


# Pembrolizumab versus paclitaxel for previously treated advanced gastric or gastroesophageal junction cancer (KEYNOTE-063): A randomized, open-label, phase 3 trial in Asian patients

Hyun Cheol Chung, MD, PhD <sup>1</sup>; Yoon-Koo Kang, MD, PhD<sup>2</sup>; Zhendong Chen, MD<sup>3</sup>; Yuxian Bai, MD<sup>4</sup>; Wan Zamaniah Wan Ishak, MD<sup>5</sup>; Byoung Yong Shim, MD<sup>6</sup>; Young Lee Park, MD<sup>7</sup>; Dong-Hoe Koo, MD, PhD<sup>8</sup>; Jianwei Lu, MD<sup>9</sup>; Jianming Xu, MD<sup>10</sup>; Hong Jae Chon, MD<sup>11</sup>; Li-Yuan Bai, MD<sup>12</sup>; Shan Zeng, MD<sup>13</sup>; Ying Yuan, MD<sup>14</sup>; Yen-Yang Chen, MD<sup>15</sup>; Kangsheng Gu, MD<sup>3</sup>; Wen Yan Zhong, PhD<sup>16</sup>; Shu Kuang, MD<sup>17</sup>; Chie-Schin Shih, MD<sup>18</sup>; and Shu-Kui Qin, MD, PhD<sup>19</sup>

**BACKGROUND:** KEYNOTE-063 (NCT03019588) investigated pembrolizumab versus paclitaxel as second-line therapy in Asian patients with advanced programmed death ligand 1 (PD-L1)-positive (combined positive score  $\geq 1$ ) gastric/gastroesophageal junction (GEJ) cancer. **METHODS:** This randomized, open-label, phase 3 study was conducted at 36 medical centers in China (mainland), Malaysia, South Korea, and Taiwan. Patients were randomly assigned 1:1 to 200 mg of pembrolizumab intravenously every 3 weeks for  $\leq 2$  years or 80 mg/m<sup>2</sup> of paclitaxel intravenously every week. Primary end points were overall survival (OS) and progression-free survival (PFS). Secondary end points were objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 and safety. **RESULTS:** Between February 16, 2017, and March 12, 2018, 94 patients were randomly assigned (47 pembrolizumab/47 paclitaxel) after screening; enrollment was stopped on March 12, 2018, based on the results of the global KEYNOTE-061 study, and patients were followed until the last patient's last visit. Median OS was 8 months (95% confidence interval [CI], 4-10 months) with pembrolizumab versus 8 months (95% CI, 5-11 months) with paclitaxel (hazard ratio [HR], 0.99; 95% CI, 0.63-1.54). Median PFS was 2 months (95% CI, 1-3 months) with pembrolizumab versus 4 months (95% CI, 3-6 months) with paclitaxel (HR, 1.62; 95% CI, 1.04-2.52). ORR was 13% for pembrolizumab versus 19% for paclitaxel. Any-grade treatment-related adverse events occurred in 28 pembrolizumab-treated patients (60%) and 42 paclitaxel-treated patients (96%); grades 3 to 5 events occurred in 5 patients (11%) and 28 patients (64%), respectively. **CONCLUSIONS:** Definitive conclusions about the efficacy of second-line pembrolizumab in Asian patients with advanced PD-L1-positive gastric/GEJ cancer are limited because of insufficient power, but pembrolizumab was well tolerated in this patient population. Efficacy followed a trend similar to that observed in the phase 3 KEYNOTE-061 trial. *Cancer* 2022;128:995-1003. © 2021 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

**KEYWORDS:** Asia, chemotherapy, gastric cancer, gastroesophageal junction cancer, pembrolizumab, programmed death 1.

## INTRODUCTION

Gastric cancer, including gastroesophageal junction (GEJ) cancer, is the fifth most commonly diagnosed cancer worldwide, accounting for >1 million new cases and ~800,000 deaths in 2018.<sup>1</sup> However, incidence and mortality vary geographically. Compared with other regions of the world, Eastern Asia has the highest incidence of gastric cancer.<sup>1,2</sup> Specifically, the age-standardized incidence rate of gastric cancer per 100,000 people in East Asia is 32.1 for men and 13.2 for women,

**Corresponding Author:** Hyun Cheol Chung, MD, PhD, Yonsei Cancer Center, Yonsei University College of Medicine, 50-1 Yonsei-RO, Seoul, 3722 South Korea (unchung8@yuhs.ac).

<sup>1</sup>Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; <sup>2</sup>Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; <sup>3</sup>Hospital of Anhui Medical University, Hefei, China; <sup>4</sup>Harbin Medical University Cancer Hospital, Harbin, China; <sup>5</sup>Clinical Oncology Unit, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia; <sup>6</sup>St. Vincent's Hospital, The Catholic University of Korea, Gyeonggi-Do, South Korea; <sup>7</sup>National Cancer Center, Goyang-si, South Korea; <sup>8</sup>Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea; <sup>9</sup>Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, China; <sup>10</sup>The People's Liberation Army General Hospital, Beijing, China; <sup>11</sup>CHA Bundang Medical Center, Seongnam, South Korea; <sup>12</sup>China Medical University Hospital and China Medical University, Taichung, Taiwan; <sup>13</sup>Xiangya Hospital, Central South University, Changsha, China; <sup>14</sup>Department of Medical Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; <sup>15</sup>Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; <sup>16</sup>MSD China, Shanghai, China; <sup>17</sup>MSD China, Beijing, China; <sup>18</sup>Merck & Co., Inc., Kenilworth, New Jersey; <sup>19</sup>People's Liberation Army Cancer Centre of Nanjing Bayi Hospital, Nanjing, China

We thank the patients and their families and caregivers as well as all primary investigators and site personnel for participating in the study.

