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ORIGINAL RESEARCH

First-Line Pembrolizumab Plus Chemotherapy for HER2-Negative Advanced Gastric Cancer: China Subgroup Analysis of the Randomized Phase 3 KEYNOTE-859 Study

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ABSTRACT

***Introduction*:** Results of the global, randomized, phase 3 KEYNOTE-859 study (*N* = 1579) showed that first-line pembrolizumab plus chemotherapy produced a statistically significant and clinically meaningful improvement in overall survival (OS) with manageable toxicity versus placebo plus chemotherapy in patients with locally advanced or metastatic human epidermal growth factor receptor 2 (HER2)–negative gastric or gastroesophageal junction cancer. This subgroup analysis was conducted to investigate outcomes in patients enrolled in mainland China.

***Methods*:** Adults with previously untreated advanced or metastatic HER2-negative gastric cancer or gastroesophageal junction adenocarcinoma were randomly assigned (1:1) to receive pembrolizumab or placebo with fluoropyrimidine- and platinum-containing chemotherapy. The primary outcome was OS. Secondary outcomes included progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR), all assessed per RECIST v1.1 by blinded independent central review, and safety.

***Results*:** Overall, 236 patients were enrolled in mainland China (126 pembrolizumab plus chemotherapy; 110 placebo plus chemotherapy). Median time from randomization to database

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cutoff (October 3, 2022) was 24.7 months (range 15.3–38.9). Median OS was 15.9 months (95% confidence interval [CI] 13.2–19.2) for pembrolizumab plus chemotherapy versus 12.2 months (95% CI 10.6–14.1) for placebo plus chemotherapy (hazard ratio [HR], 0.68; 95% CI 0.50–0.91). Median PFS was 8.1 months (95% CI 6.9–9.6) for pembrolizumab plus chemotherapy versus 5.7 months (95% CI 4.5–6.5) for placebo plus chemotherapy (HR, 0.65; 95% CI 0.48–0.88). ORR was 69.0% for pembrolizumab plus chemotherapy versus 45.5% for placebo plus chemotherapy; median DOR was 8.2 months (range 1.2+ to 34.6+) versus 5.5 months (range 1.3+ to 31.2+), respectively. Grade 3–5 treatment-related adverse events occurred in 82 patients (65.6%) treated with pembrolizumab plus chemotherapy and 54 patients (49.1%) treated with placebo plus chemotherapy.

Conclusion: Consistent with efficacy in the overall population from KEYNOTE-859, first-line pembrolizumab plus chemotherapy showed improved efficacy, versus placebo plus chemotherapy, and manageable safety in patients enrolled in mainland China.

Trial Registration: Clinicaltrials.gov: NCT03675737.

Keywords: China; Gastric adenocarcinoma; Gastroesophageal junction adenocarcinoma; HER2-negative; Pembrolizumab

Key Summary Points

Why carry out this study?

More than 30% of patients with gastric cancer in China are diagnosed with stage IV disease, which has a 5-year survival rate of < 10%.

The global, randomized, phase 3 KEYNOTE-859 study was conducted to compare the efficacy and safety of pembrolizumab plus chemotherapy with placebo plus chemotherapy for patients with previously untreated advanced or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric and gastroesophageal junction adenocarcinoma.

We report results from a subgroup analysis of the KEYNOTE-859 study in patients enrolled at sites in mainland China.

What was learned from the study?

First-line pembrolizumab plus chemotherapy showed improved efficacy, versus placebo plus chemotherapy, and manageable safety in patients enrolled in mainland China.

The data from both the global and the subgroup populations of the KEYNOTE-859 study are encouraging and provide additional support for use of pembrolizumab in combination with chemotherapy as a therapeutic option in the first-line setting.

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INTRODUCTION

In 2020, gastric cancer was the fifth most common cancer in the world, with more than 1 million new cases estimated, and the fourth leading cause of cancer death, resulting in 769,000 deaths [1, 2]. Cases in China represented almost half the global total of new gastric cancer cases (478,508; 44%) and associated deaths (373,789; 48%). Additionally, more than 30% of patients with gastric cancer in China are diagnosed with stage IV disease, which has a 5-year survival rate of < 10% [3–5].

The molecular classification of gastric cancer is based on human epidermal growth factor receptor 2 (HER2) expression in the tumoral tissue, and nearly 85% of gastric cancers are HER2-negative in Asia [6, 7]. Systemic chemotherapy with or without immunotherapy is the standard first-line treatment for advanced and metastatic HER2-negative gastric cancer in China [6]. For patients with tumors that are programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥ 5/tumor area positivity (TAP) ≥ 5%, nivolumab, sintilimab, and tislelizumab are approved for use [8].

The global, randomized, phase 3 KEYNOTE-859 study (NCT03675737) was conducted to compare the efficacy and safety of pembrolizumab plus chemotherapy with placebo plus chemotherapy for patients with previously untreated advanced or metastatic HER2-negative gastric and gastroesophageal junction (GEJ) adenocarcinoma [9]. Results from the interim analysis in the intention-to-treat (ITT) population showed that pembrolizumab plus chemotherapy produced a statistically significant and clinically meaningful improvement in overall survival [OS; 12.9 months vs. 11.5 months; hazard ratio (HR), 0.78 (95% CI 0.70–0.87); $p < 0.0001$], progression-free survival [PFS; 6.9 months vs. 5.6 months; HR, 0.76 (95% CI 0.67–0.85); $p < 0.0001$], and objective response rate [ORR; 51% vs. 42%; between-group difference, 9.3% (95% CI 4.4–14.1); $p < 0.0001$] compared with placebo plus chemotherapy [9]. These findings were consistent in patients with PD-L1–positive (CPS ≥ 1 and CPS ≥ 10) disease. Safety was manageable and consistent with the known safety profile of each agent alone. We report results from a subgroup analysis of the KEYNOTE-859 study in patients enrolled at sites in mainland China.

