

Efficacy of Pembrolizumab Monotherapy for Advanced Gastric/Gastroesophageal Junction Cancer with Programmed Death Ligand 1 Combined Positive Score ≥ 10



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ABSTRACT

Purpose: Pembrolizumab demonstrated efficacy in PD-L1–positive [combined positive score (CPS) ≥ 1] advanced gastric/gastroesophageal junction (G/GEJ) cancer in the first-, second-, and third-line setting in KEYNOTE-062, KEYNOTE-061, and KEYNOTE-059, respectively. To better delineate the specificity of CPS as a predictor of clinical outcomes, we analyzed pembrolizumab efficacy in patients with CPS ≥ 10 in these trials.

Patients and Methods: Included were patients with CPS ≥ 10 tumors from KEYNOTE-059 cohort 1 (pembrolizumab, $n = 46$; *post hoc*), KEYNOTE-061 (pembrolizumab, $n = 53$; chemotherapy, $n = 55$; *post hoc*), and KEYNOTE-062 (pembrolizumab, $n = 92$; chemotherapy, $n = 90$; primary). Efficacy outcomes were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR).

Results: In KEYNOTE-059, median follow-up was 6 months, median OS was 8 months [95% confidence interval (CI), 5.8–11.1],

ORR was 17%, and median (range) DOR was 21 months (3+ to 35+). In KEYNOTE-061, median follow-up was 9 months, median OS (pembrolizumab vs. chemotherapy) was 10 versus 8 months (HR, 0.64; 95% CI, 0.41–1.02), median PFS was 3 months versus 3 months (HR, 0.86; 95% CI, 0.56–1.33), ORR was 25% versus 9%, and median (range) DOR was not reached (4 to 26+ months) versus 7 months (3–7). In KEYNOTE-062, median follow-up was 11 months, median OS (pembrolizumab vs. chemotherapy) was 17 months versus 11 months (HR, 0.69; 95% CI, 0.49–0.97), median PFS was 3 months versus 6 months (HR, 1.09, 95% CI; 0.79–1.49), ORR was 25% versus 38%, and median (range) DOR was 19 months (1+ to 34+) versus 7 months (2+ to 30+).

Conclusions: This comprehensive analysis showed consistent improvements toward more favorable clinical outcomes with pembrolizumab across lines of therapy in patients with CPS ≥ 10 G/GEJ cancer.

Introduction

Gastric cancer ranks fifth among the most commonly diagnosed cancers worldwide and accounts for more than 1 million new cases and approximately 800,000 deaths per year (1). Evidence suggests that the programmed death 1 (PD-1) pathway may have prognostic significance in gastric cancer, with several studies demonstrating a relationship between expression of PD-L1 and overall survival (OS; refs. 2–4). Although the prevalence of immunohistochemical PD-L1 expression varies between studies, most indicate that a significant proportion (range, 25%–65%) of patients with gastric cancer overexpress PD-L1,

regardless of scoring method (2, 5). Current first-line standard-of-care therapy for patients with unresectable locally advanced recurrent or metastatic disease remains combination chemotherapy with a fluoropyrimidine and a platinum-based agent, with trastuzumab added to the regimen for patients with HER2-positive disease (6). Various agents are recommended for use in second-line therapy, including chemotherapies and immunotherapies. The anti-PD-1 inhibitor pembrolizumab is approved for the treatment of patients with gastric cancer and is among the preferred regimens as second-line therapy for patients with microsatellite instability-high (MSI-H) or mismatch

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Translational Relevance

Pembrolizumab monotherapy demonstrated a clinically meaningful survival benefit and durable antitumor activity in patients with PD-L1 combined positive score (CPS) ≥ 10 gastric or gastroesophageal junction cancer from KEYNOTE-059 cohort 1 ($n = 46$; third-line or later setting), KEYNOTE-061 ($n = 53$; second-line setting), and KEYNOTE-062 ($n = 92$; first-line setting). We observed numerically higher overall survival medians, response rates, and durations of response with pembrolizumab monotherapy than with chemotherapy in patients whose tumors expressed CPS ≥ 10 across lines of therapy. Responsiveness to immune checkpoint inhibitors and the role of pembrolizumab in the treatment paradigm of gastric cancer are still being determined, and this study adds to the existing body of evidence that the immunohistochemical PD-L1 CPS is one clinically relevant biomarker that can lead to improved clinical efficacy.

protein repair-deficient (dMMR) gastric cancer. On the basis of results from KEYNOTE-059, pembrolizumab is also approved as third-line or later therapy for patients with tumors that have a PD-L1 combined positive score (CPS) ≥ 1 (7). The ability of PD-L1 expression to predict response to immune checkpoint inhibitors beyond the approved use of third-line pembrolizumab for gastric cancer expressing CPS ≥ 1 remains unclear.

Pembrolizumab has demonstrated antitumor activity in patients with PD-L1-positive advanced gastric or gastroesophageal junction (GEJ) cancer in phase II and III trials (8–10). In cohort 1 of the global, single-arm, multicohort, phase II KEYNOTE-059 study, patients with advanced gastric or GEJ cancer whose disease progressed after ≥ 2 lines of therapy received pembrolizumab monotherapy (8). Among the 148 patients with CPS ≥ 1 tumors that were either microsatellite stable or had unknown MMR/dMMR status, 23 patients had a response, for an objective response rate (ORR) of 15.5%. The median duration of response (DOR) among these patients was 16.3 months (range, 1.6+ to 17.3+), and safety was manageable. Although the ORR was higher in patients with PD-L1-positive tumors (15.5%) than in patients with PD-L1-negative tumors (6.4%), the responses observed in the PD-L1-negative population indicated an incomplete separation of responders from nonresponders based on CPS ≥ 1 (8).