Medical writing and/or editorial assistance was provided by Kathleen Richards, PhD, and Holly C. Cappelli, PhD, CMPP, of ApotheCom (Yardley, Pennsylvania). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey.

This trial is registered at ClinicalTrials.gov (NCT03019588).

Additional supporting information may be found in the online version of this article.

**DOI:** 10.1002/cncr.34019, **Received:** May 12, 2021; **Revised:** August 23, 2021; **Accepted:** August 24, 2021, **Published online** December 8, 2021 in Wiley Online Library (wileyonlinelibrary.com)

nearly twice the rate observed in the second highest region, East Europe (17.1 and 7.5, respectively).<sup>1</sup> South Korea has the highest incidence of gastric cancer in East Asia, with age-standardized incidence rates of 57.8 and 23.5 in men and women, respectively, followed by Mongolia (47.2 and 21.7), Japan (40.7 and 16.0), and China (29.5 and 12.3).<sup>2</sup> The higher incidence of gastric cancer in East Asia may be attributable to the increased *Helicobacter pylori* infection rate, interleukin (IL) gene polymorphisms (IL-17 and IL-10), and diets rich in salt and pickled foods.<sup>2</sup>

Standard first-line treatment recommendations for unresectable locally advanced recurrent or metastatic gastric cancer include fluoropyrimidine plus a platinum agent (recommended by the Chinese Society of Clinical Oncology,<sup>3</sup> the National Comprehensive Cancer Network,<sup>4</sup> and the Korean Gastric Cancer Association<sup>5</sup>) and S-1 (tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate) or capecitabine in combination with cisplatin, as indicated by the Japanese Gastric Cancer Association.<sup>6</sup> Recently reported data in the first-line setting have demonstrated the efficacy and safety of the anti-programmed death 1 (PD-1) monoclonal antibody nivolumab in combination with chemotherapy versus chemotherapy alone. Data from the global CheckMate-649 study reported superior overall survival (OS) and progression-free survival (PFS) in patients with advanced gastric cancer/GEJ cancer/esophageal adenocarcinoma with manageable safety;<sup>7</sup> a survival advantage with nivolumab plus chemotherapy versus chemotherapy alone was observed in 606 patients with a programmed death ligand 1 (PD-L1) combined positive score (CPS)  $\geq 5$  (median OS, 14.4 vs 11.1 months; hazard ratio [HR], 0.70) but not in 955 patients with CPS  $< 5$  (median OS, 12.4 vs 12.3 months; HR, 0.94). Data from the Asian ATTRACTION-4 study showed improvement with nivolumab plus chemotherapy versus chemotherapy in PFS (median, 10.5 vs 8.3 months; HR, 0.68; [98.5% CI, 0.51-0.90]) and objective response rate (ORR) (57.5% vs 47.8%), but not in OS (median, 17.5 vs 17.2 months; HR, 0.90; 95% CI, 0.75-1.08), in patients with human epidermal growth factor receptor 2 (HER2)-negative advanced or recurrent gastric/GEJ cancer.<sup>8</sup> Although second- and third-line chemotherapies are commonly administered to patients with advanced or metastatic gastric cancer in Asia (up to 85% and 69% of patients, respectively),<sup>9-13</sup> treatment options are limited, and patients are encouraged to participate in clinical studies.<sup>3,4</sup>

Variations in geographic location have also been observed in survival rates of patients with advanced gastric cancer. OS is typically longer among Asian than non-Asian patients.<sup>9,14-16</sup> For example, the 5-year OS rate was

41% among Asian patients compared with 30% among Caucasian patients.<sup>15</sup> Differences in tumor burden and location and use of postprogression chemotherapy have been suggested as underpinning ethnic differences in survival rates,<sup>9,16</sup> although data are conflicting.<sup>15</sup>

Pembrolizumab, another anti-PD-1 monoclonal antibody, has demonstrated antitumor activity with a manageable safety profile in patients with gastric/GEJ cancer.<sup>17</sup> Based on the results of the phase 2 KEYNOTE-059 study, pembrolizumab was approved in the United States for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS  $\geq 1$ ) who experience disease progression on or after  $\geq 2$  previous lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy.<sup>18</sup> However, in July 2021, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, voluntarily withdrew pembrolizumab in this treatment setting with a 6-month delay, consistent with the recommendation from the Food and Drug Administration Oncologic Drugs Advisory Committee to ensure access to pembrolizumab for current patients who may not have received immunotherapy in earlier lines.<sup>19</sup> Pembrolizumab is also approved in the United States for patients with unresectable or metastatic microsatellite instability-high or mismatch repair-deficient solid tumors or tumor mutational burden-high ( $\geq 10$  mut/Mb) solid tumors who experience disease progression after previous treatment and who have no satisfactory alternative treatment options.<sup>18</sup>

