overall survival follows an exponential distribution with a median of 7·5 months in the paclitaxel group (based on data from the RAINBOW trial[11]), an enrolment period of 14 months, a hazard ratio (HR) of 0·67 between pembrolizumab and paclitaxel, and an annual dropout rate of 2%, we calculated that 360 patients with a CPS of 1 or higher would have to be enrolled to provide 91% power to detect an HR of 0·67 for overall survival at a one-sided α value of 0·0215. The Hwang-Shih-DeCani alpha-spending function with the gamma parameter of –4 was used to construct the actual boundaries at the final analysis on the basis of the actual α spent at the interim analysis and the number of events recorded at the interim and final analyses. The family-wise type I error rate was strictly controlled at a one-sided α of 2·50%, with 0·35% allocated to the hypothesis of progression-free survival and 2·15% allocated to the hypothesis of overall survival (appendix); superiority of pembrolizumab was only required for one of the primary endpoints to conclude a significant treatment effect for pembrolizumab. With 326 deaths observed in the population of patients with PD-L1 CPS of 1 or higher at the time of final analysis, the significance threshold for overall survival was p=0·0135 (one-sided).

For overall survival, data for patients who were alive or lost to follow-up were censored at the time of last

confirmed contact. For progression-free survival, data for patients without disease progression or who were lost to follow-up were censored at the time of last tumour assessment. For duration of response, data for patients who were alive with ongoing response at the time of analysis or who discontinued the study without radiographic evidence of progression were censored at the time of the last radiographic assessment showing response. For both progression-free survival and duration of response, data for patients who started new anticancer therapy without radiographic evidence of progression were censored at the time of the last tumour assessment before new anticancer therapy was initiated.

SAS version 9.4 was used for all statistical analyses. Overall survival, progression-free survival, and duration of response were estimated using the Kaplan-Meier method. Treatment differences in overall and progression-free survival were assessed using the log-rank test stratified by the randomisation stratification factors. HRs and their associated 95% CIs were calculated using stratified Cox proportional hazards models with Efron's method of tie handling. In a post-hoc analysis designed to account for the non-proportional hazards effect associated with the overall survival curves for immunotherapy, the treatment difference in overall survival was assessed using the weighted log-rank test from the Fleming-Harrington G(ρ–γ) family with ρ value of 1 and γ value of 1,[12] such that events that occurred at middle timepoints were weighted more heavily than early and late events, with stratification by geographical region and time to progression on first-line therapy. The response rate was compared between treatment groups using the Miettinen and Nurminen method.

This trial is registered with ClinicalTrials.gov, NCT02370498.

Role of the funding source

The funder participated in study design, data analysis and interpretation, and manuscript writing. The funder maintained the study database. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Results

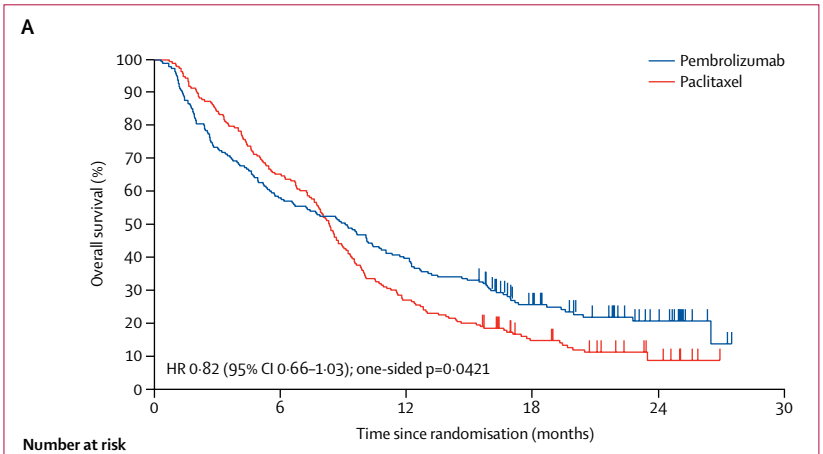
983 patients were screened for enrolment between June 4, 2015, and July 26, 2016. 593 patients met all eligibility criteria; one patient withdrew consent, and the remaining 592 patients were randomly assigned to pembrolizumab (n=296) or paclitaxel (n=296); at least one dose of treatment was received by 294 patients in the pembrolizumab group and 276 patients in the paclitaxel group (figure 1). 395 randomly allocated patients had a PD-L1 CPS of 1 or higher (196 patients in the pembrolizumab group and 199 patients in the paclitaxel group); of these, 194 patients in the pembrolizumab group and 188 patients in the paclitaxel received at least one dose of treatment. In the total population, 136 (46%) of