METHODS

Study Design

Details of the KEYNOTE-859 study design and key eligibility criteria have been published previously [9]. In brief, eligible patients were adults with previously untreated locally advanced but unresectable or metastatic HER2-negative gastric and GEJ adenocarcinoma. Patients must have had measurable disease per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), by investigator assessment, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and adequate tumor tissue for PD-L1 assessment. The study protocol and amendments, including changes that affected study design, were approved by the appropriate local or national ethics committee at each participating center. All participants provided written informed consent. The study was done in accordance with the Good Clinical Practice requirements outlined by the International Council on Harmonization, the ethical principles of the Declaration of Helsinki, and all local regulations. Institutional review boards or independent ethics committees at each site approved the protocol. The full list of participating sites and ethics committees can be found in the Supplementary Materials Table S5.

Treatment

Enrolled patients were randomly assigned (1:1) to receive pembrolizumab 200 mg or placebo, which was administrated intravenously on day 1 of each 3-week cycle for up to 35 cycles (approximately 2 years). Investigator's choice of chemotherapy was fluorouracil (800 mg/m^2 per day intravenously) administered continuously on days 1–5 of each 3-week cycle plus cisplatin (80 mg/m^2 intravenously) administered

on day 1 of each 3-week cycle, or capecitabine (oral, 1000 mg/m^2) administered twice daily on days 1–14 of each 3-week cycle plus oxaliplatin (130 mg/m^2 intravenously) administered on day 1 of each 3-week cycle. All treatments were administered until disease progression, unacceptable toxicity, or another discontinuation criterion was met. Randomization was stratified by geographic region (western Europe, Israel, North America, and Australia vs. Asia vs. rest of world), PD-L1 CPS (< 1 vs. ≥ 1), and investigator's choice of chemotherapy (fluorouracil plus cisplatin vs. capecitabine plus oxaliplatin).

Outcomes

The primary end point was OS (time from randomization to death from any cause). Secondary end points included PFS [time from randomization to first documented occurrence of progressive disease (PD) or death from any cause, whichever occurred first], ORR (proportion of patients with a best overall response of complete or partial response), and DOR (time from first complete or partial response until PD or death from any cause, whichever occurred first) per RECIST v1.1 by blinded independent central review, and safety. Adverse events (AEs) were reported using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Treatment-related AEs were determined by the investigator to be related to study treatment. Immune-mediated AEs and infusion reactions were reported based on a list of terms specified by the sponsor intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator.

Statistical Analyses

This subgroup analysis was performed for all patients enrolled at sites in China. Efficacy was evaluated for all randomly assigned patients and for patients with PD-L1–positive tumors (CPS ≥ 1 and CPS ≥ 10). Safety was assessed in all randomly assigned patients who received at least one dose of study treatment.

Overall survival, PFS, and DOR were analyzed using the nonparametric Kaplan–Meier method. Between-group differences in OS and PFS were assessed using a log-rank test. The HRs and associated 95% CIs for OS and PFS were assessed using a Cox proportional model with the Efron method of handling ties. The difference in ORR (and corresponding 95% CI) between the two treatment groups was determined using the Miettinen and Nurminen method. The data cutoff date for this subgroup analysis was October 3, 2022.

RESULTS

Demographic and Baseline Clinical Characteristics

Between November 8, 2018, and June 11, 2021, 1579 patients were randomly assigned to receive pembrolizumab plus chemotherapy (790 patients) or placebo plus chemotherapy (789 patients) in the KEYNOTE-859 study. Of these patients, 236 were enrolled at sites in mainland China (pembrolizumab plus chemotherapy, 126 patients; placebo plus chemotherapy, 110 patients). The median time from randomization to data cutoff was 24.7 months (range 15.3–38.9). Baseline demographics and disease characteristics in the China subgroup were generally similar between treatment groups (Table 1). In brief, median age was 63 years, 73.7% were male, 26.3% were female, and 86.4% had an ECOG performance status score of 1; all patients were of Asian race.

At the data cutoff date, 235 patients had received at least one dose of study treatment [pembrolizumab plus chemotherapy, 125 patients (99.2%); placebo plus chemotherapy, 110 patients (100%)] (Supplementary Fig. S1). Seven patients (5.6%) had completed treatment, and nine patients (7.2%) were still receiving treatment in the pembrolizumab plus chemotherapy group. Two patients (1.8%) had completed treatment, and six patients (5.5%) were still receiving treatment in the placebo plus chemotherapy group. The most common reason for treatment discontinuation in both groups was PD [pembrolizumab