The efficacy of pembrolizumab versus paclitaxel in advanced PD-L1-positive gastric/GEJ cancer that progressed after first-line treatment was further investigated in the KEYNOTE-061 and KEYNOTE-063 phase 3 studies.<sup>20</sup> In KEYNOTE-061, in which 26% of enrolled patients were Asian (from Hong Kong, Israel, Japan, Malaysia, Russia, Singapore, South Korea, Taiwan, and Turkey), pembrolizumab did not significantly improve OS compared with paclitaxel.<sup>20</sup> After 2 years of follow-up, median OS was longer with pembrolizumab monotherapy (9.1 months) than with paclitaxel monotherapy (8.3 months) in patients with CPS  $\geq 1$  tumors (HR, 0.82; 95% CI, 0.66-1.03; 1-sided  $P = 0.0421$ ).<sup>20</sup> In a long-term follow-up analysis after 4 years of follow-up, the OS benefit achieved with pembrolizumab was greater with increasing tumor PD-L1 expression (HR, 0.81 [CPS  $\geq 1$ ]; 0.72, [CPS  $\geq 5$ ]; 0.69 [CPS  $\geq 10$ ]); similar trends were observed for ORR and duration of response (DOR).<sup>21</sup> The safety profile of pembrolizumab continued to be favorable, with

fewer treatment-related adverse (AEs) reported in patients receiving pembrolizumab (53%) than paclitaxel (84%).<sup>21</sup> An exploratory analysis from this study also demonstrated a strong association between tissue tumor mutational burden and clinical efficacy with second-line pembrolizumab using whole exome sequencing or the FoundationOne<sup>®</sup>CDx (Foundation Medicine).<sup>22,23</sup> One potential limitation of KEYNOTE-061 was that the comparison arm received paclitaxel alone when paclitaxel plus ramucirumab had shown superior OS compared with paclitaxel, although these data were not available at the initiation of the study; paclitaxel plus ramucirumab is now one of many standard-of-care second-line therapies available for Asian patients with advanced gastric cancer whose disease has progressed on first-line chemotherapy.<sup>13</sup>

Here, we present results of the phase 3 KEYNOTE-063 study of pembrolizumab versus paclitaxel as second-line therapy in Asian patients with advanced PD-L1–positive (CPS  $\geq 1$ ) gastric/GEJ cancer.

## MATERIALS AND METHODS

### *Study Design and Patients*

KEYNOTE-063 was a randomized, open-label, phase 3 study conducted at 36 medical centers across 4 countries in Asia (China, Malaysia, South Korea, and Taiwan). Eligible patients were men and women aged  $\geq 18$  years with histologically or cytologically confirmed diagnoses of locally advanced unresectable or metastatic PD-L1–positive (CPS  $\geq 1$ ) gastric or GEJ adenocarcinoma. Patients must also have had Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)–measurable disease, Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, documented disease progression during or after first-line therapy containing any platinum/fluoropyrimidine doublet chemotherapy, and a tumor sample for PD-L1 assessment. Patients with HER2–negative tumors were eligible; those with HER2–positive tumors had to have documentation of disease progression on treatment containing trastuzumab, and those with unknown tumor status had to have their HER2 status determined locally.

The study protocol and all amendments were approved by the institutional review board or ethics committee at each institution. The study was conducted in accordance with the protocol and its amendments, the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice,

and local and national regulations. All patients provided written informed consent.

### *Randomization*

Patients were randomly assigned 1:1 to receive 200 mg of pembrolizumab intravenously every 3 weeks or 80 mg/m<sup>2</sup> of paclitaxel intravenously on days 1, 8, and 15 of each 4-week cycle. Patients were stratified by time to progression on first-line therapy (<6 vs  $\geq 6$  months) and ECOG PS (0 vs 1). Treatment continued for 35 cycles (~2 years; pembrolizumab only) or until disease progression, intolerable toxicity, investigator decision, or patient withdrawal of consent.

### *Procedures*

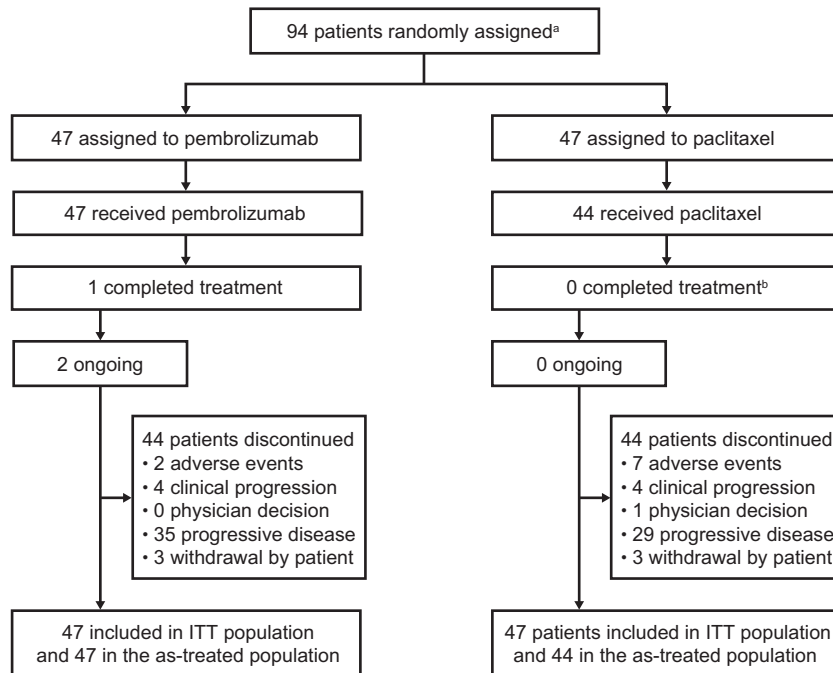
Tumor response was assessed every 6 weeks according to RECIST v1.1 by blinded central radiology review. AEs were evaluated throughout treatment and for 30 days after treatment discontinuation (90 days for serious AEs) and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. PD-L1 expression was centrally assessed during screening using PD-L1 IHC 22C3 pharmDx (Agilent). PD-L1 expression was reported as CPS, defined as the number of PD-L1–staining cells (tumor cells, macrophages, and lymphocytes) divided by the total number of viable tumor cells, multiplied by 100. PD-L1–positive tumors were defined as CPS  $\geq 1$ .