	All patients		Patients with PD-L1 CPS ≥1	
	Pembrolizumab (n=296)	Paclitaxel (n=296)	Pembrolizumab (n=196)	Paclitaxel (n=199)
Age (years)	62·5 (54–70)	60·0 (53–68)	64·0 (57–70·5)	61·0 (54–68)
≤65 years	177 (60%)	194 (66%)	107 (55%)	125 (63%)
Men	202 (68%)	208 (70%)	146 (74%)	140 (70%)
Region				
Europe, Israel, North America, and Australia	190 (64%)	187 (63%)	131 (67%)	132 (66%)
Asia	88 (30%)	89 (30%)	52 (27%)	52 (26%)
Rest of world	18 (6%)	20 (7%)	13 (7%)	15 (8%)
ECOG performance status				
0	127 (43%)	137 (46%)	88 (45%)	92 (46%)
1	169 (57%)	158 (53%)	108 (55%)	106 (53%)
2	0	1 (<1%)*	0	1 (<1%)*
Histology				
Adenocarcinoma	235 (79%)	233 (79%)	159 (81%)	158 (79%)
Tubular adenocarcinoma	20 (7%)	30 (10%)	12 (6%)	23 (12%)
Signet-ring cell carcinoma, diffuse type	15 (5%)	11 (4%)	6 (3%)	4 (2%)
Other	25 (8%)	22 (7%)	18 (9%)	14 (7%)
Missing	1 (<1%)	0	1 (<1%)*	0
Histological subtype				
Diffuse	85 (29%)	65 (22%)	51 (26%)	40 (20%)
Intestinal	44 (15%)	74 (25%)	30 (15%)	49 (25%)
Mixed	10 (3%)	10 (3%)	9 (5%)	7 (4%)
Unknown	157 (53%)	147 (50%)	106 (54%)	103 (52%)
Primary location				
Stomach	207 (70%)	200 (68%)	134 (68%)	126 (63%)
Gastro-oesophageal junction	89 (30%)	96 (32%)	62 (32%)	73 (37%)
Previous gastrectomy				
Total	45 (15%)	51 (17%)	30 (15%)	32 (16%)
Subtotal	31 (10%)	42 (14%)	19 (10%)	26 (13%)
Partial	30 (10%)	19 (6%)	18 (9%)	13 (7%)
None	190 (64%)	184 (62%)	129 (66%)	128 (64%)
PD-L1 CPS				
≥1	196 (66%)	199 (67%)	196 (100%)	199 (100%)
<1	99 (33%)	96 (32%)	0	0
Unknown	1 (<1%)	1 (<1%)	0	0
Time to progression on first-line therapy				
<6 months	186 (63%)	182 (61%)	126 (64%)	129 (65%)
≥6 months	110 (37%)	114 (39%)	70 (36%)	70 (35%)
HER2 positive	48 (16%)	62 (21%)	36 (18%)	41 (21%)
Current disease stage				
Metastatic	292 (99%)	294 (99%)	192 (98%)	198 (99%)
Locally advanced	4 (1%)	2 (<1%)	4 (2%)	1 (<1%)
Peritoneal metastasis	82 (28%)	84 (28%)	50 (26%)	49 (25%)
Presence of ascites	47 (16%)	43 (15%)	20 (10%)	26 (13%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed death ligand 1. CPS=combined positive score. *The ECOG performance status was 0 during screening but increased to 2 at the time of randomisation; this patient did not receive study treatment.

Table 1: **Baseline characteristics in the overall and PD-L1 CPS ≥1 intention-to-treat populations**

296 patients in the pembrolizumab group and 171 (58%) of 296 patients in the paclitaxel group received at least one subsequent therapy. The most common subsequent therapies in the pembrolizumab group were paclitaxel (96 [32%] of 296 patients), irinotecan hydrochloride (60 [20%]), and ramucirumab (47 [16%]); no patients received subsequent immunotherapy. The most common subsequent therapies in the paclitaxel group were irinotecan (108 [36%] of 296 patients), fluorouracil (47 [16%]), and ramucirumab (47 [16%]); 30 (10%) of 296 patients received subsequent immunotherapy.