Table 1 Baseline demographic and clinical characteristics in the China subgroup

	Pembrolizumab + chemotherapy (*n* = 126)			Placebo + chemotherapy (*n* = 110)		
	ITT *n* = 126	PD-L1 CPS ≥ 1 *n* = 100	PD-L1 CPS ≥ 10 *n* = 50	ITT *n* = 110	PD-L1 CPS ≥ 1 *n* = 90	PD-L1 CPS ≥ 10 *n* = 40
Age, median (range), years	62.5 (25–77)	63.0 (25–77)	64.0 (41–75)	63.0 (23–78)	64.0 (28–76)	65.0 (31–74)
Age ≥ 65 years	45 (35.7)	38 (38.0)	23 (46.0)	46 (41.8)	41 (45.6)	21 (52.5)
Sex						
Male	91 (72.2)	72 (72.0)	35 (70.0)	83 (75.5)	72 (80.0)	33 (82.5)
Female	35 (27.8)	28 (28.0)	15 (30.0)	24 (24.5)	18 (20.0)	7 (17.5)
ECOG PS score 1	111 (88.1)	88 (88.0)	44 (88.0)	93 (84.5)	77 (85.6)	35 (87.5)
Primary tumor location						
Adenocarcinoma of the GEJ	16 (12.7)	15 (15.0)	10 (20.0)	21 (19.1)	18 (20.0)	9 (22.5)
Adenocarcinoma of the stomach	110 (87.3)	85 (85.0)	40 (80.0)	89 (80.9)	72 (80.0)	31 (77.5)
Disease status						
Locally advanced	5 (4.0)	4 (4.0)	4 (8.0)	4 (3.6)	4 (4.4)	2 (5.0)
Metastatic	121 (96.0)	96 (96.0)	46 (92)	106 (96.4)	86 (95.6)	38 (95.0)
Microsatellite instability status[a]						
High	1 (0.8)	1 (1.0)	1 (2.0)	2 (1.8)	2 (2.2)	1 (2.5)
Low or microsatellite stable	61 (48.4)	49 (49.0)	29 (58.0)	37 (33.6)	29 (32.2)	13 (32.5)
Missing	64 (50.8)	50 (50.0)	20 (40.0)	70 (63.6)	58 (64.4)	25 (62.5)
Unknown	0	0	0	1 (0.9)	1 (1.1)	1 (2.5)
Histologic subtype[b]						
Diffuse	29 (23.0)	20 (20.0)	7 (14.0)	13 (11.8)	9 (10.0)	5 (12.5)
Intestinal	23 (18.3)	19 (19.0)	9 (18.0)	16 (14.5)	9 (10.0)	3 (7.5)
Indeterminate	73 (57.9)	60 (60.0)	33 (66.0)	81 (73.6)	72 (80.0)	32 (80.0)
Liver metastases	71 (56.3)	56 (56.0)	27 (54.0)	55 (50.0)	43 (47.8)	21 (52.5)

Table 1 continued

	Pembrolizumab + chemotherapy (*n* = 126)			Placebo + chemotherapy (*n* = 110)		
	ITT *n* = 126	PD-L1 CPS ≥ 1 *n* = 100	PD-L1 CPS ≥ 10 *n* = 50	ITT *n* = 110	PD-L1 CPS ≥ 1 *n* = 90	PD-L1 CPS ≥ 10 *n* = 40
Prior gastrectomy or esophagectomy[c]	26 (20.6)	14 (14.0)	4 (8.0)	32 (29.1)	21 (23.3)	7 (17.5)
Combination chemotherapy at randomization						
Capecitabine and oxaliplatin	126 (100)	100 (100)	50 (100)	109 (99.1)	89 (98.9)	39 (97.5)
Fluorouracil and cisplatin	0	0	0	1 (0.9)	1 (1.1)	1 (2.5)

Data are *n* (%) unless otherwise specified

CPS combined positive score, *ECOG PS* Eastern Cooperative Oncology Group performance status, *GEJ* gastroesophageal junction, *ITT* intention-to-treat, *PD-L1* programmed cell death ligand 1

[a]One patient in the placebo plus chemotherapy group had unknown microsatellite instability status

[b]One patient in the pembrolizumab plus chemotherapy group had unknown histologic subtype

[c]One patient in each treatment group had missing prior gastrectomy/esophagectomy data

plus chemotherapy, 74 patients (59.2%); placebo plus chemotherapy, 62 patients (56.4%)]. There were 132 patients (55.9%) who received any subsequent systemic anticancer, including 18.2% who received subsequent PD-(L)1 inhibitor therapy (Supplementary Table S1).

Efficacy

By the data cutoff date, 173 patients in the China subgroup had died [pembrolizumab plus chemotherapy, 88 patients (69.8%); placebo plus chemotherapy, 85 patients (77.3%)]. The median OS was 15.9 months (95% CI 13.2–19.2) for pembrolizumab plus chemotherapy versus 12.2 months (95% CI 10.6–14.1) for placebo plus chemotherapy (HR, 0.68; 95% CI 0.50–0.91; Fig. 1A); 24-month OS rates were 33.0% and 21.7%, respectively. Eighty-eight patients (69.8%) in the pembrolizumab plus chemotherapy group and 83 patients (75.5%) in the placebo plus chemotherapy group experienced disease progression or died. The median PFS was 8.1 months (95% CI 6.9–9.6) for pembrolizumab plus chemotherapy versus 5.7 months (95% CI 4.5–6.5) for placebo plus chemotherapy (HR, 0.65; 95% CI 0.48–0.88; Fig. 2a); 24-month PFS rates were 14.7% and 11.2%, respectively. The ORR was 69.0% (95% CI 60.2–77.0) for pembrolizumab plus chemotherapy versus 45.5% (95% CI 35.9–55.2) for placebo plus chemotherapy (Supplementary Table S2); disease control rates (DCR) were 88.9% (95% CI 82.1–93.8) and 83.6% (95% CI 75.4–90.0), respectively. The median DOR was 8.2 months (range 1.2+ to 34.6+) for pembrolizumab plus chemotherapy versus 5.5 months (range 1.3+ to 31.2+) for placebo plus chemotherapy.