In the randomized, open-label, phase III KEYNOTE-061 study, patients with advanced gastric or GEJ cancer whose disease progressed after first-line therapy received pembrolizumab or paclitaxel (9). Among the 395 patients with CPS ≥ 1 tumors, pembrolizumab did not significantly prolong survival compared with paclitaxel [median OS, 9.1 vs. 8.3 months; HR, 0.82; 95% confidence interval (CI), 0.66–1.03; one-sided $P = 0.0421$]. Although there was also no improvement in progression-free survival (PFS) or response rates, pembrolizumab monotherapy did offer more durable responses and a favorable safety profile compared with paclitaxel.

The randomized phase III KEYNOTE-062 study enrolled patients with advanced gastric or GEJ cancer who had not previously received therapy for advanced disease (10). Among the 506 patients with CPS ≥ 1 tumors, OS with pembrolizumab was noninferior to that with cisplatin plus 5-fluorouracil (5-FU) or capecitabine (HR, 0.91; 99.2% CI, 0.69–1.18; prespecified noninferiority margin, 1.2). Pembrolizumab did not improve PFS or ORR but demonstrated a better tolerability profile than chemotherapy.

The predictive value of PD-L1 in gastric cancer is unclear given that multiple studies with immune checkpoint inhibitors other than pembrolizumab have demonstrated similar responses in patients regardless of PD-L1 status. In addition, the absence of a standard PD-L1 IHC assay and scoring method across studies makes cross-study comparisons difficult. In the phase I/II CheckMate-032 study of patients with chemotherapy-refractory advanced esophagogastric cancer, responses were observed with nivolumab alone and with nivolumab in combination with ipilimumab regardless of PD-L1 status [defined as tumor proportion score (TPS) with a cutoff of 1% using PD-L1 IHC 28–8 pharmDx (Agilent Technologies; ref. 11)]. Response rates were numerically higher in patients with PD-L1-positive tumors, but the sample sizes were small. The phase III ATTRACTION-2 study randomly assigned patients with advanced gastric or GEJ cancer who had previously received two or more lines of therapy to receive nivolumab or placebo (12). In an exploratory analysis evaluating PD-L1 expression (defined as TPS with a cutoff of 1%) and OS, median OS was numerically higher with nivolumab than with placebo regardless of PD-L1 positivity. Outcomes based on PD-L1 status were also evaluated with avelumab in patients with gastric cancer in the phase Ib JAVELIN Solid Tumor trial (13), the phase III JAVELIN Gastric 300 trial (14), and the phase III JAVELIN Gastric 100 trial (15). There were no significant differences in outcomes among patients with PD-L1-positive or PD-L1-negative tumors. For all three studies, PD-L1 positive was defined as $\geq 1\%$ of tumor cells using PD-L1 IHC 73–10 pharmDx. However, exploratory analysis using 22C3 pharmDx suggested a survival benefit with maintenance avelumab over chemotherapy in patients with CPS ≥ 1 tumors (HR, 0.72; 95% CI, 0.49–1.05; refs. 15 and 16).

In addition to measuring PD-L1 expression on tumor cells and before the development of CPS, pembrolizumab studies assessed response by mononuclear inflammatory cell density score (MIDS). The CheckMate-032, ATTRACTION-2, and JAVELIN Gastric studies did not evaluate MIDS, which might have provided different results, highlighting the need to continue exploring patient subgroups likely to respond to PD-1/PD-L1 inhibitors.

Among the limited PD-L1 data available for patients with gastric or GEJ cancer, the open-label phase Ib KEYNOTE-012 study (NCT01848834) evaluated the antitumor activity of pembrolizumab in patients with PD-L1-positive recurrent or metastatic adenocarcinoma of the stomach or GEJ (17). PD-L1 expression was measured in 35 patients with available biopsy samples at baseline using TPS and MIDS. When response was evaluated using TPS, ORR was 24% for patients with TPS 0%, 0% for patients with TPS 1% to 49%, and 33% for patients with TPS $\geq 50\%$. When response was evaluated using MIDS, ORR was 0% for MIDS 0, 25% for MIDS 1, 12% for MIDS 2, 44% for MIDS 3, and 0% for MIDS 4. Although conclusions are limited because of the small numbers of patients, these findings do not demonstrate an association between response and high PD-L1 expression using TPS though there may be an association between high MIDS and response. The study provided evidence of the importance of measuring PD-L1 expression in immune cells, as opposed to tumor cells exclusively, in patients with gastric cancer based on analysis of the results and on the use of CPS. In the CheckMate-649 study in patients with gastric or GEJ cancer or esophageal adenocarcinoma, nivolumab plus chemotherapy provided statistically significant improvements in OS and PFS compared with chemotherapy alone in patients with CPS ≥ 5 tumors (18). A statistically significant OS benefit was also shown in patients with CPS ≥ 1 tumors and in the all-randomly assigned population, showing an enrichment of OS benefit as the CPS cutoff increased (18).