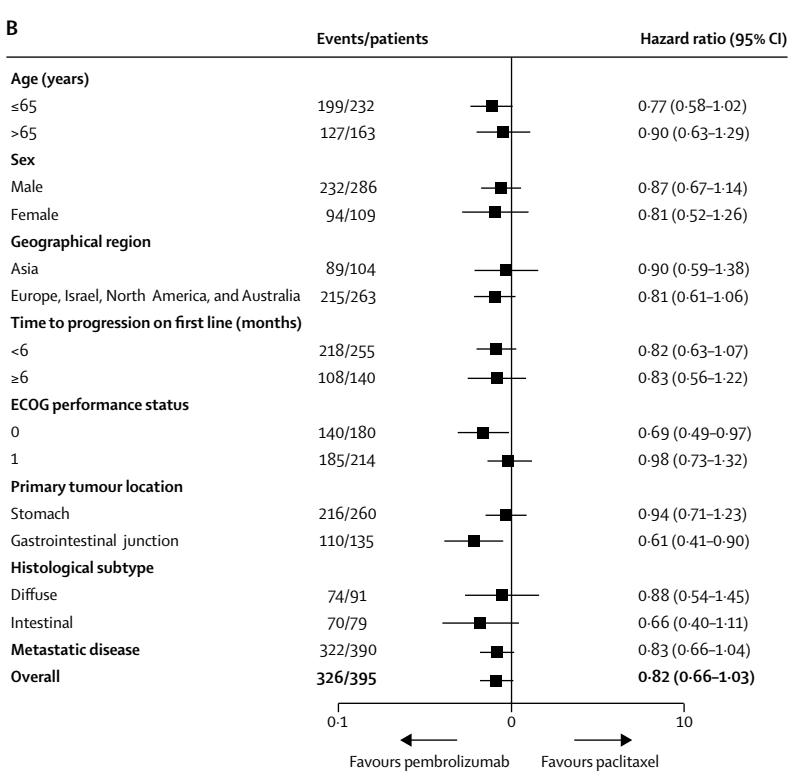


***Figure 2*: Analysis of overall survival in the PD-L1 combined positive score ≥1 population**
(A) Kaplan-Meier analysis. (B) Protocol-specified subgroup analysis. PD-L1=programmed death ligand 1. ECOG=Eastern Cooperative Oncology Group.

As of Oct 26, 2017 (data cutoff date), median follow-up was 7·9 months (IQR 3·4–14·6) in the total population and 8·5 months (3·7–15·7) in the population with a PD-L1 CPS of 1 or higher. No patients remained on paclitaxel, whereas 15 (5%) of 296 patients in the pembrolizumab group, including 13 (7%) of 196 patients with a CPS of 1 or higher, remained on pembrolizumab (figure 1). Additionally, eight (3%) of 296 patients in the pembrolizumab group completed study treatment, including seven (4%) of 196 patients with a PD-L1 CPS of 1 or higher.

Baseline demographics and disease characteristics were as expected and were generally balanced between groups in the total population and the population with a PD-L1 CPS of 1 or higher (table 1). Most patients were male, had gastric adenocarcinoma, had HER2-negative tumours, and had disease progression within 6 months of first-line therapy.

At the time of data cutoff, 326 patients in the population with a PD-L1 CPS of 1 or higher had died (151 [77%] of 196 patients in the pembrolizumab group and 175 [88%] of 199 patients in the paclitaxel group). Pembrolizumab did not significantly prolong overall survival (HR 0·82, 95% CI 0·66–1·03; one-sided p=0·0421). Median overall survival was 9·1 months (95% CI 6·2–10·7) for pembrolizumab and 8·3 months (95% CI 7·6–9·0) for paclitaxel (figure 2). The estimated proportion of patients surviving at 12 months was 40% (95% CI 33–47) with pembrolizumab and 27% (21–33) with paclitaxel; proportions at 18 months were 26% (95% CI 20–32) and 15% (10–20), respectively. In a post-hoc analysis of the treatment difference in overall survival using the weighted log-rank test, the one-sided p-value was 0·0009.

The treatment effect for pembrolizumab versus paclitaxel was mostly similar across subgroups of the population with PD-L1 CPS of 1 or higher, with overlapping CIs in all subgroups (figure 2). Among these protocol-specified subgroups, the pembrolizumab treatment effect was greater in patients with an ECOG performance status of 0 and in patients with a primary tumour in the gastro-oesophageal junction. Median overall survival in patients with an ECOG performance status of 0 was 12·3 months (95% CI 9·7–15·9) with pembrolizumab versus 9·3 months (8·3–10·5) with paclitaxel (HR 0·69, 95% CI 0·49–0·97; figure 3A); median overall survival in patients with an ECOG performance status of 1 was 5·4 months (95% CI 3·7–7·7) with pembrolizumab versus 7·5 months (95% CI 5·3–8·4) with paclitaxel (HR 0·98, 95% CI 0·73–1·32; figure 3B). In post-hoc analysis, the pembrolizumab treatment effect was greater for patients with a PD-L1 CPS of 10 or higher (HR 0·64, 95% CI 0·41–1·02; median overall survival 10·4 months [95% CI 5·9–17·3] with pembrolizumab *vs* 8·0 months [5·1–9·9] with paclitaxel; figure 3C) and for patients whose tumours had high levels of microsatellite instability, irrespective of the CPS

(HR 0·42, 95% CI 0·13–1·31; median overall survival not reached [95% CI 5·6 months–not reached] *vs* 8·1 months [2·0–16·7]; appendix). In the protocol-specified subgroup with a PD-L1 CPS less than 1, the HR was 1·20 (95% CI 0·89–1·63), and median overall survival was 4·8 months (95% CI 3·9–6·1) with pembrolizumab versus 8·2 months (6·8–10·6) with paclitaxel (appendix).