### *Outcomes*

Dual primary end points were OS, defined as time from randomization to death from any cause, and PFS per RECIST v1.1, defined as time from randomization to the first documented disease progression or death from any cause, whichever occurred first. Secondary end points were ORR per RECIST v1.1, defined as the proportion of patients who experienced complete or partial response, and safety and tolerability. DOR per RECIST v1.1, defined as the time from first documented complete or partial response to disease progression or death from any cause, was investigated as an exploratory end point.

### *Statistical Analysis*

Efficacy was assessed in the intention-to-treat (ITT) population, which comprised all patients who were randomly assigned to treatment. OS, PFS, and DOR were analyzed using Kaplan-Meier estimates; a stratified Cox proportional hazards model with the Efron method for handling ties was used to estimate HRs and associated 95% CIs.



**Figure 1.** Patient disposition.

<sup>a</sup>Intended enrollment for KEYNOTE-063 was 360 but was halted at 94 because pembrolizumab did not significantly prolong overall survival over paclitaxel in the KEYNOTE-061 study (NCT02370498).<sup>18</sup>

<sup>b</sup>There was no maximum number of doses of paclitaxel. ITT indicates intention-to-treat.

ORR was analyzed using the stratified Miettinen and Nurminen method to detect between-group differences. Safety was assessed in the as-treated population, which comprised all patients who received  $\geq 1$  dose of study treatment.

This study planned to enroll 360 patients; the timing of the final analysis was event driven. After 290 OS events had been observed, the study was expected to have ~91% power to demonstrate the superiority of pembrolizumab compared with paclitaxel in this setting at a 1-sided  $\alpha$  of 0.0215 if the underlying HR for OS was 0.67. However, because of early termination of the study, statistical power is lacking for the current analysis, which used a database cutoff date of October 8, 2019. This trial is registered with ClinicalTrials.gov (NCT03019588).

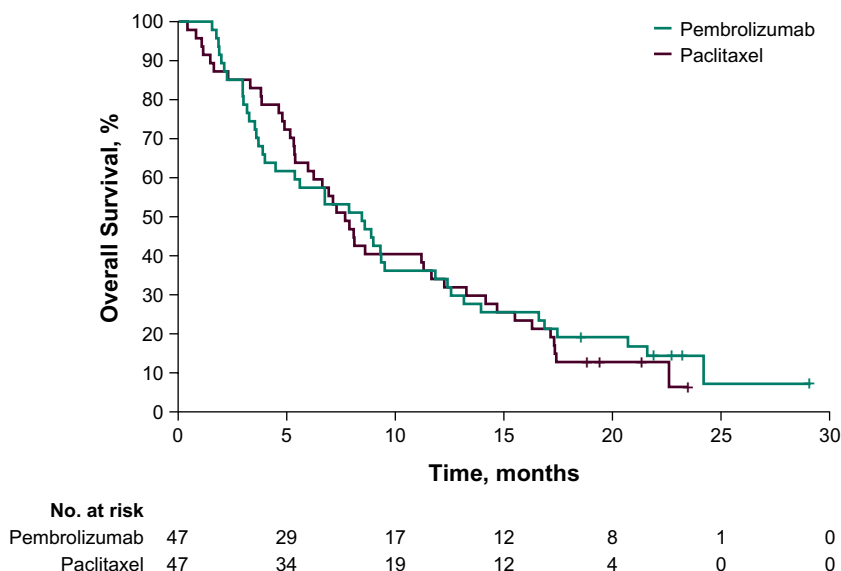
## RESULTS

After the KEYNOTE-063 study began, results of the global KEYNOTE-061 study (NCT02370498) showed that pembrolizumab did not significantly prolong OS compared with paclitaxel in patients previously treated for advanced gastric cancer.<sup>20</sup> As a result, screening and enrollment was terminated for the KEYNOTE-063 study on March 12, 2018. The study ended on June 21, 2021, after the last patient’s last visit.

**TABLE 1.** Baseline Characteristics

Characteristic, No. (%)	Pembrolizumab (n = 47)	Paclitaxel (n = 47)
Age, median (range), y	61 (32-75)	61 (37-91)
Male	32 (68)	37 (79)
ECOG PS		
0	14 (30)	12 (26)
1	33 (70)	35 (74)
Country		
China	23 (49)	21 (45)
Malaysia	2 (4)	2 (4)
South Korea	20 (43)	18 (38)
Taiwan	2 (4)	6 (13)
TTP on first-line therapy		
$\geq 6$ months	17 (36)	17 (36)
$< 6$ months	30 (64)	30 (64)
Primary location at diagnosis		
GEJ	6 (13)	3 (6)
Stomach	41 (87)	44 (94)
Metastatic disease	47 (100)	46 (98)
Number of metastatic sites		
0-2 sites	23 (49)	23 (49)
$\geq 3$ sites	24 (51)	24 (51)
Previous surgery for gastric cancer	24 (51)	22 (47)
Gastric ulceration		
Yes	8 (17)	11 (23)
No	26 (55)	18 (38)
Unknown	13 (28)	18 (38)
Histology		
Adenocarcinoma	46 (98)	46 (98)
Mucinous carcinoma	1 (2)	1 (2)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; TTP, time to progression.