A recent meta-analysis of randomized controlled trials of PD-1/PD-L1 inhibitors in patients with advanced solid tumors, including three trials in patients with gastric or GEJ cancer, suggested that enriching for PD-L1 status by increasing the minimum proportion of stained cells can increase efficacy in a dose-response relationship (19). On the basis of the experience with pembrolizumab in gastric cancer clinical trials, CPS ≥ 10 was chosen for further evaluation in this analysis to better delineate the specificity of CPS as a predictor of clinical outcomes with pembrolizumab monotherapy. Herein, we characterize clinical outcomes with pembrolizumab monotherapy across lines of therapy in patients with CPS ≥ 10 advanced gastric or GEJ cancer by analyzing patients with CPS ≥ 10 tumors enrolled in cohort 1 of KEYNOTE-059 (*post hoc* analysis), in KEYNOTE-061 (*post hoc* analysis), and in KEYNOTE-062 (primary analysis).

Patients and Methods

Study design

The designs of KEYNOTE-059 cohort 1, KEYNOTE-061, and KEYNOTE-062 have been described previously (8–10). In brief, all three trials evaluated the efficacy of pembrolizumab 200 mg administered intravenously every 3 weeks for up to 35 cycles (~2 years) for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. In KEYNOTE-059, patients were enrolled regardless of PD-L1 expression status. In KEYNOTE-061, patients were randomly assigned 1:1 to receive pembrolizumab monotherapy or standard-dose paclitaxel administered intravenously. Initially, patients were enrolled regardless of PD-L1 expression status, but enrollment was then restricted to those with CPS ≥ 1 tumors (9). In KEYNOTE-062, patients were randomly assigned (1:1:1) to receive pembrolizumab monotherapy, pembrolizumab plus chemotherapy (standard-dose cisplatin plus 5-FU or capecitabine administered intravenously or orally, respectively), or placebo plus chemotherapy (hereafter referred to as chemotherapy); patients were required to have CPS ≥ 1 tumors (10). The current analysis of KEYNOTE-062 includes only those patients enrolled in the pembrolizumab monotherapy and chemotherapy groups.

PD-L1 expression was assessed in archival or newly collected tumor samples using PD-L1 IHC 22C3 pharmDx (Agilent Technologies; refs. 8–10) and was measured using CPS [defined as the number of PD-L1-staining cells (tumor cells, lymphocytes, macrophages) as a proportion of the total number of tumor cells multiplied by 100; ref. 20]. Samples were not reanalyzed for this analysis. For all three trials, the primary analysis populations were patients with CPS ≥ 1 tumors. Analysis of outcomes in patients with CPS ≥ 10 was *post hoc* for KEYNOTE-059 and KEYNOTE-061 but was part of the prespecified primary analysis for KEYNOTE-062.

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

Outcomes and statistical considerations

For the current analysis, we evaluated clinical outcomes in all patients with CPS ≥ 10 tumors who received ≥ 1 dose of study drug. Results were analyzed for each of the trials separately (i.e., results were not pooled across trials). Efficacy endpoints included OS, PFS, ORR [complete response (CR) plus partial response (PR)], and DOR.

Response was assessed by central review per RECIST v1.1. The Kaplan–Meier method was used to calculate OS, PFS, and DOR. HRs and their associated 95% CIs were calculated using stratified Cox proportional hazards models with the Efron method of tie handling. In KEYNOTE-059, ORR was calculated using the Clopper–Pearson method. In KEYNOTE-061 and KEYNOTE-062, treatment differences in OS and PFS were assessed using the log-rank test with HRs estimated using a stratified Cox regression model. Response rate was compared using the Miettinen and Nurminen method. In KEYNOTE-062, the prespecified hypotheses included OS analysis of pembrolizumab versus chemotherapy in patients with PD-L1 CPS ≥ 10 with a planned enrollment for 80% power to detect a HR of 0.58 at $\alpha = 0.75\%$ (one-sided). Full details of the statistical analysis have been published previously (10).

Data cut-off dates for this analysis were August 8, 2018, for KEYNOTE-059, October 26, 2017, for KEYNOTE-061, and March 26, 2019, for KEYNOTE-062.

All three trials are registered with ClinicalTrials.gov [NCT02335411 (KEYNOTE-059), NCT02370498 (KEYNOTE-061), NCT02494583 (KEYNOTE-062)].

Data sharing

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ (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 United States and European Union 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.

Results

All patients enrolled in KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 had evaluable tumor samples for PD-L1 status with the exception of 2 patients each in KEYNOTE-059 cohort 1 and KEYNOTE-061; 31% (46/148), 18% (108/592), and 36% (182/506), respectively, had CPS ≥ 10 tumors (**Table 1**). Follow-up duration is reported in **Table 1**. Baseline characteristics for patients with CPS ≥ 10 tumors

Table 1. Incidence of PD-L1-positive tumors and follow-up of patients with CPS ≥ 10 tumors.

Incidence	KEYNOTE-059	KEYNOTE-061		KEYNOTE-062	
	Pembrolizumab	Pembrolizumab	Chemotherapy	Pembrolizumab	Chemotherapy
Patients with CPS ≥ 1 , <i>n/N</i> (%)	148/259 (57)	196/296 (66)	199/296 (67)	256/256 (100)	250/250 (100)
Patients with CPS ≥ 10 , <i>n/N</i> (%)	46/259 (18)	53/296 (18)	55/296 (19)	92/256 (36)	90/250 (36)
Median follow-up (range), months	6 (<1–38)	10 (<1–28)	8 (1–27)	17 (<1–38)	11 (1–35)

Abbreviations: CPS, combined positive score; PD-L1, programmed death ligand 1.

were generally comparable between the pembrolizumab and chemotherapy groups in KEYNOTE-061 and KEYNOTE-062 (Table 2).