In the population with PD-L1 CPS of 1 or higher, 361 patients had disease progression or died, including 177 (90%) of 196 patients in the pembrolizumab group and 184 (94%) of 199 patients in the paclitaxel group. The HR for progression-free survival for pembrolizumab versus paclitaxel was 1·27 (95% CI 1·03–1·57; figure 4). Median progression-free survival was 1·5 months (95% CI 1·4–2·0) for pembrolizumab and 4·1 months (3·1–4·2) for paclitaxel. The estimated proportion of patients alive and without disease progression at 12 months was 14% (95% CI 9–19) and 9% (5–14), respectively. The HR for progression-free survival in the protocol-specified population with PD-L1 CPS less than 1 was 2·05 (95% CI 1·50–2·79; appendix).

In the population of patients with a PD-L1 CPS of 1 or higher, confirmed responses were observed in 31 of 196 patients in the pembrolizumab group (response rate 16%, 95% CI 11–22) and in 27 of 199 patients in the paclitaxel group (response rate 14%, 95% CI 9–19); complete responses were observed in seven (4%) of 196 patients in the pembrolizumab group and five (3%) of 199 patients in the paclitaxel group. Responses were more durable in the pembrolizumab group than in the paclitaxel group, with a median response duration of 18·0 months (95% CI 8·3–not estimable) versus 5·2 months (3·2–15·3; appendix). Response rates in the subgroups with PD-L1 CPS less than 1 and CPS of 10 or higher and in ECOG performance status subgroups of the population with a PD-L1 CPS of 1 or higher are shown in the appendix. In a post-hoc analysis of patients whose tumours had high levels of microsatellite instability, irrespective of CPS, responses were observed in seven (47%) of 15 patients in the pembrolizumab group and in two (17%) of 12 patients in the paclitaxel group.

Similar to the findings for progression-free and overall survival, pembrolizumab did not prolong time to progression compared with paclitaxel (appendix). As expected, the treatment effect for pembrolizumab for overall survival was less in the total population than in the population with a PD-L1 CPS of 1 or higher; similarly,