In the PD-L1 CPS ≥ 1 population, 140 patients had died by the data cutoff date [pembrolizumab plus chemotherapy, 69 patients (69.0%); placebo plus chemotherapy, 71 patients (78.9%)]. The median OS was 15.8 months (95% CI 12.2–19.9) for pembrolizumab plus chemotherapy versus 11.9 months (95% CI 10.0–14.1) for placebo plus chemotherapy (HR, 0.64; 95% CI 0.46–0.90; Fig. 1b); 24-month OS rates were 35.2% and 20.6%, respectively. Seventy patients (70%) in the pembrolizumab plus chemotherapy

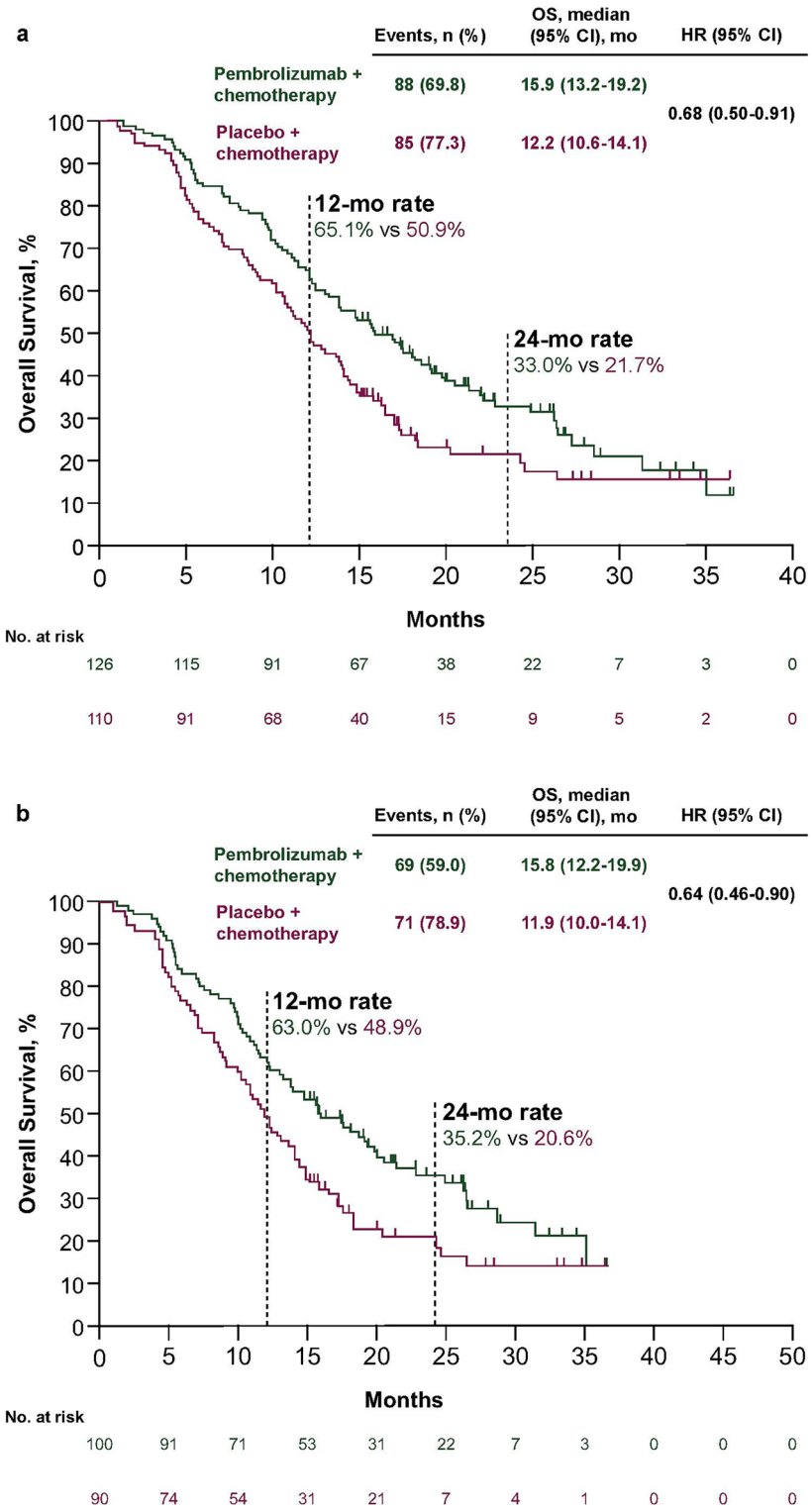

Fig. 1 Kaplan–Meier estimates of overall survival in the China subgroup. **A** ITT population, **B** PD-L1 CPS ≥ 1 population, and **C** PD-L1 CPS ≥ 10 population. *CPS* combined positive score, *HR* hazard ratio, *ITT* intention-to-treat, *OS* overall survival, *PD-L1* programmed cell death ligand 1