OS and PFS in the CPS ≥ 10 population

In KEYNOTE-059, median OS was 8 months (95% CI, 5.8–11.1). OS rates were 33% at 12 months and 15% at 24 months (Fig. 1A). In KEYNOTE-061, median OS was 10 months (95% CI, 5.9–17.3) with pembrolizumab and 8 months (95% CI, 5.1–9.9) with chemotherapy (HR, 0.64; 95% CI, 0.41–1.02). The OS rates for pembrolizumab and chemotherapy were 45% versus 23% at 12 months and 35% versus 18% at 18 months, respectively (Fig. 1B). In KEYNOTE-062, median OS was 17 months (95% CI, 9.1–23.1) with pembrolizumab and 11 months (95% CI, 8.5–13.8) with chemotherapy (HR 0.69; 95% CI, 0.49–0.97). The OS rates for pembrolizumab and chemotherapy were 57% versus 47% at 12 months and 39% versus 22% at 24 months, respectively (Fig. 1C). Kaplan–Meier curves showed improved OS in the CPS ≥ 10 population compared with the CPS ≥ 1 population from the original studies (Fig. 1A–C).

In KEYNOTE-059, median PFS was 2 months (95% CI, 2.0–3.4; Fig. 2A). In KEYNOTE-061, median PFS was 3 months (95%

CI, 1.4–3.1) with pembrolizumab and 3 months (95% CI, 2.7–4.1) with chemotherapy (HR, 0.86; 95% CI, 0.56–1.33; Fig. 2B). In KEYNOTE-062, median PFS was 3 months (95% CI, 1.6–5.4) with pembrolizumab and 6 months (95% CI, 5.4–6.9) with chemotherapy (HR, 1.09; 95% CI, 0.79–1.49; Fig. 2C). Kaplan–Meier curves of PFS in the CPS ≥ 10 population compared with the CPS ≥ 1 population from the original studies are shown in Fig. 2A–C.

Response in the CPS ≥ 10 population

In KEYNOTE-059, the confirmed ORR was 17% ($n = 8$); 1 patient achieved CR and 7 achieved PR (Table 3). The median DOR was 21 months (range, 3+ to 35+; Fig. 3A); five responders (71%) had a response duration ≥ 6 months. In KEYNOTE-061, confirmed ORR was 25% ($n = 13$) for pembrolizumab-treated patients; 5 patients achieved CR and 8 PR (Table 3). In chemotherapy-treated patients, the ORR was 9% ($n = 5$); 1 patient achieved CR and 4 achieved PR. The median DOR was not reached (range, 4 to 26+ months) for pembrolizumab and was 7 months (range, 3–7) for chemotherapy (Fig. 3B); 10 responders (77%) treated with pembrolizumab and one responder (53%) treated with chemotherapy had a response duration ≥ 6 months.

Table 2. Baseline characteristic of patients with CPS ≥ 10 tumors.

Characteristic	KEYNOTE-059	KEYNOTE-061		KEYNOTE-062	
	Pembrolizumab <i>n</i> = 46	Pembrolizumab <i>n</i> = 53	Chemotherapy <i>n</i> = 55	Pembrolizumab <i>n</i> = 92	Chemotherapy <i>n</i> = 90
Median age, years (range)	63 (30–79)	66 (35–79)	60 (37–76)	59 (20–81)	65 (31–82)
Male, <i>n</i> (%)	34 (74)	35 (66)	35 (64)	64 (70)	64 (71)
Race, <i>n</i> (%)					
White	38 (83)	34 (64)	38 (69)	58 (63)	58 (64)
Asian	3 (7)	17 (32)	13 (24)	27 (29)	23 (26)
Black	1 (2)	1 (2)	1 (2)	2 (2)	1 (1)
American Indian or Alaska Native	0	1 (2)	2 (4)	3 (3)	5 (6)
Multiple	1 (2)	0	1 (2)	1 (1)	3 (3)
Missing	3 (7)	0	0	0	0
ECOG PS, <i>n</i> (%)					
0	25 (54)	24 (45)	24 (44)	47 (51)	34 (38)
1	21 (46)	29 (55)	31 (56)	45 (49)	56 (62)
No. of previous therapies for metastatic disease, <i>n</i> (%)					
2	21 (46)	—	—	—	—
3	14 (30)	—	—	—	—
4	8 (17)	—	—	—	—
≥ 5	3 (7)	—	—	—	—
Tumor site, <i>n</i> (%) ^a					
Stomach	22 (48)	35 (66)	35 (64)	68 (74)	69 (77)
GEJ	23 (50)	18 (34)	20 (36)	24 (26)	20 (22)
MSI-H, <i>n</i> (%)	2 (4)	8 (15)	5 (9)	11 (12)	10 (11)

Abbreviations: CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction. MSI-H, microsatellite instability-high.

^aIn KEYNOTE-062, one patient (1.1%) had a tumor site of “missing.”

