JAMA Oncology | Original Investigation

Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer
Phase 2 Clinical KEYNOTE-059 Trial

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IMPORTANCE Therapeutic options are needed for patients with advanced gastric cancer whose disease has progressed after 2 or more lines of therapy.

OBJECTIVE To evaluate the safety and efficacy of pembrolizumab in a cohort of patients with previously treated gastric or gastroesophageal junction cancer.

DESIGN, SETTING, AND PARTICIPANTS In the phase 2, global, open-label, single-arm, multicohort KEYNOTE-059 study, 259 patients in 16 countries were enrolled in a cohort between March 2, 2015, and May 26, 2016. Median (range) follow-up was 5.8 (0.5-21.6) months.

INTERVENTION Patients received pembrolizumab, 200 mg, intravenously every 3 weeks until disease progression, investigator or patient decision to withdraw, or unacceptable toxic effects.

MAIN OUTCOMES AND MEASURES Primary end points were objective response rate and safety. Objective response rate was assessed by central radiologic review per Response Evaluation Criteria in Solid Tumors, version 1.1, in all patients and those with programmed cell death 1 ligand 1 (PD-L1)–positive tumors. Expression of PD-L1 was assessed by immunohistochemistry. Secondary end points included response duration.

RESULTS Of 259 patients enrolled, most were male (198 [76.4%]) and white (200 [77.2%]); median (range) age was 62 (24-89) years. Objective response rate was 11.6% (95% CI, 8.0%-16.1%; 30 of 259 patients), with complete response in 2.3% (95% CI, 0.9%-5.0%; 6 of 259 patients). Median (range) response duration was 8.4 (1.6+ to 17.3+) months (+ indicates that patients had no progressive disease at their last assessment). Objective response rate and median (range) response duration were 15.5% (95% CI, 10.1%-22.4%; 23 of 148 patients) and 16.3 (1.6+ to 17.3+) months and 6.4% (95% CI, 2.6%-12.8%; 7 of 109 patients) and 6.9 (2.4 to 7.0+) months in patients with PD-L1–positive and PD-L1–negative tumors, respectively. Forty-six patients (17.8%) experienced 1 or more grade 3 to 5 treatment-related adverse events. Two patients (0.8%) discontinued because of treatment-related adverse events, and 2 deaths were considered related to treatment.

CONCLUSIONS AND RELEVANCE Pembrolizumab monotherapy demonstrated promising activity and manageable safety in patients with advanced gastric or gastroesophageal junction cancer who had previously received at least 2 lines of treatment. Durable responses were observed in patients with PD-L1–positive and PD-L1–negative tumors. Further study of pembrolizumab for this group of patients is warranted.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02335411

JAMA Oncol. 2018;4(5):e180013. doi:10.1001/jamaoncol.2018.0013
Published online March 15, 2018.Corrected on March 7, 2019.

Supplemental content

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Worldwide, gastric cancer is the fifth most common type of malignant neoplasm.[1] In 2013 it led to 723 100 deaths.[2,3] In Western countries, most patients with gastric adenocarcinoma present with advanced disease, and treatment options are limited.[4] First-line chemotherapy most commonly comprises a platinum and a fluoropyrimidine, with median survival ranging from 8 to 17 months across regions.[4,5] Disease progression after first-line chemotherapy is common; second-line treatment options include ramucirumab, alone or combined with a taxane or irinotecan.[6-8] Therapeutic options are lacking for patients whose disease progresses after 2 or more lines of systemic therapy.[6-8] New treatment options based on a fundamental understanding of gastric cancer biology are needed.

Comprehensive molecular analysis of 295 gastric adenocarcinomas, as part of The Cancer Genome Atlas,[9] identified amplification of genes encoding programmed cell death 1 ligand 1 (PD-L1) and PD-L2 in a subset of tumors, and results of other studies in gastric cancer have demonstrated PD-L1 expression by immunohistochemistry.[10] Together with PD-L1 and PD-L2, programmed cell death 1 (PD-1) regulates the balance between T-cell activation and tolerance in response to antigenic stimulation.[11]

Pembrolizumab, a selective, humanized, high-affinity IgG4-κ monoclonal antibody designed to bind PD-1, conferred a 22% objective response rate (ORR) in a phase 1b trial of 39 patients with PD-L1–positive advanced gastric or gastroesophageal junction adenocarcinoma (KEYNOTE-012 study).[12] We conducted a 3-cohort phase 2 trial (KEYNOTE-059 study) in which cohort 1 was designed to further define the safety and activity of pembrolizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma who experienced disease progression after 2 or more lines of therapy.