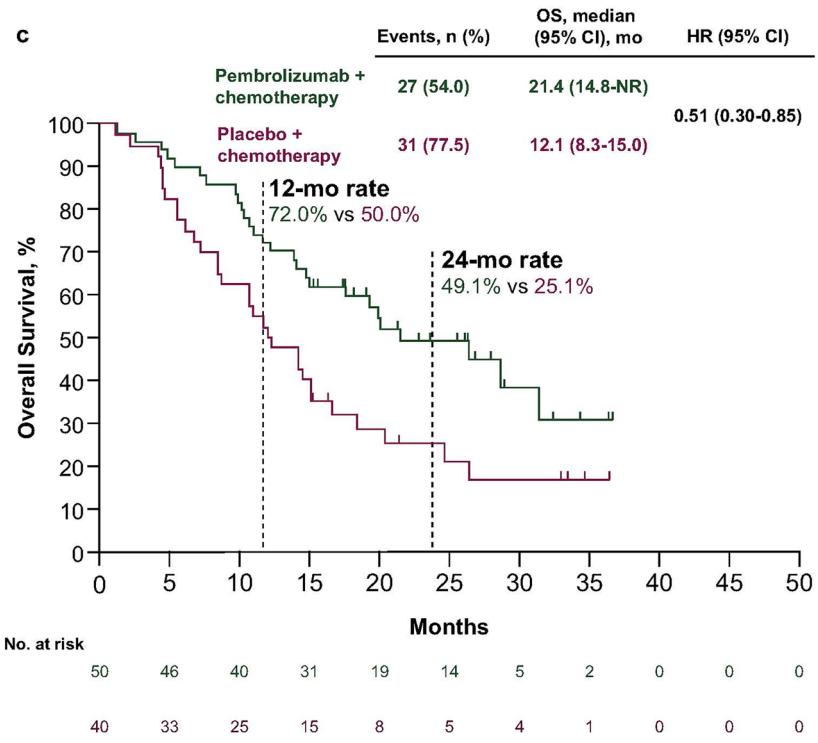

Fig. 1 continued

group and 70 patients (77.8%) in the placebo plus chemotherapy group experienced disease progression or died. The median PFS was 7.2 months (95% CI 6.7–8.6) for pembrolizumab plus chemotherapy versus 5.7 months (95% CI 4.4–6.5) for placebo plus chemotherapy (HR, 0.65; 95% CI 0.46–0.90; Fig. 2b); 24-month PFS rates were 16.5% and 10.5%, respectively. The ORR was 67.0% (95% CI 56.9–76.1) for pembrolizumab plus chemotherapy versus 45.6% (95% CI 35.0–56.4) for placebo plus chemotherapy (Supplementary Table S2); DCRs were 87.0% (95% CI 78.8–92.9) and 84.4% (95% CI 75.3–91.2), respectively. The median DOR was 8.3 months (range 1.2+ to 34.6+) for pembrolizumab plus chemotherapy versus 6.9 months (range 1.3+ to 31.2+) for placebo plus chemotherapy.

In the PD-L1 CPS ≥ 10 population, 58 patients had died by the data cutoff date [pembrolizumab plus chemotherapy, 27 patients (54.0%); placebo plus chemotherapy, 31 patients (77.5%)]. The median OS was 21.4 months (95% CI 14.8 to not reached) for pembrolizumab plus chemotherapy versus 12.1 months (95% CI 8.3–15.0) for placebo plus chemotherapy (HR, 0.51; 95% CI 0.30–0.85; Fig. 1c); 24-month OS rates were 49.1% versus 25.1%, respectively. Thirty patients (60.0%) in the pembrolizumab plus chemotherapy group and 33 patients (82.5%) in the placebo plus chemotherapy group experienced disease progression or died. The median PFS was 9.6 months (95% CI 8.1–14.8) for pembrolizumab plus chemotherapy versus 5.7 months (95% CI 4.4–6.9) for placebo plus chemotherapy (HR, 0.45; 95% CI 0.27–0.74; Fig. 2c); 24-month PFS rates were 29.0% versus 7.9%, respectively. The ORR was 80.0% (95% CI 66.3–90.0) for pembrolizumab plus chemotherapy versus 47.5% (95% CI 31.5–63.9) for placebo plus chemotherapy (Supplementary Table S2); DCRs were 90.0% (95% CI 78.2–96.7) and 90.0% (95% CI 76.3–97.2), respectively. The median DOR was 11.1 months (range 1.2+ to 34.6+) for pembrolizumab plus chemotherapy versus 6.9 months (range 2.2+ to 31.2+) for placebo plus chemotherapy.