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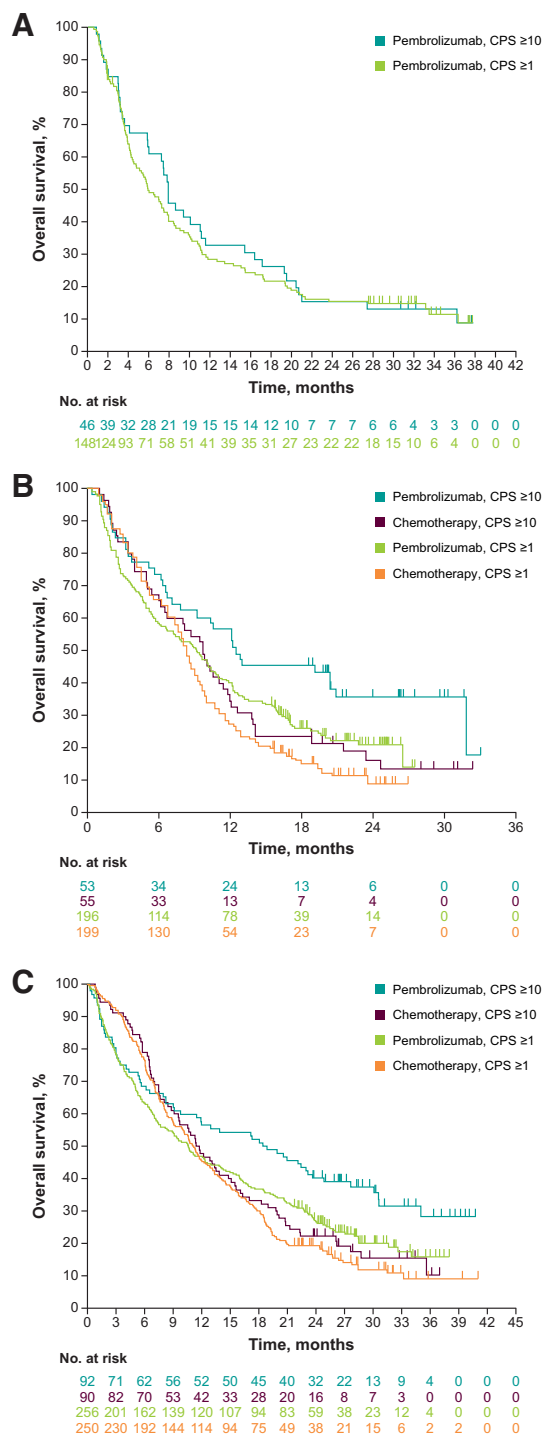


Figure 1. Kaplan-Meier estimates of OS in patients with CPS ≥ 1 and CPS ≥ 10 tumors. **A**, Patients receiving third-line and later pembrolizumab in KEYNOTE-059 cohort 1. **B**, Patients receiving second-line pembrolizumab or chemotherapy in KEYNOTE-061. **C**, Patients receiving first-line pembrolizumab or chemotherapy in KEYNOTE-062. CPS, combined positive score; OS, overall survival.

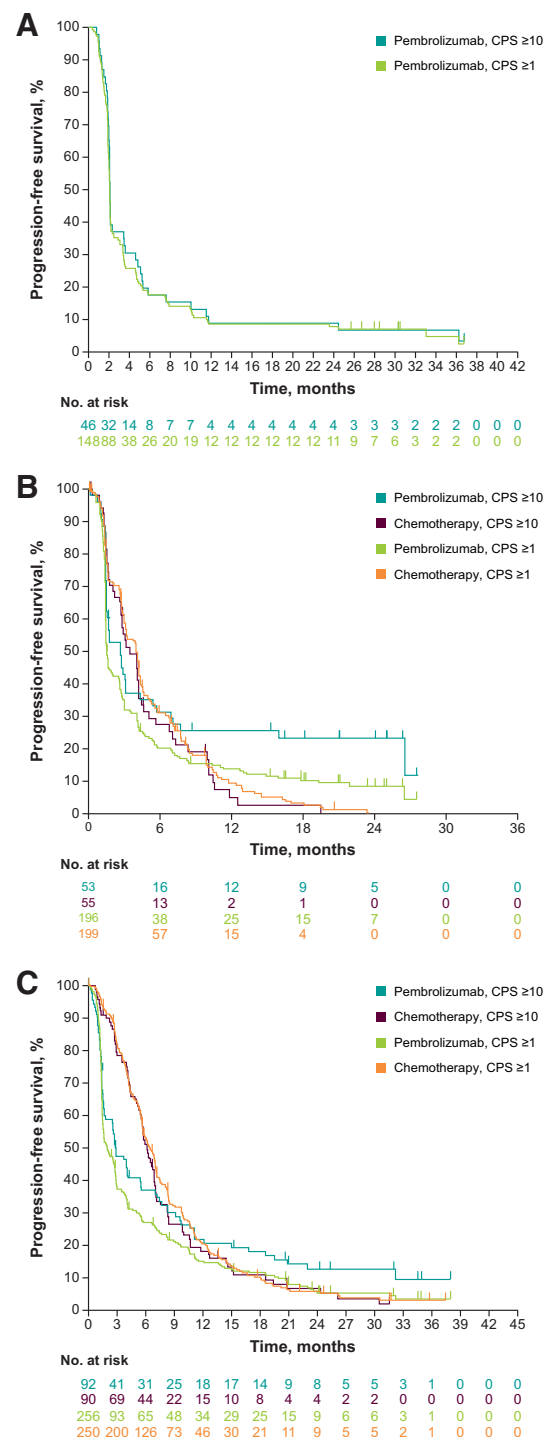


Figure 2. Kaplan-Meier estimates of PFS in patients with CPS ≥ 1 and CPS ≥ 10 tumors. **A**, Patients receiving third-line and later pembrolizumab in KEYNOTE-059 cohort 1. **B**, Patients receiving second-line pembrolizumab or chemotherapy in KEYNOTE-061. **C**, Patients receiving first-line pembrolizumab or chemotherapy in KEYNOTE-062. CPS, combined positive score; PFS, progression-free survival.