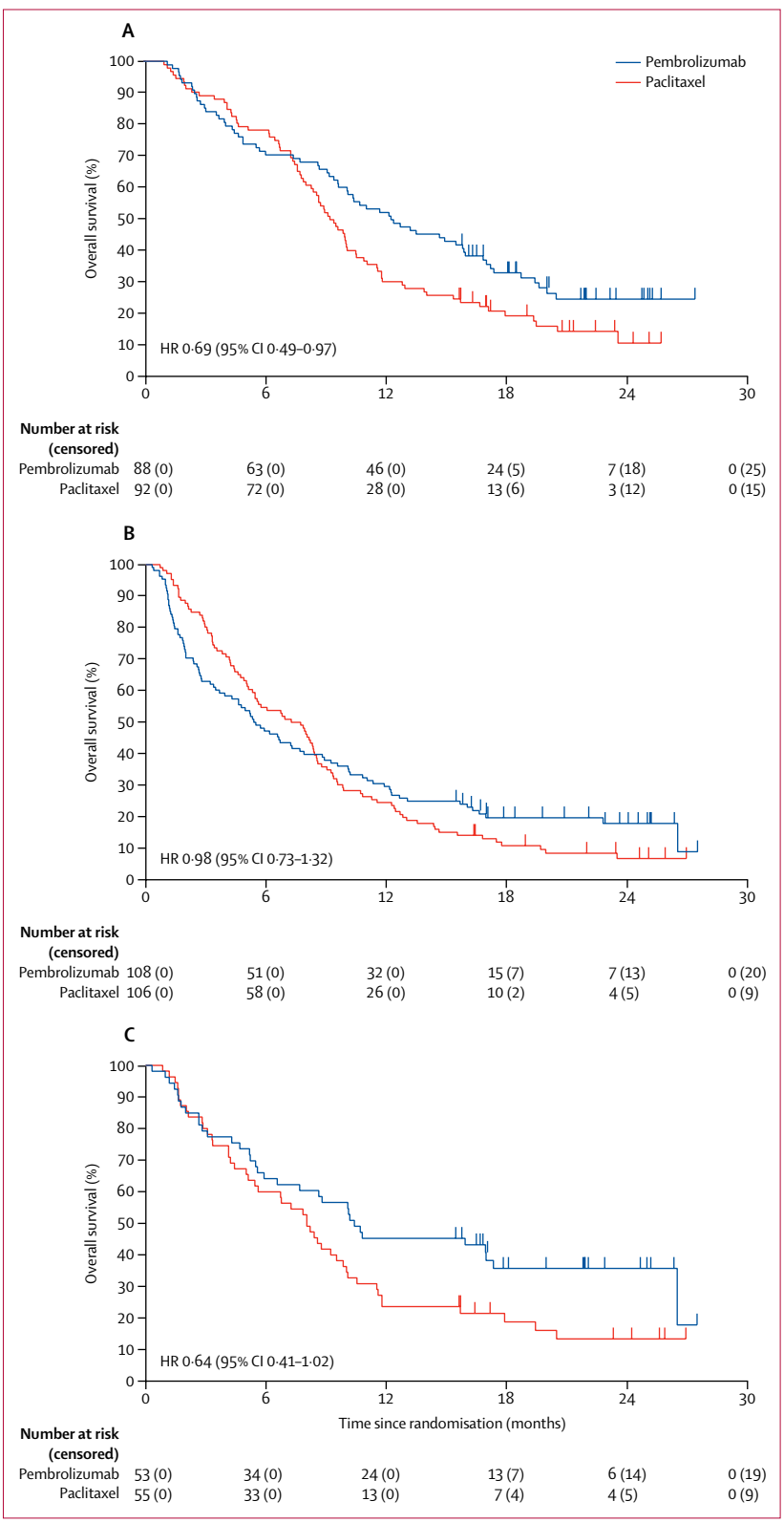


Figure 3: **Kaplan-Meier analysis of overall survival in select subgroups of the PD-L1 combined positive score ≥1 population**
(A) Protocol-specified subgroup analysis of patients with an ECOG performance status of 0 in the combined positive score of 1 or higher population. (B) Protocol-specified subgroup analysis of patients with an ECOG performance status of 1 in the combined positive score of 1 or higher population. (C) Post-hoc subgroup analysis of patients with a PD-L1 combined positive score of 10 or higher. PD-L1=programmed death ligand 1. ECOG=Eastern Cooperative Oncology Group.

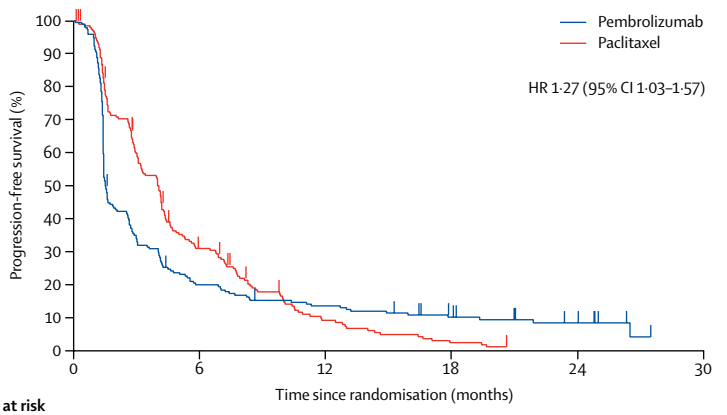


Figure 4: **Kaplan-Meier analysis of progression-free survival in the population with a PD-L1 combined positive score of 1 or higher**
PD-L1=programmed death ligand 1.

	Pembrolizumab (n=294)		Paclitaxel (n=276)	
	Any grade	Grade 3–5	Any grade	Grade 3–5
Related to treatment				
Any	155 (53%)	42 (14%)	232 (84%)	96 (35%)
Occurring in ≥10% of patients in either group*				
Fatigue	35 (12%)	7 (2%)	64 (23%)	13 (5%)
Decreased appetite	24 (8%)	2 (<1%)	43 (16%)	0
Nausea	17 (6%)	1 (<1%)	50 (18%)	2 (<1%)
Diarrhoea	16 (5%)	1 (<1%)	38 (14%)	1 (<1%)
Anaemia	10 (3%)	7 (2%)	39 (14%)	12 (4%)
Alopecia	1 (<1%)	0	111 (40%)	3 (1%)
Neuropathy, peripheral	1 (<1%)	0	40 (14%)	6 (2%)
Neutrophil count decreased	0	0	35 (13%)	28 (10%)
Peripheral sensory neuropathy	0	0	35 (13%)	3 (1%)
Of special interest*†				
Hypothyroidism	23 (8%)	0	1 (<1%)	0
Hyperthyroidism	12 (4%)	0	1 (<1%)	0
Pneumonitis	8 (3%)	2 (<1%)	0	0
Infusion reactions	5 (2%)	0	13 (5%)	1 (<1%)
Hepatitis	4 (1%)	4 (1%)	0	0
Hypophysitis	4 (1%)	2 (<1%)	0	0
Colitis	3 (1%)	1 (<1%)	4 (1%)	3 (1%)
Severe skin reactions	1 (<1%)	1 (<1%)	1 (<1%)	0
Type 1 diabetes	1 (<1%)	0	0	0
Pancreatitis	0	0	1 (<1%)	1 (<1%)

*Events are listed in descending order in the pembrolizumab group. †Adverse events of interest to pembrolizumab are based on their likely immune aetiology, irrespective of attribution to study treatment. In addition to the specific preferred terms listed, related terms were also included.

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

the HRs for progression-free survival and time to progression in the total population were higher than those in the population with a PD-L1 CPS of 1 or higher (appendix). Although the response rate was lower for pembrolizumab in the total population, the duration of response was the same as that observed in the population with a PD-L1 CPS of 1 or higher (appendix). Outcomes for progression-free survival, time to progression, and response rate based on RECIST v1.1 by investigator assessment were generally similar to assessment by masked and independent central review (appendix).