Key Points

Question Is pembrolizumab monotherapy safe and effective in patients with previously treated gastric and gastroesophageal junction cancer?

Findings Among 259 patients with previously treated gastric and gastroesophageal junction cancer enrolled in the phase 2 KEYNOTE-059 single-arm, multicohort trial, pembrolizumab demonstrated manageable safety. The objective response rate was 11.6% (30 of 259 patients), and complete responses were observed in 2.3% of patients (6 of 259); the median (range) response duration was 8.4 (1.6 + to 17.3+) months (+ indicates that patients had no progressive disease at their last assessment).

Meaning These results support further development of pembrolizumab for patients with gastric and gastroesophageal junction cancer who have received 2 or more lines of therapy.

Methods

Study Design and Sample Size

The KEYNOTE-059 study is a multicenter, open-label, nonrandomized, 3-cohort, phase 2 trial of pembrolizumab that was conducted at 67 sites in 17 countries in patients with advanced gastric or gastroesophageal junction adenocarcinoma. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Institutional review boards and independent ethics committees for each institution approved the protocol and its amendments (Supplement 1). All patients provided written informed consent. Results for cohort 1 are presented.

Patients in cohort 1 received pembrolizumab monotherapy via a 30-minute infusion (as outpatients) at a fixed dose of 200 mg on day 1 of each 3-week cycle. Treatment continued until confirmed progression based on immune-related Response Evaluation Criteria in Solid Tumors (irRECIST), unacceptable toxic effects, investigator or patient decision to withdraw, nonadherence to trial treatment or procedures, or completion of 35 cycles (approximately 2 years) of pembrolizumab treatment. To account for potential pseudoprogression, patients could continue treatment beyond initial disease progression assessed by radiographic imaging per RECIST version 1.1 as specified in eAppendix 1 in Supplement 2. After radiographic confirmation of progression, irRECIST was applied to direct clinical management to account for the possibility of tumor flare, which can be observed with immunotherapies.[13] Patients with responsive or stable disease who discontinued pembrolizumab could resume pembrolizumab for up to 1 year if progression occurred after treatment discontinuation. Dose reduction was not permitted; however, interruption or discontinuation was allowed if toxic effects occurred. Pembrolizumab was withheld if treatment-related adverse events (AEs) and severe or life-threatening AEs occurred.

Tumor response was assessed by radiographic imaging 9 weeks after treatment start, then every 6 weeks for the first year and every 9 weeks thereafter. Response was confirmed by repeated radiographic assessment 4 or more weeks from the first documentation of response. The primary end point was ORR, per RECIST version 1.1, assessed by central imaging review.[14]

Adverse events were monitored throughout treatment and for 30 days after the last study dose (90 days for serious AEs and events of clinical interest). Patients who discontinued treatment for reasons other than progression were followed up for disease status until progression, initiation of nonstudy cancer treatment, withdrawal of consent, or loss to follow-up.

Enrollment of patients with PD-L1–negative tumors was paused after the first 42 patients were enrolled in cohort 1 for a planned interim analysis by an independent data monitoring committee to assess ORR and treatment futility in patients with PD-L1–negative tumors. The criterion for futility was met if the upper bound of the 95% confidence interval of ORR was less than 20%. Based on this criterion, if at least 1 responder was observed among approximately 25 patients with PD-L1–negative tumors, enrollment of patients with PD-L1–negative tumors would resume. After enrollment of 42 patients, the independent data monitoring committee determined that the futility criterion was not met. Enrollment of patients (regardless of tumor PD-L1 expression) resumed to enroll an additional 135 patients. The estimated sample size for

this cohort was approximately 210 participants; the rationale is presented in eAppendix 1 and eTable 1 in Supplement 2).