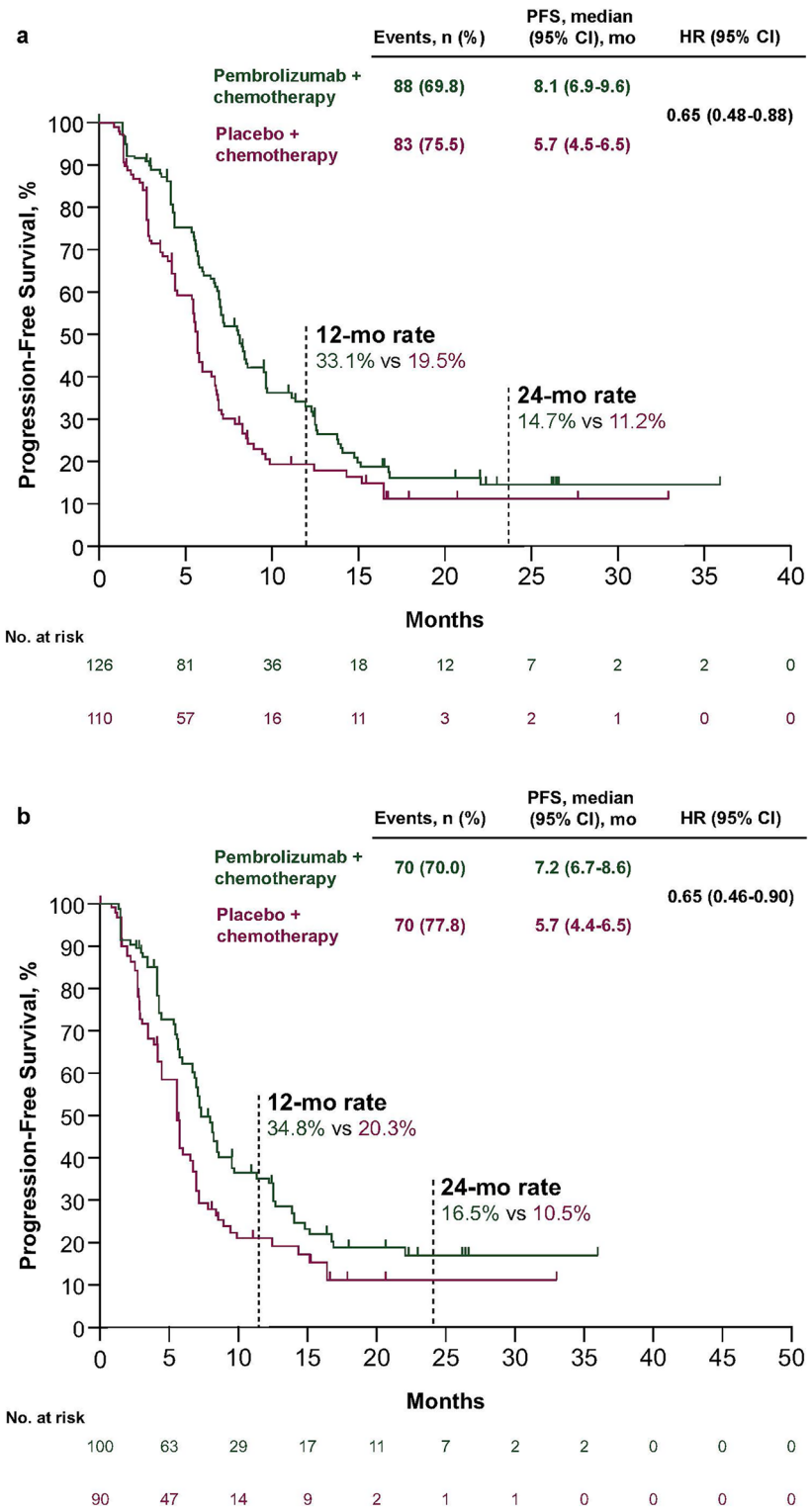

Fig. 2 Kaplan–Meier estimates of progression-free survival in the China subgroup. **A** ITT population, **B** PD-L1 CPS ≥ 1 population, and **C** PD-L1 CPS ≥ 10 population. *CPS* combined positive score, *HR* hazard ratio, *ITT* intention-to-treat, *PFS* progression-free survival, *PD-L1* programmed cell death ligand 1