Of 570 patients who received at least one dose of study treatment, irrespective of PD-L1 CPS, the mean treatment duration was 4·4 months (SD 6·1) in the 294 patients who received at least one dose of pembrolizumab and 3·5 months (3·4) in the 276 patients who received at least one dose of paclitaxel. Adverse events attributed to study treatment by the investigator occurred in 155 (53%) of 294 patients treated with pembrolizumab and 232 (84%) of 276 patients treated with paclitaxel (table 2). These events were of grade 3–5 severity in 42 (14%) of 294 patients in the pembrolizumab group and 96 (35%) of 276 patients in the paclitaxel group and led to discontinuation of study treatment in nine (3%) patients and 15 (5%) patients, respectively. Deaths attributed to study treatment occurred in three (1%) of 294 patients in the pembrolizumab group (colitis, interstitial lung disease, and death in one patient each) and in one (<1%) of 276 patients in the paclitaxel group (pulmonary embolism).

Adverse event profiles were as expected for pembrolizumab and paclitaxel (table 2). The most common grade 3–5 adverse events attributed to study treatment were anaemia (seven [2%] of 294 patients) and fatigue (seven [2%]) in the pembrolizumab group and decreased neutrophil count (28 [10%] of 276 patients) and neutropenia (20 [7%]) in the paclitaxel group. Adverse events of interest to pembrolizumab based on their likely immune aetiology, irrespective of attribution to study treatment, occurred in 54 (18%) of 294 patients treated with pembrolizumab and 21 (8%) of 276 patients treated with paclitaxel (table 2). The only adverse events of interest of grade 3–5 severity that occurred in two or more patients in the pembrolizumab group were hepatitis (four [1%] of 294 patients), hypophysitis (two [<1%]), and pneumonitis (two [<1%]).

Discussion

In this randomised, open-label, phase 3 study, pembrolizumab did not significantly improve overall survival compared with paclitaxel in patients with advanced gastric or gastro-oesophageal junction cancer with a PD-L1 CPS of 1 or higher that progressed after one line of chemotherapy containing a platinum and fluoropyrimidine. The overall survival curve for the pembrolizumab group appeared to plateau at about 20 months, supporting a long-term benefit for pembrolizumab in some patients. There was no improvement in progression-free survival or response rate; however, pembrolizumab responses were more durable than paclitaxel responses. The lack of a progression-free survival benefit with pembrolizumab is consistent with findings from other studies of second-line

PD-1 inhibition in advanced cancers, including the KEYNOTE-045 study[13] of pembrolizumab versus investigator's choice of chemotherapy for previously treated advanced urothelial cancer. The safety profile of pembrolizumab was consistent with that previously observed for pembrolizumab in patients with advanced solid tumours and was better overall than that of paclitaxel, with a lower frequency of treatment-related adverse events of any grade, of grade 3 or worse severity, and that led to treatment discontinuation.

The median overall survival in the paclitaxel group was generally consistent with that previously observed for paclitaxel given as second-line therapy for advanced gastric cancer.[11,14] Although the combination of ramucirumab and paclitaxel significantly improved overall survival compared with paclitaxel alone in the second-line advanced gastric cancer setting[11] and is currently the global standard-of-care second-line therapy for patients with advanced gastric cancer and a good performance status, this was not the case when KEYNOTE-061 was designed in late 2014. We therefore chose paclitaxel monotherapy for our control group. We acknowledge that future studies of second-line therapy should use ramucirumab plus paclitaxel combination therapy as the comparator.

Protocol-specified subgroup analysis in the primary population of patients with a PD-L1 CPS of 1 or higher showed that patients with an ECOG performance status of 0 had a greater relative treatment effect with pembrolizumab compared with patients who had a performance status of 1, as did patients with a primary tumour location of the gastro-oesophageal junction compared with the stomach. Better ECOG performance status was also associated with a higher response rate and longer overall survival with pembrolizumab in KEYNOTE-059.[9] The prognostic effect of performance status in KEYNOTE-061 appeared to be more pronounced in the pembrolizumab group than in the paclitaxel group. Further analysis is necessary to determine why the prognostic effect differs between treatment groups.

Combination therapy with pembrolizumab and cytotoxic chemotherapy could help overcome the delayed response of pembrolizumab and the less durable responses of cytotoxic chemotherapy. Data from a small phase 1 cohort of KEYNOTE-059 suggest that pembrolizumab combined with cisplatin and 5-fluorouracil or capecitabine has a manageable safety profile and promising antitumour activity in patients with previously untreated advanced gastric or gastro-oesophageal cancer.[15] In the ongoing phase 3 KEYNOTE-062 study (NCT02494583), the efficacy and safety of this combination is being compared with those of cisplatin and 5-fluorouracil or capecitabine and those of pembrolizumab monotherapy in patients with previously untreated advanced gastric or gastro-oesophageal cancer.