Table 3. Response summary in patients with CPS ≥ 10 tumors.

	KEYNOTE-059	KEYNOTE-061		KEYNOTE-062	
	Pembrolizumab <i>n</i> = 46	Pembrolizumab <i>n</i> = 53	Chemotherapy <i>n</i> = 55	Pembrolizumab <i>n</i> = 92	Chemotherapy <i>n</i> = 90
ORR, <i>n</i> (%)	8 (17)	13 (25)	5 (9)	23 (25)	34 (38)
CR	1 (2)	5 (9)	1 (2)	7 (8)	4 (4)
PR	7 (15)	8 (15)	4 (7)	16 (17)	30 (33)
SD	9 (20)	12 (23)	28 (51)	23 (25)	39 (43)
PD	24 (52)	23 (43)	11 (20)	29 (32)	8 (9)
Not available ^a	5 (11)	5 (9)	11 (20)	17 (19)	9 (10)
Median time to response, months, (range)	2 (2–4)	2 (1–3)	2 (1–4)	1 (1–7)	2 (1–7)
Median DOR, months, (range)	21 (3+ to 35+)	NR (4 to 26+)	7 (3 to 7)	19 (1+ to 34+)	7 (2+ to 30+)

Abbreviations: CI, confidence interval; CPS, combined positive score; CR, complete response; DOR, duration of response; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.

^aIndicates patients without an evaluable assessment or patients who had a baseline assessment but no postbaseline assessment as of the data cut-off date (due to missing, discontinuing, or death before the first postbaseline assessment).

In KEYNOTE-062, confirmed ORR was 25% (*n* = 23) for pembrolizumab-treated patients; 7 patients achieved CR and 16 achieved PR (Table 3). In chemotherapy-treated patients, the ORR was 38% (*n* = 34); 4 patients achieved CR and 30 achieved PR. The median DOR was 19 months (range, 1+ to 34+) for pembrolizumab and 7 months (range, 2+ to 30+) for chemotherapy (Fig. 3C); 18 responders (82%) treated with pembrolizumab and 16 responders (53%) treated with chemotherapy had a response duration ≥ 6 months. Kaplan–Meier curves showed DOR in the CPS ≥ 10 population compared with the CPS ≥ 1 population from the original studies.

Discussion

In the primary analysis of patients with CPS ≥ 1 gastric or GEJ cancer who were enrolled in KEYNOTE-059 cohort 1, KEYNOTE-061, and KEYNOTE-062, pembrolizumab monotherapy demonstrated promising antitumor activity. In KEYNOTE-061 and KEYNOTE-062, pembrolizumab was associated with an improved safety profile, but it did not significantly improve survival outcomes compared with chemotherapy (8–10). The current analysis in patients with CPS ≥ 10 tumors revealed durable responses and elongation of the tails of the Kaplan–Meier OS curves with pembrolizumab monotherapy across lines of therapy. However, pembrolizumab monotherapy did not numerically improve PFS in this analysis of KEYNOTE-061 or KEYNOTE-062 or ORR in KEYNOTE-062 compared with chemotherapy. The relationship between OS and PFS in clinical trials of immune checkpoint inhibitors has been investigated in several tumor types, including gastric cancer; differences in PFS and OS benefit as well as direction of outcomes are likely attributable to the mechanism of action, specific disease, and population under study (21).