Patients were allocated by nonrandom assignment. Tumor PD-L1 expression was masked for the study team in the initial all-comers enrollment phase for cohort 1 until the interim analysis. After the interim analysis, tumor PD-L1 expression was unmasked to the sponsor.

Patient Population

Patients in cohort 1 were enrolled at 52 sites in 16 countries (eAppendix 2 in Supplement 2). Eligible patients were aged 18 years or older; had histologically or cytologically confirmed recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma (only Siewert types II and III) incurable by locally approved therapies; had measurable disease (based on RECIST version 1.1) assessed by central imaging review (BioClinica)[14]; had disease progression after 2 or more prior chemotherapy regimens that included a fluoropyrimidine and a platinum doublet (as adjuvant treatment or for metastatic disease; perioperative, neoadjuvant, or adjuvant regimens were not considered previous regimens unless the patient's disease progressed during or within 6 months after adjuvant therapy); had human epidermal growth factor receptor 2 (HER2)/neu-negative (or HER2/neu-positive, if previously treated with trastuzumab) disease; had Eastern Cooperative Oncology Group performance status 0 or 1; had adequate organ function; and had a life expectancy of 3 months or longer. Patients must have provided a new or archival tissue sample for PD-L1 biomarker analysis before study entry. Exclusion criteria are presented in eAppendix 1 in Supplement 2.

Outcomes

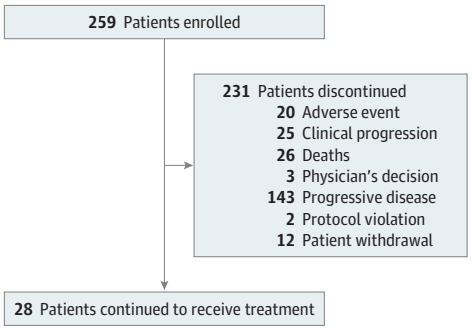
Primary objectives were safety and tolerability of pembrolizumab and ORR per RECIST version 1.1 (assessed by central review) in all patients and in those with PD-L1–positive tumors. Secondary objectives included duration of response (per RECIST version 1.1 by central review) in all patients and in those with PD-L1–positive tumors. Supportive analyses included disease control rate (complete response [CR], partial response, or stable disease for ≥2 months), progression-free survival (PFS) per RECIST version 1.1 by central imaging review, and overall survival (OS) in all patients and in those with PD-L1–positive tumors.

Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).[15] Attribution to treatment, time of onset, duration, resolution, and any concomitant medications administered were recorded. Immune-mediated AEs, regardless of attribution or immune relatedness by investigator, were also noted and graded.

Statistical Analysis

Efficacy and safety were analyzed in all patients who received at least 1 dose of pembrolizumab. The primary end point of ORR with 95% confidence intervals was estimated using the Clopper-Pearson method.[16] Patients with missing data were counted as nonresponders. Time-to-event end points were estimated using the Kaplan-Meier method. Exploratory analyses of response and duration of response were conducted in patient subgroups by line of therapy, line of therapy and tumor PD-L1 status, and microsatellite instability (MSI) status. Safety and tolerability were analyzed using descriptive statistics. Analyses were conducted using SAS statistical software version 9.3 (SAS Institute, Inc).

Figure 1. Enrollment of Patients for Cohort 1 of the KEYNOTE-059 Study



Eligible patients were 18 years or older; had histologically or cytologically confirmed recurrent or metastatic gastric or gastroesophageal cancer; and had disease progression after 2 or more prior chemotherapy regimens that included a fluoropyrimidine and a platinum doublet.