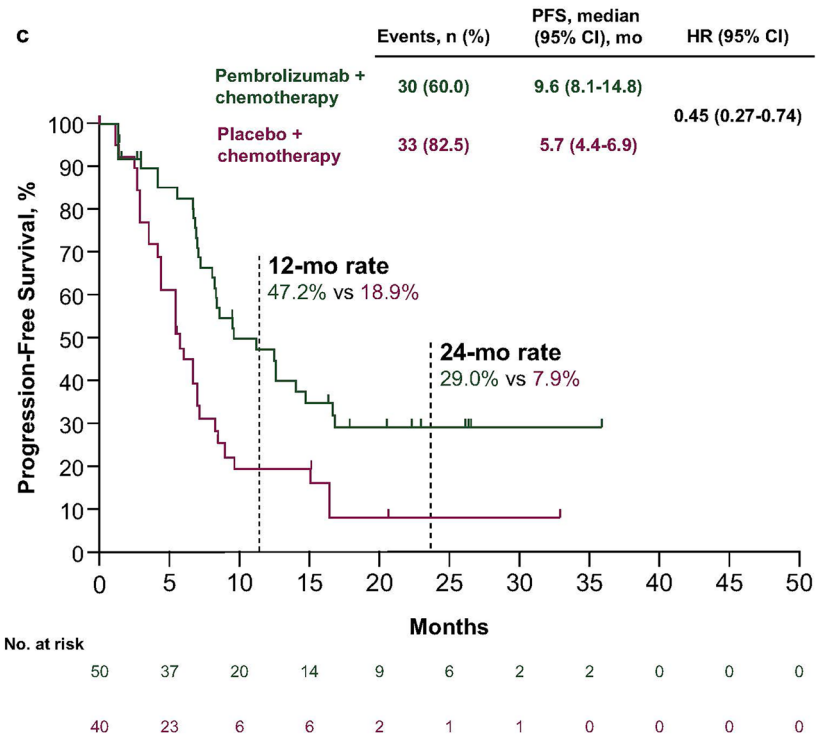

Fig. 2 continued

Safety

AEs of any cause occurred in 125 patients (100%) in the pembrolizumab plus chemotherapy group and 107 patients (97.3%) in the placebo plus chemotherapy group (Supplementary Table S3); events leading to discontinuation of any treatment were reported for 28 patients (22.4%) and 19 patients (17.3%), respectively (Supplementary Table S3). Treatment-related AEs were reported in 125 patients (100%) in the pembrolizumab plus chemotherapy group and 104 patients (94.5%) in the placebo plus chemotherapy group (Table 2); grade 3–5 events were reported in 82 patients (65.6%) and 54 patients (49.1%), respectively. The most common treatment-related AEs (incidence ≥ 45%) were platelet count decreased [71 patients (56.8%) in the pembrolizumab plus chemotherapy group vs. 57 patients (51.8%) in the placebo plus chemotherapy group], aspartate aminotransferase increased [61 patients (48.8%) vs. 38 patients (34.5%)], and anemia [57 patients (45.6%) vs. 53 patients (48.2%)]. Treatment-related AEs leading to discontinuation of any treatment were reported for 25 patients (20%) in the pembrolizumab plus chemotherapy group and 11 patients (10%) in the placebo plus chemotherapy group. Three treatment-related deaths were reported: one patient (0.8%) in the pembrolizumab plus chemotherapy group (death) and two patients (1.8%) in the placebo plus chemotherapy group (one cerebral hemorrhage and one abnormal hepatic function). A summary of AE data by sex are reported in Supplementary Table S4.

Immune-mediated AEs and infusion reactions were reported by 43 patients (34.4%) in the pembrolizumab plus chemotherapy group and 18 patients (16.4%) in the placebo plus chemotherapy group (Table 3); grade 3–5 events were experienced by nine patients (7.2%) and two patients (1.8%), respectively. The most common immune-mediated AEs and infusion reactions (incidence ≥ 5%) were hypothyroidism

Table 2 Treatment-related adverse events with incidence of ≥ 10% in either group in the China subgroup

	Pembrolizumab + chemotherapy *n* = 125		Placebo + chemotherapy *n* = 110	
	Any grade	Grade 3–5	Any grade	Grade 3–5
Any event	125 (100)	82 (65.6)	104 (94.5)	54 (49.1)
Platelet count decreased	71 (56.8)	29 (23.2)	57 (51.8)	14 (12.7)
Aspartate aminotransferase increased	61 (48.8)	3 (2.4)	38 (34.5)	1 (0.9)
Anemia	57 (45.6)	15 (12.0)	53 (48.2)	5 (4.5)
Neutrophil count decreased	56 (44.8)	14 (11.2)	47 (42.7)	11 (10.0)
White blood cell count decreased	50 (40.0)	4 (3.2)	42 (38.2)	3 (2.7)
Nausea	42 (33.6)	3 (2.4)	38 (34.5)	3 (2.7)
Alanine aminotransferase increased	41 (32.8)	1 (0.8)	19 (17.3)	0
Blood bilirubin increased	39 (31.2)	4 (3.2)	25 (22.7)	0
Decreased appetite	34 (27.2)	2 (1.6)	28 (25.5)	2 (1.8)
Vomiting	34 (27.2)	4 (3.2)	34 (30.9)	4 (3.6)
Palmar-plantar erythrodysesthesia syndrome	32 (25.6)	7 (5.6)	19 (17.3)	1 (0.9)
Hypoalbuminemia	26 (20.8)	0	20 (18.2)	0
Diarrhea	22 (17.6)	3 (2.4)	14 (12.7)	4 (3.6)
Hypoesthesia	21 (16.8)	1 (0.8)	15 (13.6)	1 (0.9)
Hypothyroidism	20 (16.0)	0	7 (6.4)	0
Fatigue	19 (15.2)	4 (3.2)	14 (12.7)	3 (2.7)
Thrombocytopenia	17 (13.6)	6 (4.8)	11 (10.0)	4 (3.6)
Hypokalemia	12 (9.6)	2 (1.6)	11 (10.0)	2 (1.8)
Neurotoxicity	11 (8.8)	0	11 (10.0)	0
Bilirubin conjugated increased	10 (8.0)	2 (1.6)	13 (11.8)	0
Malaise	10 (8.0)	1 (0.8)	11 (10.0)	0
Weight decreased	9 (7.2)	0	15 (13.6)	0

Data are *n* (%)

[23 patients (18.4%) in the pembrolizumab plus chemotherapy group vs. seven patients (6.4%) in the placebo plus chemotherapy group], and infusion reactions [11 patients (8.8%) vs. six patients (5.5%)]. No deaths from immune-mediated AEs or infusion reactions were reported.