Consistent with results of KEYNOTE-059[9] and study findings for pembrolizumab in other tumour types,[16–18] a relationship between greater PD-L1 expression and a greater treatment effect for pembrolizumab was found in KEYNOTE-061. These data reinforce the utility of PD-L1 expression for selecting patients for treatment with pembrolizumab monotherapy. Of note, data from the Asian ATTRACTION-2 study, in which the anti-PD-1 monoclonal antibody nivolumab was compared with placebo in patients with advanced gastric cancer whose disease progressed after two or more previous chemotherapy regimens, showed a significant benefit for nivolumab in all patients, including those with PD-L1-negative tumours.[19] However, PD-L1 expression in ATTRACTION-2 was assessed retrospectively on tumour cells using the 28-8 pharmDx assay, with PD-L1 expression available for only 39% of patients. In KEYNOTE-061, PD-L1 expression was prospectively assessed on tumour cells and tumour-associated lymphocytes and macrophages using the 22C3 pharmDx assay, which might be a better predictor of outcomes than tumour PD-L1 expression alone.

Defects in mismatch repair result in tumours that have an increased number of somatic mutations, which could induce an innate antitumour immune response and render tumours more responsive to immune checkpoint blockade.[20] On the basis of data from phase 1 and phase 2 studies,[21–23] in which levels of microsatellite instability were assessed locally using PCR or immunohistochemistry, pembrolizumab was approved in the USA for the treatment of patients with previously treated advanced solid tumours of any type that have a high level of microsatellite instability. In a post-hoc exploratory analysis of this study, patients whose tumours had high levels of microsatellite instability (as assessed retrospectively at a central laboratory by PCR and irrespective of PD-L1 CPS) had a particularly large treatment effect with pembrolizumab. These findings confirm the use of mismatch repair deficiency and microsatellite instability as predictive biomarkers for pembrolizumab. Analyses of other biomarkers that might predict response to pembrolizumab, including the presence of Epstein-Barr virus RNA,[8,24] are ongoing.

Examination of the Kaplan-Meier curve for overall survival in the primary population of patients with a PD-L1 CPS of 1 or higher showed that for about the first 8 months after randomisation, the paclitaxel group outperformed the pembrolizumab group. At 8 months, the survival curves crossed. After this divergence, the separation in favour of pembrolizumab was sustained, probably because of the greater durability of benefit in those patients who had response or prolonged stable disease. The crossing of survival curves has been observed in studies of PD-1 and PD-L1 inhibitors in other tumour types[13,25–27] and might reflect the time it takes to induce an effective antitumour immune response. The delayed onset of benefit for immunotherapy and the violation of the proportional hazards assumption highlight the need for alternative statistical methods to

accurately assess the benefit of these therapies.[28] One alternative is to use the weighted log-rank test. A post-hoc analysis of the treatment difference between pembrolizumab and paclitaxel using the weighted log-rank test, such that more weight was placed on the events that occurred around the middle of the follow-up duration (ie, around the time at which the overall survival curves crossed) and less weight on events that occurred early or late, resulted in a one-sided p-value of 0·0009.

To the best of our knowledge, this is the first published report of findings from a global, randomised, active-controlled trial of an immune checkpoint inhibitor in advanced gastric cancer. The other published report of a randomised study of a checkpoint inhibitor for advanced gastric cancer was the aforementioned ATTRACTION-2 study of nivolumab versus placebo in patients from Japan, South Korea, and Taiwan whose disease progressed after two or more prior chemotherapy regimens.[19]

A limitation of this study is the open-label design, which led to the larger number of patients who were randomised but did not receive study treatment in the paclitaxel group than in the pembrolizumab group. These patients probably went on to receive other therapies, which could have affected the results in the paclitaxel group and thus the relative benefit of pembrolizumab versus paclitaxel. Although the treatment groups appeared well balanced, the exclusion of patients with a PD-L1 CPS less than 1 after 83% of patients were enrolled and the change in stratification factors after 21% of patients were enrolled might have introduced bias that affected the results.

Our data show that pembrolizumab monotherapy did not significantly improve overall survival compared with paclitaxel in patients with advanced gastric cancer with a PD-L1 CPS of 1 or higher that progressed on first-line chemotherapy containing a platinum and fluoropyrimidine. However, a benefit from pembrolizumab emerged with long-term follow-up, with clinically meaningful 12-month and 18-month survival estimates of about 40% and 26%, respectively. Protocol-specified and post-hoc exploratory subgroup analyses suggest that the treatment effect of pembrolizumab might be more pronounced in patients with a better performance status, greater levels of PD-L1 expression, and tumours with high levels of microsatellite instability. Along with the favourable safety profile, these data support further exploration to identify patients who are likely to benefit from pembrolizumab monotherapy and the ongoing development of pembrolizumab as part of combination therapy regimens.