Biomarker Analysis

Expression of PD-L1 was assessed in tumor biopsy samples by the pharmDx immunohistochemistry assay (PD-L1 IHC 22C3; Agilent Technologies). Tumors were considered PD-L1 positive if the combined positive score (number of PD-L1–positive cells [tumor cells, macrophages, lymphocytes] divided by the total number of tumor cells, multiplied by 100) was 1 or greater. We assessed DNA mismatch repair across 5 mononucleotide repeat markers (NR21, NR24, BAT25, BAT26, MONO27) using DNA extracted from formalin-fixed, paraffin-embedded tumor samples and blood (normal control) using the MSI Analysis System, version 1.2 (Promega). In MSI-high tumors, 2 or more markers were changed, compared with normal controls. Gene expression profiles from pretreatment tumor samples of pembrolizumab-treated patients were analyzed to identify immune-related signatures correlating with clinical benefit. Through a process of testing, validation, and refinement of immune-related gene expression sets across a variety of tumor types, the 18-gene (*CCL5*, *CD27*, *CD274* [*PD-L1*], *CD-276* [*B7-H3*], *CD8A*, *CMKLR1*, *CXCL9*, *CXCR6*, *HLA-DQA1*, *HLA-DRB1*, *HLA-E*, *IDO1*, *LAG3*, *NKG7*, *PDCD1LG2* [*PD-L2*], *PSMB10*, *STAT1*, *TGIT*) T-cell-inflamed gene expression signature was developed.[17,18] Detailed methods are presented in eAppendix 1 in Supplement 2.

Results

Between March 2, 2015, and May 26, 2016, 259 patients were enrolled in cohort 1 (**Figure 1**). Median (range) age was 62 (24-89) years, and most patients were male (198 [76.4%]) and white

Table 1. Objective Tumor Response

Best Overall Response[a]	Participants (n = 259) No.	% (95% CI)
Objective response (CR+PR)	30	11.6 (8.0-16.1)
Disease control (CR+PR+SD ≥2 mo)	70	27.0 (21.7-32.9)
CR	6	2.3 (0.9-5.0)
PR	24	9.3 (6.0-13.5)
SD	42	16.2 (11.9-21.3)
Progressive disease	145	56.0 (49.7-62.1)
Nonevaluable	7	2.7 (1.1-5.5)
No assessment[b]	35	13.5 (9.6-18.3)
Duration of response, median (range), mo	8.4 (1.6+ to 17.3+)[c]	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

[a] Only confirmed responses are included.

[b] No assessment represents patients who had a baseline assessment but no postbaseline assessment at the time of the data cutoff date. Reasons for no assessment include missing, treatment discontinuation, or death before the first postbaseline radiologic imaging study.

[c] + Indicates no progressive disease at last assessment.

(200 [77.2%]) (eTable 2 in Supplement 2). Approximately half the patients (134 [51.7%]) had received 2 prior therapies for metastatic disease, whereas the others received 3 or more prior treatments; 133 patients (51.4%) had tumors at the gastroesophageal junction (eTable 2 in Supplement 2). Tissue for PD-L1 immunohistochemistry consisted of surgical resection specimens (47 [18.1%]), biopsy samples from primary lesions (137 [52.8%]), and metastatic sites (71 [27.4%]). Among 259 patients, 148 (57.1%) were PD-L1 positive, 109 (42.1%) were PD-L1 negative, and 2 (0.8%) had unknown PD-L1 expression.

At data cutoff (January 16, 2017), median (range) follow-up was 5.8 (0.5-21.6) months among all patients and 11.1 (10.9-24.7) months among living patients; 28 patients (10.8%) continued to receive study treatment. The most common reason for treatment discontinuation was disease progression (168 patients [64.9%]) (Figure 1). Twenty-six patients (10.0%) died; 20 (7.7%) discontinued because of AEs; 12 (4.6%) withdrew consent; 3 (1.2%) discontinued at the physician's discretion; and 2 (0.8%) were discontinued because of protocol violation.

Among 259 patients, 30 (11.6%; 95% CI, 8.0%-16.1%) experienced objective response based on central radiologic assessment per RECIST version 1.1, and 6 (2.3%; 95% CI, 0.9%-5.0%) experienced CR (**Table 1**). Median (range) time to objective response was 2.1 (1.7-6.6) months. Among 223 patients who had 1 or more postbaseline radiologic imaging assessments, 95 (42.6%) experienced reduction in measurable tumor size (**Figure 2**A). Median (range) duration of response was 8.4 (1.6+ to 17.3+) months (+ indicates that patients had no progressive disease at their last assessment); responses were ongoing in 16 of 30 responders (53.3%) (Figure 2B). Decrease in tumor burden was maintained over several assessments (Figure 2C).