**Figure 2.** Kaplan-Meier estimates of overall survival.

Between February 6, 2017, and March 12, 2018, 94 patients had been randomly assigned to pembrolizumab (n = 47) or paclitaxel (n = 47) (Fig. 1). As of October 8, 2019, the median time from randomization to data cutoff was 24 months (range, 19-31). One of 47 patients (2%) in the pembrolizumab group completed all 35 cycles of treatment. No patients remained on paclitaxel, whereas 2 patients (4%) in the pembrolizumab group remained on pembrolizumab. Most patients discontinued treatment because of progressive disease (n = 64; 70%) (Fig. 1). Overall, 50 patients (53%) went on to receive third-line therapy.

Baseline demographics and disease characteristics were generally well balanced between treatment groups (Table 1). Median age was 61 years in both treatment groups, and most patients were men (73%) and had ECOG PS 1 (72%). Most patients were enrolled at centers in China (n = 44; 47%) and South Korea (n = 38; 40%). Overall, 60 patients (64%) experienced disease progression within 6 months of treatment with first-line therapy.

Twenty-four of 47 patients (51%) in the pembrolizumab group and 26 of 47 patients (55%) in the paclitaxel group received subsequent therapy; 2 of 47 patients (4%) and 7 of 47 patients (15%), respectively, received subsequent immunotherapy.

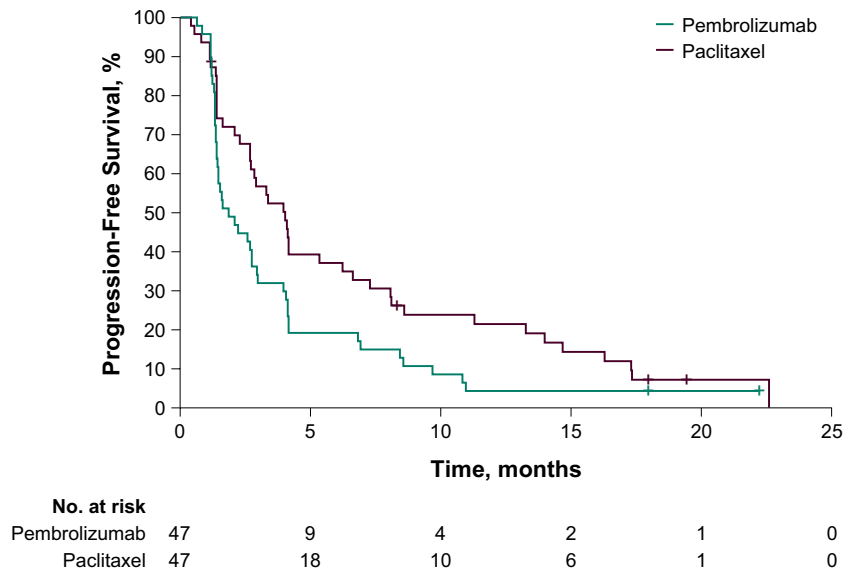
At the time of data cutoff, 83 patients had died (41 of 47 patients [87%] in the pembrolizumab group and 42 of 47 patients [89%] in the paclitaxel group).

Median OS was 8 months (95% CI, 4-10) in the pembrolizumab group and 8 months (95% CI, 5-11) in the paclitaxel group (HR, 0.99; 95% CI, 0.63-1.54) (Fig. 2). Eighty-eight patients experienced disease progression or died (45 of 47 patients [96%] in the pembrolizumab group and 43 of 47 patients [92%] in the paclitaxel group). Median PFS was 2 months (95% CI, 1-3) in the pembrolizumab group and 4 months (95% CI, 3-6) in the paclitaxel group (HR, 1.62; 95% CI, 1.04-2.52) (Fig. 3).

Confirmed responses were observed in 6 of 47 patients in the pembrolizumab group (ORR, 13%) and 9 of 47 patients in the paclitaxel group (ORR, 19%); complete response was observed in 2 of 47 patients (4%) in the pembrolizumab group and 3 of 47 patients (6%) in the paclitaxel group (Table 2). Median DOR was 8 months (range, 3-20+) in the pembrolizumab group and 12 months (range, 2-17+) in the paclitaxel group (Fig. 4; Table 2). Notably, 4 patients in each treatment group had responses lasting ≥6 months. Response duration with paclitaxel by patient, including country of enrollment, is shown in Supporting Table 1.

AEs attributed by the investigator to study treatment (treatment-related AEs) occurred in 28 of 47 pembrolizumab-treated patients (60%) and 42 of 44 paclitaxel-treated patients (96%) (Table 3). Grades 3 to 5 treatment-related AEs occurred in 5 of 47 pembrolizumab-treated patients (11%) and 28 of 44





**Figure 3.** Kaplan-Meier estimates of progression-free survival.

**TABLE 2.** Summary of BICR-Confirmed Responses

Response, No. (%)	Pembrolizumab (n = 47)	Paclitaxel (n = 47)
Objective response	6 (13)	9 (19)
Complete response	2 (4)	3 (6)
Partial response	4 (9)	6 (13)
Stable disease <sup>a</sup>	10 (21)	15 (32)
Disease control rate <sup>b</sup>	16 (34)	24 (51)
Progressive disease	25 (53)	12 (26)
Not available <sup>c</sup>	6 (13)	11 (23)
Time to response, median (range), mo	3 (1-3)	1 (1-4)
Duration of response, median (range), mo <sup>d</sup>	8 (3-20+)	12 (2-17+)