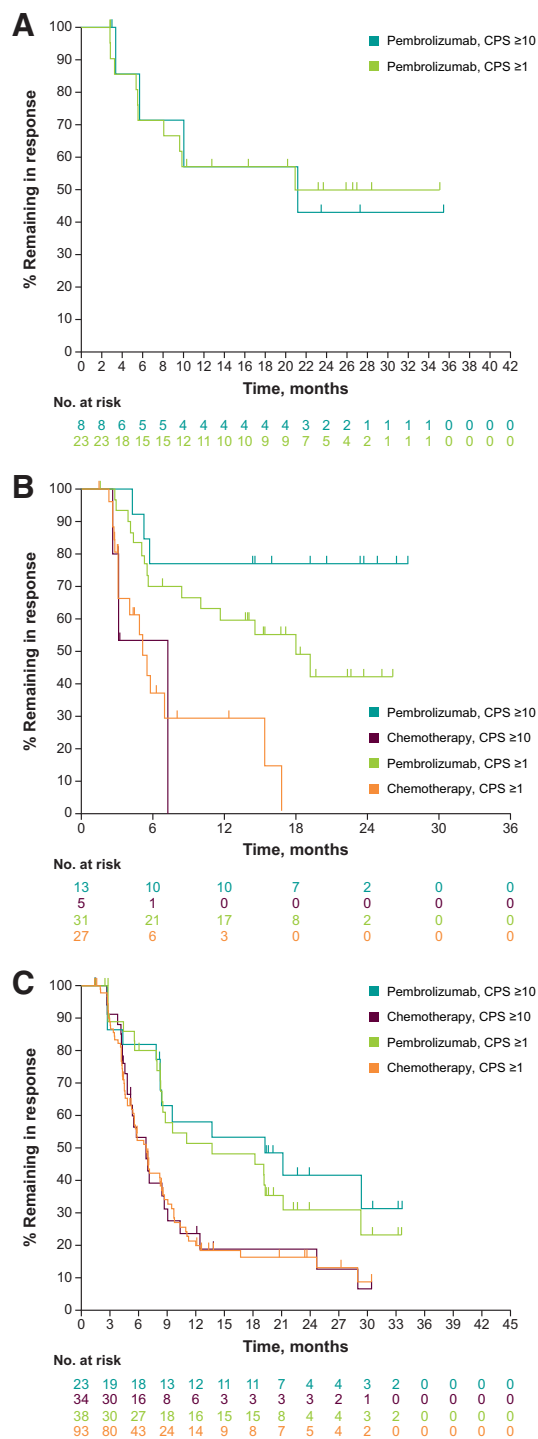
In addition to other factors including MSI and HER2 status, PD-L1 expression can provide important guidance for patient selection in clinical practice and is used to select patients eligible for pembrolizumab therapy. On the basis of a recent meta-analysis showing an expression–response relationship between PD-L1 and OS, we evaluated whether an increase in PD-L1 positivity from CPS ≥ 1 to CPS ≥ 10 resulted in improved responses to pembrolizumab (19). In comparing the current analysis of CPS ≥ 10 tumors, in which patient numbers are small, with previously reported data in patients with CPS ≥ 1 tumors, we observed numerically higher median OS, ORR, and DOR with pembrolizumab therapy by increasing the CPS cutoff from ≥ 1 to ≥ 10 . In KEYNOTE-059, median OS increased from 6 to 8 months, and the

12-month OS rate increased from 24% to 33%, the ORR increased from 16% to 17%, and the DOR increased from 16 to 21 months (8). In KEYNOTE-061, median OS increased from 9 to 10 months, and the 12-month OS rate increased from 40% to 45%, the 18-month OS rate increased from 26% to 35%, the ORR increased from 16% to 25%, and the DOR increased from 18 months to not reached (9, 22). In KEYNOTE-062, median OS increased from 11 to 17 months, and the 12-month OS rate increased from 47% to 57%, the 24-month OS rate increased from 27% to 39%, the ORR increased from 15% to 25%, and the DOR increased from 14 to 19 months (10). In KEYNOTE-061, the HR for OS decreased from 0.82 for CPS ≥ 1 to 0.64 for CPS ≥ 10 (9), and in KEYNOTE-062, the HR for OS decreased from 0.91 for CPS ≥ 1 to 0.69 for CPS ≥ 10 (10). In KEYNOTE-062, the combination of pembrolizumab and chemotherapy was not superior to chemotherapy for OS in patients with CPS ≥ 1 or CPS ≥ 10 tumors (10). Thus, increasing the CPS cutoff to CPS ≥ 10 in patients with gastric or GEJ cancer may provide greater treatment benefit for patients eligible to receive pembrolizumab monotherapy.

The clinical benefit of using higher PD-L1 cutoffs with pembrolizumab has also been evaluated in other tumor types. Evidence from the phase III KEYNOTE-181 study in patients with advanced/metastatic esophageal cancer demonstrated a significant benefit with a high CPS cutoff. Among 222 patients with CPS ≥ 10 tumors, second-line pembrolizumab monotherapy significantly improved OS versus chemotherapy (HR, 0.69; 95% CI, 0.52–0.93; *P* = 0.0074; ref. 23). In the phase III KEYNOTE-048 trial in patients with untreated locally incurable recurrent or metastatic head and neck squamous cell carcinoma, pembrolizumab monotherapy demonstrated a greater survival benefit than cetuximab plus chemotherapy in the population with CPS ≥ 20 tumors (HR, 0.61; 95% CI, 0.45–0.83; *P* = 0.0007) than in the population with CPS ≥ 1 tumors (HR, 0.78; 95% CI, 0.64–0.96; *P* = 0.0086; ref. 24). In the single-arm phase II KEYNOTE-052 study in patients with locally advanced and unresectable or metastatic urothelial cancer, response to pembrolizumab monotherapy increased with increasing CPS cutoff (CPS ≥ 1 , 11%; CPS > 1 to < 10 , 20%; CPS ≥ 10 , 39%; ref. 25). In patients with advanced recurrent ovarian cancer enrolled in the phase II KEYNOTE-100 study, higher PD-L1 expression also correlated with higher response to pembrolizumab monotherapy (CPS ≥ 1 , 5.7%; CPS ≥ 10 , 10.0%; ref. 26).

Limitations of the current analysis include the *post hoc* nature of KEYNOTE-059 cohort 1 and KEYNOTE-061 and the small patient

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**Figure 3.**

Kaplan-Meier estimates of DOR in patients with CPS ≥ 1 and CPS ≥ 10 tumors. **A**, Patients receiving third-line and later pembrolizumab in KEYNOTE-059 cohort 1. **B**, Patients receiving second-line pembrolizumab or chemotherapy in KEYNOTE-061. **C**, Patients receiving first-line pembrolizumab or chemotherapy in KEYNOTE-062. CPS, combined positive score; DOR, duration of response.

numbers within each subgroup. Furthermore, biomarker enrichment can predict response, but prevalence can decrease with higher CPS enrichment. Taken together, definitive conclusions cannot be made from this analysis.