Median PFS, assessed by central radiologic review per RECIST version 1.1, was 2.0 months (95% CI, 2.0-2.1), with 6-month PFS of 14.1% (95% CI, 10.1%-18.7%) (eFigure 1A in Supplement 2). Median OS was 5.6 months (95% CI, 4.3-6.9) (eFigure 1B in Supplement 2), with 6-month OS of 46.5% (95% CI, 40.2%-52.6%) and 12-month OS of 23.4% (95% CI, 17.6%-29.7%). Additional PFS and OS analyses by subgroups are presented in eAppendix 1 and eFigure 2 in Supplement 2.

Additionally, we examined centrally reviewed ORR by patient and disease characteristics (eFigure 3 in Supplement 2). Among patients with PD-L1-positive tumors, ORR was 15.5% (95% CI, 10.1%-22.4%; 23 of 148 patients), with 2.0% (95% CI, 0.4%-5.8%) experiencing CR (eTable 3 in Supplement 2). Among patients with PD-L1-negative tumors, ORR was 6.4% (95% CI, 2.6%-12.8%; 7 of 109 patients), with 2.8% (95% CI, 0.6%-7.8%) experiencing CR. Median (range) response duration was 16.3 (1.6+ to 17.3+) months and 6.9 (2.4 to 7.0+) months in patients with PD-L1–positive and PD-L1–negative tumors, respectively.

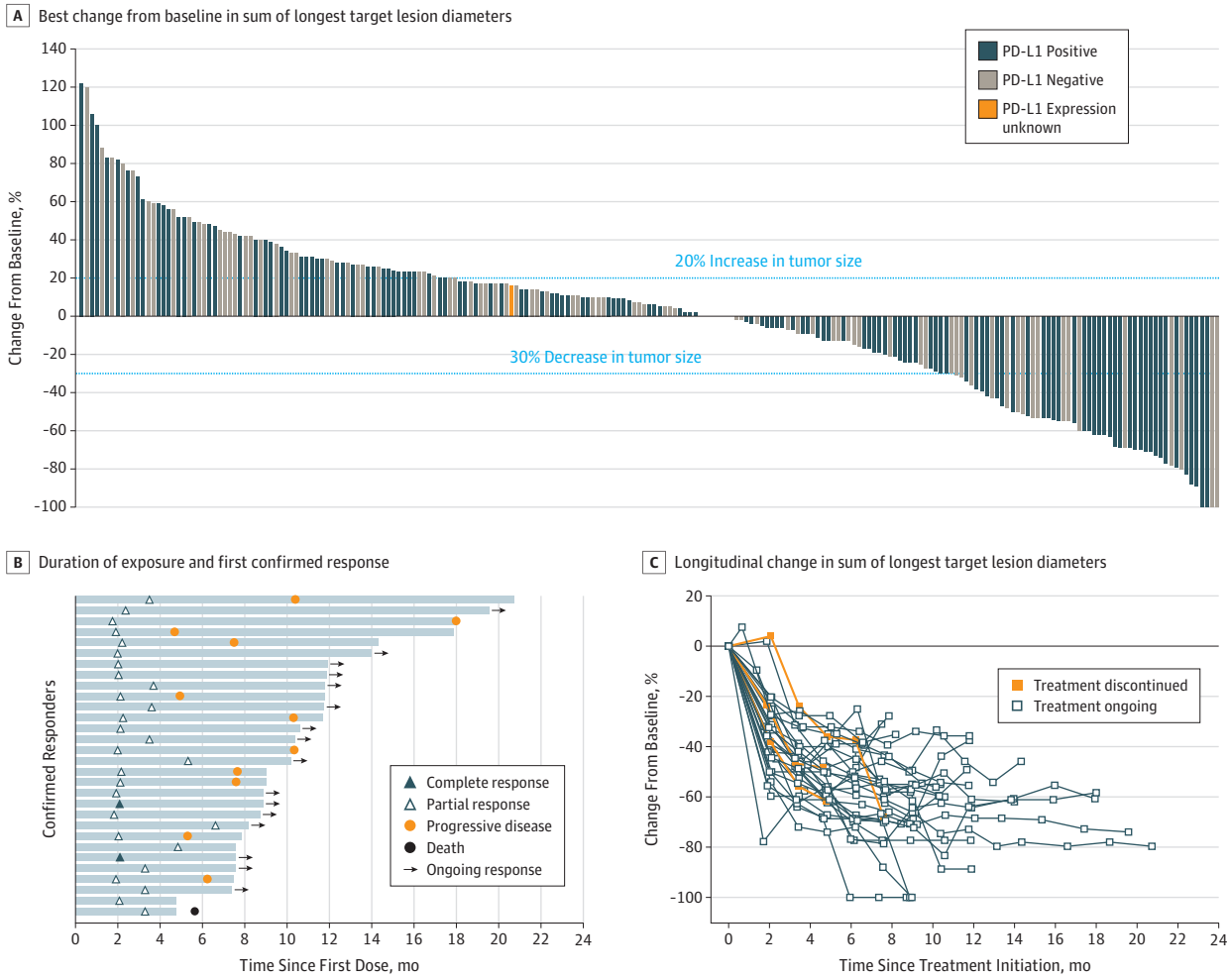
The ORR was 16.4% (95% CI, 10.6%-23.8%) in patients who received pembrolizumab as third-line treatment and 6.4% (95% CI, 2.8%-12.2%) in patients who received pembrolizumab as fourth-line or later treatment (eTable 4 in Supplement 2). Patients who received pembrolizumab as third-line treatment for PD-L1-positive tumors experienced an ORR of 22.7% (95% CI, 13.8%-33.8%), with 2.7% (95% CI, 0.3%-9.3%) experiencing CR (eTable 5 in Supplement 2); median (range) duration of response was 8.1 (1.6+ to 17.3+) months. Patients with PD-L1-negative tumors who received pembrolizumab as third-line treatment had an ORR of 8.6% (95% CI, 2.9%-19.0%), with 3.4% (95% CI, 0.4%-11.9%) experiencing CR; median (range) response duration was 6.9 (4.4+ to 7.0+) months.