Abbreviation: BICR, blinded independent central review.  
<sup>a</sup>Included patients with stable disease and patients with noncomplete response/nonprogressive disease.  
<sup>b</sup>Disease control rate defined as proportion of patients with complete response, partial response, or stable disease.  
<sup>c</sup>Patients with no postbaseline assessment available for response evaluation or patients who were not evaluable.  
<sup>d</sup>“+” indicates there was no progressive disease at the time of last disease assessment.

paclitaxel-treated patients (64%). The most common any-grade treatment-related AEs (incidence >10%) were fatigue (13%) and hypothyroidism (11%) in the pembrolizumab group and alopecia (48%), decreased neutrophil count (39%), decreased white blood cell count (30%), decreased appetite (25%), anemia (18%), asthenia (14%), neutropenia (14%), fatigue (11%), nausea (11%), increased aspartate aminotransferase (11%), and peripheral neuropathy (11%) in the paclitaxel group (Table 3).

**TABLE 3.** Adverse Event Summary

AE, No. (%)	Pembrolizumab (n = 47)	Paclitaxel (n = 44)
Any	46 (98)	43 (98)
Treatment-related AE	28 (60)	42 (96)
Grades 3-5	5 (11)	28 (64)
Led to discontinuation	1 (2)	6 (14)
Led to death <sup>a</sup>	0	2 (5)
Treatment-related AEs occurring in ≥10% of patients in either group		
Fatigue	6 (13)	5 (11)
Hypothyroidism	5 (11)	0
Nausea	2 (4)	5 (11)
Alopecia	1 (2)	21 (48)
Anemia	1 (2)	8 (18)
Decreased appetite	1 (2)	11 (25)
Neutrophil count decreased	1 (2)	17 (39)
White blood cell count decreased	1 (2)	13 (30)
Aspartate aminotransferase increased	0	5 (11)
Asthenia	0	6 (14)
Peripheral neuropathy	0	5 (11)
Neutropenia	0	6 (14)

Abbreviation: AE, adverse event.  
<sup>a</sup>Two paclitaxel-treated patients died of treatment-related pneumonia.

Treatment-related AEs led to discontinuation in 1 of 47 pembrolizumab-treated patients (2%) (pneumonitis) and 6 of 44 paclitaxel-treated patients (14%) (2 cases each of herpes zoster and pneumonia, 1 case each of asthenia and peripheral sensory neuropathy). No pembrolizumab-treated patients (0%) but 2 of 44 paclitaxel-treated patients (5%) had a treatment-related AE (treatment-related pneumonia in each) that resulted in death.

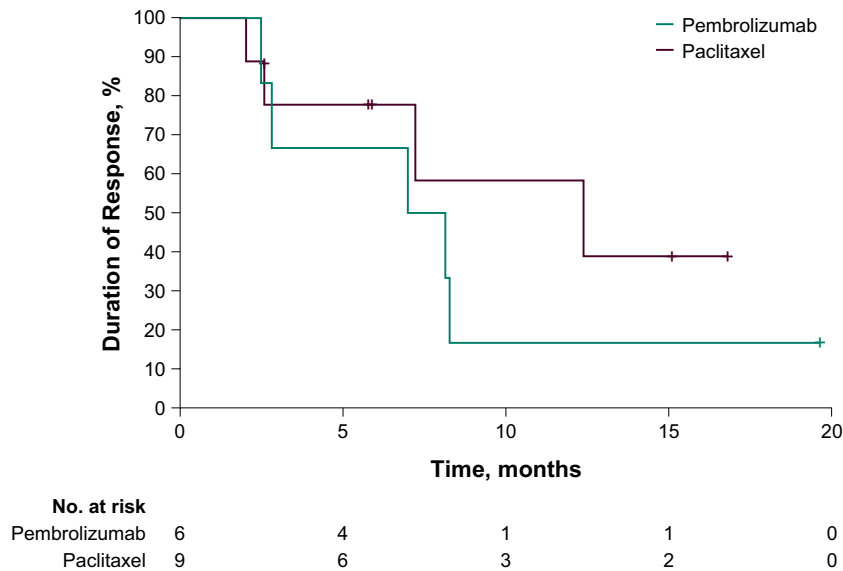


Figure 4. Kaplan-Meier estimates of duration of response.

Immune-mediated AEs and infusion reactions occurred in 9 of 47 pembrolizumab-treated patients (19%) and 5 of 44 paclitaxel-treated patients (11%). Among pembrolizumab-treated patients, the observed immune-mediated AEs were hypothyroidism (n = 5; 11%), hyperthyroidism (n = 3; 6%), and adrenal insufficiency, drug hypersensitivity, pneumonitis, and thyroiditis (n = 1 each; 2%).

DISCUSSION

There is an unmet need for second-line treatment options in Asian patients with advanced or metastatic PD-L1-positive gastric/GEJ cancer. Second-line immunotherapy studies in Asian patients with gastric/GEJ cancer are limited, but recent data suggest immunotherapy may provide survival benefits for patients with advanced or metastatic gastric cancer compared with best supportive care.<sup>12</sup> Given that pembrolizumab did not significantly prolong OS compared with paclitaxel in patients participating in the global phase 3 KEYNOTE-061 study;<sup>20</sup> however, KEYNOTE-063 enrollment was discontinued after 94 patients. Consequently, the current analysis from KEYNOTE-063 was underpowered for the planned comparison between treatment groups, limiting interpretation of the outcomes, but it can provide important insights into this patient population.