DISCUSSION

Data for the global population of KEYNOTE-859 indicated the broad utility of pembrolizumab as first-line treatment for patients with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma [9]. The addition of

pembrolizumab to chemotherapy produced clinically meaningful improvements in efficacy. Kaplan–Meier curves for OS and PFS separated early and remained separated throughout the evaluation period in favor of the pembrolizumab plus chemotherapy group. In addition, more complete responses were observed, and the responses were more durable, with pembrolizumab plus chemotherapy than with placebo plus chemotherapy. In the current China subgroup analysis, treatment with pembrolizumab plus chemotherapy showed improvement in efficacy compared with placebo plus chemotherapy, most notably in ORR (69.0% vs. 45.5%), that was generally consistent with the global population [9]. Additionally, the HRs for OS and PFS were numerically lower for the China subgroup than for the global population [OS, 0.68 (95% CI 0.50–0.91) vs. 0.75 (95% CI 0.70–0.87); PFS, 0.65 (95% CI 0.48–0.88) vs. 0.76 (95% CI 0.67–0.85)]; however, definitive conclusions cannot be drawn from this subgroup analysis.

Overall, the safety profile of pembrolizumab in combination with chemotherapy observed in the KEYNOTE-859 global population and China subgroup was manageable and generally consistent with the safety profiles of pembrolizumab monotherapy or chemotherapy alone, and no new safety concerns were identified [9]. Notably, the incidence of treatment-related AEs was generally similar between treatment groups in the China subgroup, and most immune-mediated AEs and infusion reactions were grade 1 or 2 in severity.

The results of the present China subgroup analysis of KEYNOTE-859 are consistent with those reported for nivolumab in the phase 3 CheckMate 649 and phase 2/3 ATTRACTION-4 studies in patients with advanced gastric cancer and GEJ and esophageal adenocarcinoma [10, 11]. A subgroup analysis from the CheckMate 649 study showed an OS benefit in the Asian subgroup with an HR of 0.76 (95% CI 0.59–0.97) [10], and results from the ATTRACTION-4 study

Table 3 Immune-mediated adverse events and infusion reactions in the China subgroup

	Pembrolizumab + chemotherapy *n* = 125		**Placebo + chemotherapy *n* = 110**	
	Any grade	**Grade 3 or 4[a]**	**Any grade**	**Grade 3 or 4[a]**
Any event	43 (34.4)	9 (7.2)	18 (16.4)	2 (1.8)
Hypothyroidism	23 (18.4)	0	7 (6.4)	0
Infusion reactions	11 (8.8)	0	6 (5.5)	0
Hyperthyroidism	6 (4.8)	0	3 (2.7)	0
Colitis	4 (3.2)	3 (2.4)	0	0
Pneumonitis	3 (2.4)	1 (0.8)	1 (0.9)	0
Thyroiditis	3 (2.4)	0	0	0
Type 1 diabetes mellitus	3 (2.4)	3 (2.4)	0	0
Hepatitis	2 (1.6)	0	0	0
Hypoparathyroidism	1 (0.8)	0	0	0
Pancreatitis	1 (0.8)	1 (0.8)	0	0
Severe skin reactions	1 (0.8)	1 (0.8)	1 (0.9)	1 (0.9)
Myocarditis	0	0	1 (0.9)	1 (0.9)

Data are *n* (%)

[a]No grade 5 events were reported

showed a significantly improved PFS with an HR of 0.68 (98.51% CI 0.51–0.90; $p = 0.0007$) in Asian patients [10, 11]. However, cross-trial comparisons should be interpreted with caution because of differences in study population, statistical design, biomarker testing, chemotherapy regimen, regional variations, and subsequent therapy use.

The current analysis had certain limitations. The sample size of the China subgroup was relatively small compared with that of the global population (236 vs. 1579 patients, respectively). Furthermore, analyses of the end points were descriptive and no formal statistical testing was conducted. However, the clinically meaningful improvements in OS, PFS, and ORR in the China subgroup indicate the clinical benefit of pembrolizumab plus chemotherapy in this population. Lastly, the influence of specific characteristics on treatment outcomes in different subgroups would be a suitable objective for future analyses.

CONCLUSIONS

In this phase 3 KEYNOTE-859 study, we aimed to compare the efficacy and safety of pembrolizumab plus chemotherapy with placebo plus chemotherapy for patients with previously untreated advanced or metastatic HER2-negative gastric and GEJ adenocarcinoma, and the current analysis focused on the China subgroup. The data from both the global and the subgroup populations are encouraging and provide additional support for use of pembrolizumab in combination with chemotherapy as a therapeutic option in the first-line setting for advanced HER2-negative gastric cancer or GEJ adenocarcinoma in patients from mainland China.

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Data Availability. Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial

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

Declarations

Conflict of Interest. Yixiang Mao is an employee of MSD China, Shanghai, China, and owns stock in Merck & Co., Inc., Rahway, NJ, USA. Run Guo and Yi Zuo are employees of MSD China, Beijing, China. Sonal Bordia is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and owns stock in Merck & Co., Inc., Rahway, NJ, USA. Shukui Qin, Yuxian Bai, Jin Li, Hongming Pan, Suxia Luo, Yanli Qu, Feng Ye, Lin Yang, Tianshu Liu, Wei Li, Xi Chen, Jianwei Yang, Jieer Ying, Xiaoyan Lin, Lin Zhao, Xinjun Liang, and Shouguo Li report no conflict of interest.

Ethical Approval. The study protocol and amendments, including changes that affected study design, were approved by the appropriate local or national ethics committee at each participating center. All participants provided written informed consent. The study was done in accordance with the Good Clinical Practice requirements outlined by the International Council on Harmonization, the ethical principles of the Declaration of Helsinki, and all local regulations. Institutional review boards or independent ethics committees at each site approved the protocol. The full list of participating sites and ethics committees can be found in the Supplementary Materials Table S5.

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