Of 259 patients enrolled, 174 patients (67.2%) with available matching tissue and blood samples were assessed for MSI, of which 7 (4.0%) had samples that were MSI-high. Among 7 patients with MSI-high samples, 4 experienced objective response (57.1%; 95% CI, 18.4%-90.1%); among 167 patients with non–MSI-high samples, 15 experienced objective response (9.0%; 95% CI, 5.1%-14.4%) (eTable 6 in Supplement 2). The ORR for additional subgroups is shown in eFigure 3 in Supplement 2.

The 18-gene T-cell-inflamed gene expression profiling score demonstrated a higher score in aggregate for responders than for nonresponders (eFigure 4A in Supplement 2). A higher gene expression profiling score was significantly associated with improved propensity for response using regression testing ($P = .01$) (eFigure 4A in Supplement 2) and improved PFS ($P = .002$) (eFigure 4B in Supplement 2). There was a nonlinear positive association between T-cell-inflamed gene expression profiling score and PD-L1 expression (Spearman ρ of 0.54; $P < .001$) (eFigure 4C in Supplement 2). For all PD-L1 immunohistochemistry scores greater than 20, T-cell-inflamed gene expression profiling scores were in the upper half of the range, but PD-L1 immunohistochemistry scores less than 20 were associated with a broad range of gene expression profiling scores (eFigure 4C in Supplement 2).