Contributors

KS, XC, CM, SPK, AO, and CSF participated in the conception, design, or planning of the study. KS, YJB, MDM, MM, MHR, LF, TO, CC, HCC, KM, EG, WM, RM, ESS, AO, and CSF participated in the acquisition of the data. XC participated in the statistical analysis of the data. KS, YJB, MDM, MM, MHR, LF, TO, CC, HCC, KM, EG, WM, RM, ESS, XC, CM, SPK, AO, and CSF participated in the interpretation of the results. KS, XC, CM, and SPK participated in drafting of the manuscript. All author provided critical review or revision of the manuscript. All authors approved to submit the manuscript for publication.

Declaration of interests

KS reports personal fees outside the submitted work for serving in a consulting or advisory role from Astellas Pharma, Lilly, Bristol-Myers Squibb, Takeda, Pfizer, and Ono Pharmaceutical; personal fees as honoraria outside the submitted work from Novartis, AbbVie, and Yakult; and grants outside the submitted work from Lilly, Ono Pharmaceutical, Dainippon Sumoitomo Pharma, Daiichi Sankyo, Taiho Pharmaceutical, Chugai Pharma, and MSD. YJB reports grants to the institution for clinical trials outside the submitted work from AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serono, Bayer, GlaxoSmithKline, Bristol-Myers Squibb, Pfizer, Eli Lilly, Boehringer Ingelheim, MacroGenics, Boston Biomedical, FivePrime, CKD, Ono, Otsuka, Taiho, Takeda, BeiGene, Hanmi, Green Cross, Curis, Daiichi Sankyo, and Astellas and other for serving in a consulting or advisory outside the submitted work from AstraZeneca, Novartis, Genentech/Roche, MSD, Pfizer, Bayer, Bristol-Myers Squibb, Eli Lilly, Merck Serono, FivePrime, Taiho, Ono, ADC Therapeutics, Green Cross, and Samyang Biopharm. MM reports personal fees for advisory boards, lectures, and speakers' bureau outside the submitted work from MSD. MHR reports other outside the submitted work for serving in a consultant/advisory role and receiving honorarium from Dae Hwa Pharmaceutical, Eli Lilly, Bristol-Myers Squibb, ONO Pharmaceutical, and Taiho. TO reports personal fees during the conduct of the study for serving as an investigator from Merck & Co. CC reports personal fees outside the submitted work for serving as a speaker from MSD, Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, and Tecnofarma; personal fees outside the submitted work for serving as a principal investigator from MSD, Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, Roche, AstraZeneca, Astellas, and Novartis; personal fees outside the submitted work for serving as a consultant or advisory board member from MSD, Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, Tecnofarma, AstraZeneca, and Lilly; and personal fees outside the submitted work for participating in a sponsored educational program from MSD, Bristol-Myers Squibb, Boehringer Ingelheim, and Tecnofarma. HCC reports grants outside the submitted work from Lilly, GlaxoSmithKline, MSD, Merck-Serono, Bristol-Myers Squibb/Ono, and Taiho; personal fees outside the submitted word for serving on a speakers' bureau from Merck-Serono, Lilly, and Foundation Medicine; and personal fees outside the submitted work for serving as a consultant from Taiho, Celltrion, MSD, Lilly, Quintiles, Bristol-Myers Squibb, and Merck-Serono. KM reports grants outside the submitted work from Ono Pharmaceutical, MSD, Daiichi Sankyo, Kyowa Hakko Kirin, Shionogi Pharmaceutical, and Gilead Sciences and personal fees outside the submitted work from Chugai Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical, Merck Serono, Eli Lilly, and Takult Honsha. E Goekkurt reports personal fees during the conduct of the study for serving as an investigator from MSD; personal fees outside the submitted work for giving lectures from MSD, Lilly, and Servier; and personal fees outside the submitted work for serving in an advisory role from MSD, Bristol-Myers Squibb, Lilly, Sanofi, Servier, and Merck. RSM reports grants outside the submitted work from Pfizer, Amgen, and Celgene; personal fees outside the submitted work from Clovis, Pfizer, and Bristol-Myers Squibb; and research funding outside the submitted work from Bristol-Myers Squibb, Merck, Bayer, and Janssen. XC reports personal fees during the conduct of the study for serving as a full-time employee of Merck Sharp & Dohme, a subsidiary of Merck & Co, Kenilworth, NJ, USA. SPK reports personal fees during the conduct of the study for serving as a full-time employee of Merck Sharp & Dohme, a subsidiary of Merck & Co. CM reports personal fees during the conduct of the study for serving as a full-time employee of Merck Sharp & Dohme, a subsidiary of Merck & Co, Kenilworth, NJ, USA. AO reports grants during the conduct of the study from Bristol-Myers Squibb and personal fees during the conduct of the study from Bristol-Myers Squibb, Ono Pharmaceutical Company, and Chugai. CSF reports personal fees outside the submitted work for serving as a consultant from Entrinsic Health, Genentech, Merck & Co, Sanofi, Five Prime Therapeutics, Merrimack, Bayer, Agios, Taiho, Kew, Eli Lilly, and Bain Capital and personal fees outside the submitted work for serving as a board member from CytomX. All other authors declare no competing interests.

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