In this analysis, these data suggest that pembrolizumab monotherapy given as first-line (KEYNOTE-062), second-line (KEYNOTE-061), and third-line and later (KEYNOTE-059) therapy showed a clinically meaningful median and long-term survival benefit in patients with CPS ≥ 10 gastric or GEJ tumors and more durable responses compared with chemotherapy. This study adds to the existing body of evidence that the immunohistochemical PD-L1 CPS is one clinically relevant biomarker that can lead to improved clinical efficacy and validates the importance of refining the PD-L1 CPS biomarker companion diagnostic as we attempt to define the optimal role of pembrolizumab in gastric cancer. Although evidence from the current analysis and in other tumor types has validated scoring of PD-L1 expression using tumor and immune cells (i.e., CPS) to predict response to pembrolizumab, large and prospective trials are needed to validate the optimal CPS cutoff for patients with gastric or GEJ cancer.

Authors' Disclosures

Z.A. Wainberg reports advisory/consultancy for AstraZeneca, Bayer, Daiichi, FivePrime, Lilly, Merck, and Molecular Therapeutics; research grant/funding (to his institution) from AstraZeneca, Daiichi, FivePrime, Lilly, and Merck; and travel/accommodations/expenses for Bayer, Daiichi, Lilly, Merck, and Molecular Therapeutics. C.S. Fuchs reports consulting for Agios, Amylin Pharmaceuticals, Bain Capital, CytomX Therapeutics, Daiichi-Sankyo, Eli Lilly, Entrinsic Health, EvolveImmune Therapeutics, Genentech, Merck, Taiho, and Unum Therapeutics; serves as a director for CytomX Therapeutics and owns unexercised stock options for CytomX and Entrinsic Health; is a co-founder of EvolveImmune Therapeutics and has equity in this private company; and has provided expert testimony for Amylin Pharmaceuticals and Eli Lilly. J. Tabernero reports consultancy for Array Biopharma, AstraZeneca, Bayer, BeiGene, Biocartis, Boehringer-Ingelheim, Chugai, F. Hoffmann-La Roche Ltd, Foundation Medicine, Genentech Inc, Genmab A/S, HalioDX SAS, Halozyne, Imugene Limited, Inflection Biosciences Limited, Ipsen, Kura Oncology, Lilly, MSD, Menarini, Merck Serono, Merrimack, Merus, Molecular Partners, Novartis, Peptomyc, Pfizer, Pharmacyclis, ProteoDesign SL, Rafael Pharmaceuticals, Roche Diagnostics, Sanofi, SeaGen, Seattle Genetics, Servier, Symphogen, Taiho, and VCN Biosciences. K. Shitara reports an advisory role for AbbVie Inc, Astellas Pharma, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Merck, Novartis, Ono Pharmaceutical, Pfizer Inc, Taiho Pharmaceutical, and Takeda Pharmaceuticals; research funding for Astellas Pharma, Chugai Pharma, Dainippon Sumitomo Pharma, Daiichi Sankyo, Eli Lilly and Company, Medi Science, Merck, Ono Pharmaceutical, and Taiho Pharmaceutical; and honoraria (lecture fee) for AbbVie Inc, Novartis, and Yakult. K. Muro reports research funding (to his institution) from Daiichi Sankyo, Mediscience Planning, MSD, Parexel International, Pfizer, Sanofi, Solasia Pharma, and Sumitomo Dainippon Pharma; honoraria for speaking from Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical, Takeda Pharmaceutical, and Sanofi; and advisory/consultancy for Amgen, AstraZeneca, and Ono Pharmaceutical Co., Ltd. E. Van Cutsem reports consulting/advisory role for Array, AstraZeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daiichi, Halozyne, GSK, Pierre-Fabre, Incyte, Ipsen, Lilly, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, Merck KGaA, Novartis, Pierre Fabre, Roche, Servier, Sirtex, and Taiho; and grants (to institution) from Amgen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Ipsen, Lilly, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, Merck KGaA, Novartis, Roche, and Servier. Y.-J. Bang reports consulting/advisory for Astellas, AstraZeneca, Bayer, BeiGene, BMS, Daiichi-Sankyo, Eli Lilly, Genentech/Roche, Genexine, GreenCross, Hammi, Merck-Serono, MSD, Novartis, Samyang Biopharm, and Taiho, and grants (to the institution for clinical trials) from Astellas, AstraZeneca, Bayer, BeiGene, Boehringer-Ingelheim, Bostin Biomedical, BMS, CKD Pharma, Curis, Daiichi-Sankyo, Eli Lilly, FivePrime, Genentech/Roche, Genexine GreenCross, GSK, MacroGenics, Merck Serono, MSD, Novartis, Ono, Pfizer, Taiho, and Takeda. H.C. Chung reports research support from Amgen, BeiGene, BMS/Ono, GSK, Lilly, MSD, Merck-Serono, and Taiho; honoraria from Lilly and Merck-Serono; and consultancy for Amgen, BeiGene, BMS, Celltrion, Gloria, Lilly, Merck-Serono, MSD, Quintiles, Taiho, and Zymeworks. K. Yamaguchi

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Efficacy of Pembrolizumab Monotherapy for Advanced Gastric/Gastroesophageal Junction Cancer with Programmed Death Ligand 1 Combined Positive Score ≥ 10

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