At data cutoff, the median (range) duration of exposure among 259 patients was 2.1 (0.03-21.40) months, and the median (range) number of treatment administrations was 4.0 (1.0-32.0). All-cause, any-grade AEs were reported in 248 patients (95.8%), with 159 patients (61.4%) experiencing 1 or more grade 3 to grade 5 AEs. Overall, 156 patients (60.2%) experienced 1 or more treatment-related AEs of any grade, and 46

Figure 2. Tumor Response in 223 Patients



Of 259 patients enrolled, 223 had 1 or more postbaseline radiologic imaging assessments. Response was assessed in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by central imaging at baseline and after at least 1 postbaseline tumor assessment. A, Best change from baseline in sum of longest target lesion diameters per patient (n = 223). PD-L1 indicates programmed cell death 1 ligand 1. B, Duration of exposure and first confirmed response (partial or complete response) in responders (n = 30). Bar length indicates time to last imaging assessment. C, Longitudinal change in sum of longest target lesion diameters from baseline in patients with partial or complete response (n = 30).

patients (17.8%) experienced 1 or more grade 3 to grade 5 treatment-related AEs. Most treatment-related AEs were mild to moderate; the most common any-grade AEs were fatigue, pruritus, rash, hypothyroidism, decreased appetite, anemia, nausea, diarrhea, and arthralgia (**Table 2** and eTable 7 in Supplement 2). Two patients (0.8%) discontinued treatment because of treatment-related AEs (bile duct stenosis and abnormal hepatic function) (eAppendix 1 in Supplement 2). Two deaths (0.8%; acute kidney injury and pleural effusion) were considered related to study treatment by the investigator.

Overall, 46 patients (17.8%) experienced at least 1 immune-mediated AE of any grade; the most common were hypothyroidism (23 [8.9%]), hyperthyroidism (9 [3.5%]), and colitis (6 [2.3%]) (eTable 8 in Supplement 2). Most immune-mediated AEs were low grade; 12 patients (4.6%) experienced grade 3 or 4 events, and none were fatal (grade 5). Pneumonitis occurred in 5 patients (1.9%). There were no reports of immune-mediated cardiomyopathy or Stevens-Johnson syndrome. Of 46 patients who experienced immune-mediated AEs, 13 (28.3%) received concomitant systemic corticosteroids and 10 (21.7%) experienced treatment interruption because of immune-mediated AEs.

Discussion

Patients with advanced gastric cancer whose disease progresses after 2 or more lines of therapy have limited treatment options. In this multicenter, open-label, single-arm, phase 2 trial of patients with previously treated metastatic gastric or gastroesophageal junction adenocarcinoma, pembrolizumab demonstrated manageable toxic effects and promising antitumor activity. Pembrolizumab elicited durable objective responses, by central review, in 30 of 259 patients (11.6%)

Table 2. Treatment-Related Adverse Events in 259 Patients[a]

Event	Any Grade, No. (%)	Grade 3, No. (%)
Fatigue	49 (18.9)	6 (2.3)
Pruritus	23 (8.9)	0
Rash	22 (8.5)	2 (0.8)
Hypothyroidism	20 (7.7)	1 (0.4)
Decreased appetite	19 (7.3)	0
Anemia	18 (6.9)	7 (2.7)
Nausea	18 (6.9)	2 (0.8)
Diarrhea	17 (6.6)	3 (1.2)
Arthralgia	15 (5.8)	1 (0.4)

[a] The table lists events that occurred in at least 5% of patients. There were 0 grade 4-5 events.

and CR in 6 patients (2.3%). Moreover, 95 patients (42.4%) experienced reduction in measurable tumor size. Only 46 patients (17.8%) experienced a grade 3 to grade 5 treatment-related AE, and the overall toxicity profile was similar to that reported for pembrolizumab across a spectrum of advanced malignant neoplasms.[12,19-25]

Objective response and CR were observed irrespective of PD-L1 tumor expression and across all examined lines of therapy. The ORR seemed higher in patients with PD-L1-positive vs PD-L1-negative tumors (23 of 148 [15.5%] vs 7 of 109 [6.4%], respectively); nonetheless, patients with PD-L1-negative tumors also experienced objective responses, including CR in 3 patients (2.8%).

Responses were durable in the overall population (median [range] duration, 8.4 [1.6+ to 17.3+] months), with a longer response duration in patients with PD-L1-positive tumors (median [range] duration, 16.3 [1.6+ to 17.3+] months). These results suggest the potential for pembrolizumab to confer sustained responses and disease control in patients with advanced gastric or gastroesophageal junction adenocarcinoma.