In general, baseline characteristics were consistent between Asian patients with PD-L1 CPS ≥1 in the current study and in the global population of KEYNOTE-061 with PD-L1 CPS ≥1 (Supporting Table 2). However,

Asian patients in the current study had marginally worse functional status than the global KEYNOTE-061 population (72% vs 54%, respectively, had ECOG PS 1) and higher rates of stomach as the primary location at diagnosis (90% vs 66%), adenocarcinoma histology (98% vs 80%), and previous surgery for gastric cancer (49% vs 35%), which might have influenced treatment outcomes (Supporting Table 2).<sup>19</sup>

In the limited KEYNOTE-063 patient population, pembrolizumab did not numerically improve clinical outcomes compared with paclitaxel in Asian patients with advanced PD-L1-positive gastric cancer. Although cross-study comparisons should be interpreted with caution, efficacy and safety findings were consistent with the larger global KEYNOTE-061 study in patients with PD-L1 CPS ≥1 (Supporting Table 3).<sup>20</sup> Interestingly, DOR in pembrolizumab-treated patients was relatively shorter in KEYNOTE-063 than in KEYNOTE-061 (median, 8 vs 18 months) but increased in paclitaxel-treated patients (median, 12 vs 5 months, respectively).<sup>20</sup>

In the phase 3 RAINBOW study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated gastric/GEJ adenocarcinoma, the median OS with paclitaxel in patients enrolled in Japan, South Korea, Hong Kong, Singapore, and Taiwan was better than in other regions (11 vs 6 months).<sup>13</sup> Similarly, the Asian subgroup analysis for OS from KEYNOTE-061 demonstrated an HR for death of 0.90 (95% CI, 0.59-1.38) compared with other regions

(HR, 0.81; 95% CI, 0.61-1.06), indicating better performance with paclitaxel in Asian patients.<sup>20</sup> Taken together, when planning a treatment strategy for Asian patients with advanced gastric cancer, continuum of care should be taken into account, with appropriate timing of immunotherapy and safe and effective use of cytotoxic chemotherapy.

In KEYNOTE-063, pembrolizumab was well tolerated and led to comparatively fewer treatment-related AEs than paclitaxel. The safety profiles of both treatment groups were consistent with what has been reported in the literature, and no new safety concerns were observed.

This study is limited by its early termination, which resulted in a smaller than planned sample size of Asian patients with advanced PD-L1-positive gastric/GEJ cancer; hence, definitive conclusions cannot be drawn. Additionally, microsatellite instability status was not tested. Further studies are needed to establish which patients are most likely to benefit from pembrolizumab immunotherapy. Another limitation is that the comparison arm received paclitaxel alone when paclitaxel plus ramucirumab is currently one of the standard-of-care therapies available for patients with advanced gastric cancer whose disease progressed on chemotherapy; this therapy option was not available at the initiation of KEYNOTE-063.

In Asian patients with advanced PD-L1-positive gastric/GEJ cancer, efficacy data should be viewed with caution and definitive conclusions are limited; however, second-line pembrolizumab monotherapy was well tolerated in this patient population. As immune checkpoint inhibitors are increasingly becoming part of the first-line treatment in combination with chemotherapy in advanced gastric/GEJ cancer, further evaluation of their role in second-line treatment is needed.

## FUNDING SUPPORT

Funding for this study was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey.

## CONFLICT OF INTEREST DISCLOSURES

Hyun Cheol Chung reports grants (for research to institution) from Amgen, Bristol-Myers Squibb/Ono, Eli Lilly, GSK, Incyte, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, Merck-Serono, Taiho, and Zymework; honoraria from Eli Lilly and Merck-Serono; and consultancy fees from Amgen, BeiGene, Bristol-Myers Squibb, Celltrion, Eli Lilly, Gloria, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, Merck-Serono, Quintiles, Taiho, and Zymeworks. Yoon-Koo Kang reports advisory fees from ALX Oncology, Amgen, Bristol-Myers Squibb, Daehwa, MacroGenics, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, Novartis, Surface Oncology, and Zymeworks. Wan Zamaniah

Wan Ishak reports honoraria for lectures from Amgen Malaysia, DKSH Malaysia, Eisai Malaysia, Eli Lilly Malaysia, Ipsen Malaysia, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, Merck Serono Malaysia, Pfizer Malaysia, and Roche Malaysia; travel grants from Amgen Malaysia, Celgene Malaysia, Eisai Malaysia, Eli Lilly Malaysia, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, and Roche Malaysia; and is an advisory board member for Celgene Malaysia, Eli Lilly Malaysia, Eisai Malaysia, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey. Wen Yan Zhong is an employee of MSD China, Beijing, China. Shu Kuang is an employee of MSD China, Beijing, China. Chie-Schin Shih is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey and a stockholder of Merck & Co., Inc., Kenilworth, New Jersey.

## AUTHOR CONTRIBUTIONS

**Hyun Cheol Chung:** Data acquisition, data analysis, interpretation of the results, drafting of the manuscript, and critically reviewing or revising the manuscript for important intellectual content. **Yoon-Koo Kang:** Data acquisition, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content. **Zhendong Chen:** Data acquisition and critically reviewing or revising the manuscript for important intellectual content. **Yuxian Bai:** Data acquisition and critically reviewing or revising the manuscript for important intellectual content. **Wan Zamaniah Wan Ishak:** Data acquisition, drafting of the manuscript, and critically reviewing or revising the manuscript for important intellectual content. **Byoung Yong Shim:** Data acquisition and critically reviewing or revising the manuscript for important intellectual content. **Young Lee Park:** Data acquisition, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content. **Dong-Hoe Koo:** Data acquisition and critically reviewing or revising the manuscript for important intellectual content. **Jianwei Lu:** Data acquisition and critically reviewing or revising the manuscript for important intellectual content. **Jianming Xu:** Data acquisition, data analysis, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content. **Li-Yuan Bai:** Data acquisition, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content. **Shan Zeng:** Data acquisition and critically reviewing or revising the manuscript for important intellectual content. **Ying Yuan:** Data acquisition and critically reviewing or revising the manuscript for important intellectual content. **Yen-Yang Chen:** Data acquisition and critically reviewing or revising the manuscript for important intellectual content. **Kangsheng Gu:** Data acquisition and critically reviewing or revising the manuscript for important intellectual content. **Chie-Schin Shih:** Data acquisition, data analysis, interpretation of the results, drafting of the manuscript, and critically reviewing or revising the manuscript for important intellectual content. **Shu-Kui Qin:** Data acquisition and critically reviewing or revising the manuscript for important intellectual content. **Wen Yan Zhong:** Analysis of the data and critically reviewing or revising the manuscript for important intellectual content. **Hong Jae Chon:** Interpretation of the results and critically reviewing or revising the manuscript for important intellectual content. **Shu Kuang:** Interpretation of the results and critically reviewing or revising the manuscript for important intellectual content. All coauthors have given final approval to the manuscript.

## DATA AVAILABILITY

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey (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](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 United States and Europe 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.

## REFERENCES

- Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
- Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. *Prz Gastroenterol*. 2019;14:26-38.
- Wang FH, Shen L, Li J, et al. The Chinese Society of Clinical Oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer. *Cancer Commun*. 2019;39:10.
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): Gastric cancer (version 4.2020). Published December 23, 2020. Accessed April 23, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/gastric.pdf](https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf)
- Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean Practice Guideline for Gastric Cancer 2018: an evidence-based, multidisciplinary approach. *J Gastric Cancer*. 2019;19:1-48.
- Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer*. 2021;24:1-21.
- Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-esophageal junction, and esophageal adenocarcinoma (CheckMate 649): a randomized, open-label, phase 3 trial. *Lancet*. 2021;398:27-40.
- Boku N, Ryu MH, Oh DY, et al. Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study [abstract]. *Ann Oncol*. 2020;31:S1192.
- Takashima A, Iizumi S, Boku N. Survival after failure of first-line chemotherapy in advanced gastric cancer patients: differences between Japan and the rest of the world. *Jpn J Clin Oncol*. 2017;47:583-589.
- Carter GC, Kaltenboeck A, Ivanova J, et al. Real-world treatment patterns among patients with advanced gastric cancer in South Korea. *Cancer Res Treat*. 2017;49:578-587.
- Choi IS, Choi M, Lee JH, et al. Treatment patterns and outcomes in patients with metastatic gastric cancer receiving third-line chemotherapy: a population-based outcomes study. *PLoS One*. 2018;13:e0198544.
- Smyth EC, Moehler M. Late-line treatment in metastatic gastric cancer: today and tomorrow. *Ther Adv Med Oncol*. 2019;11:1758835919867522.
- Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-esophageal junction adenocarcinoma (RAINBOW): a double-blind, randomized phase 3 trial. *Lancet Oncol*. 2014;15:1224-1235.
- Gill S, Shah A, Le N, et al. Asian ethnicity-related differences in gastric cancer presentation and outcome among patients treated at a Canadian cancer center. *J Clin Oncol*. 2003;21:2070-2076.
- Jin H, Pinheiro PS, Callahan KE, et al. Examining the gastric cancer survival gap between Asians and Whites in the United States. *Gastric Cancer*. 2017;20:573-582.
- Sawaki A, Yamada Y, Yamaguchi K, et al. Regional differences in advanced gastric cancer: exploratory analyses of the AVAGAST placebo arm. *Gastric Cancer*. 2018;21:429-438.
- 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.
- KEYTRUDA® (pembrolizumab) injection, for intravenous use. 10/2021. Merck Sharp & Dohme Corp.: Whitehouse Station, NJ; 2021.
- Merck & Co., Inc. Merck provides update on KEYTRUDA® (pembrolizumab) indication in third-line gastric cancer in the US. Kenilworth, NJ: Merck and Co., Inc.; 2021.
- Shitara K, Özgüroğlu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-esophageal junction cancer (KEYNOTE-061): a randomized, open-label, controlled, phase 3 trial. *Lancet*. 2018;392:123-133.
- Fuchs CS, Özgüroğlu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated patients with PD-L1-positive advanced gastric or gastroesophageal junction cancer (GC): update from the phase III KEYNOTE-061 trial [abstract]. *J Clin Oncol*. 2020;38:4503.
- Fuchs CS, Özgüroğlu M, Bang YJ, et al. The association of molecular biomarkers with efficacy of pembrolizumab versus paclitaxel in patients with gastric cancer (GC) from KEYNOTE-061 [abstract]. *J Clin Oncol*. 2020;38:4512.
- Shitara K, Özgüroğlu M, Bang YJ, et al. The association of tissue tumor mutational burden (tTMB) using the Foundation Medicine genomic platform with efficacy of pembrolizumab versus paclitaxel in patients (pts) with gastric cancer (GC) from KEYNOTE-061 [abstract]. *J Clin Oncol*. 2020;38:4537.