Patients who received pembrolizumab as third-line therapy (22 patients [16.4%]) experienced response superior to that of patients who received pembrolizumab in later lines (8 patients [6.4%]). The ORR in patients with PD-L1-positive tumors receiving pembrolizumab as a third-line treatment (17 patients [22.7%]) was comparable with that in a recent phase 1b trial of patients with PD-L1-positive gastric cancer who received pembrolizumab in earlier lines of therapy for advanced disease (22%).[12]

Rates of response to pembrolizumab in third or later lines of therapy in our findings were lower than rates used to calculate sample size. However, results with pembrolizumab were comparable with those of recent trials of currently available treatments for second-line therapy for advanced gastric cancer,[26-31] which demonstrated ORRs from 0% to 28% and median OS from 4.0 to 9.6 months. Our results are also consistent with a recent meta-analysis of 5 randomized clinical trials to compare targeted therapies or chemotherapy with the best standard of care in patients for whom first- or second-line therapy was ineffective.[32] Results of studies of other PD-1- and PD-L1-directed antibodies as monotherapy have also documented responses in patients with advanced esophagogastric cancers.[33-38] In a recent phase 3 trial (ATTRACTION-02) conducted exclusively in Asia, nivolumab monotherapy conferred an 11.2% response rate and a median survival of 5.3 months.[38] These studies had similar objectives and end points; however, important differences in patient demographics and disease characteristics (eg, 77.2% of patients were white and 51.4% of patients had tumors of the gastroesophageal junction in this study) preclude cross-trial comparisons.

The T-cell-inflamed gene expression profiling score was significantly associated with pembrolizumab response, and a significant nonlinear association was found between T-cell-inflamed gene expression profiling score and PD-L1 expression. These results suggest the potential for T-cell-inflamed gene expression profiling score and PD-L1 expression as biomarkers for treatment selection in the clinic, but confirmation in future trials is warranted. Ongoing work to identify new molecular profiles for gastric cancer might further optimize treatment selection. In the recent Cancer Genome Atlas analysis of gastric cancer, PD-L1 amplifications were more common in Epstein-Barr virus–positive and MSI-high tumors than in tumors without these markers.[9,39] Although data on Epstein-Barr virus status were not available in our trial, we observed a higher ORR in patients with MSI-high tumors than in patients with non–MSI-high tumors. Nonetheless, prevalence of MSI-high tumors was very low in this population (4%), and most responses were observed in non-MSI-high patients. To date, no clinically validated biomarkers provide complete separation of responders from nonresponders. Improvement in sensitivity and response enrichment to guide patient selection for pembrolizumab monotherapy will most likely come from combining information on multiple biomarkers.

Limitations

While this study provides valuable insight into the efficacy and safety of pembrolizumab monotherapy in patients with previously treated metastatic gastric or gastroesophageal junction adenocarcinoma, its single-arm nature limits our ability to compare the findings directly with available therapies for this patient population. Additionally, although this study included biomarker and gene expression analyses, sample sizes for these analyses were small; thus, interpretation of these results is challenging. Ongoing and future large randomized clinical trials of pembrolizumab in metastatic gastric or gastroesophageal junction cancer that include the assessment of multiple biomarkers have the potential to build upon the results presented here.

Conclusions

For most patients with progressive gastric cancer, the benefit of chemotherapy beyond second-line therapy is marginal. These patients have limited treatment options and poor prognosis. The current results suggest that pembrolizumab offers a promising new treatment option, providing high and durable responses, for advanced gastric or gastroesophageal junction adenocarcinoma that progresses after second-line

treatment. Pembrolizumab demonstrates a mechanism of action, duration of response, and toxicity profile distinct from and nonoverlapping with standard chemotherapy for gastroesophageal adenocarcinoma. Ongoing randomized clinical trials are being conducted to assess pembrolizumab in earlier lines of therapy and in combination with chemotherapy for patients with advanced gastroesophageal adenocarcinoma.[40,41]

ARTICLE INFORMATION

Accepted for Publication: December 11, 2017.

Published Online: March 15, 2018. doi:10.1001/jamaoncol.2018.0013

Correction: This article was corrected on March 7, 2019, to correct omissions in the Conflict of Interest Disclosures.

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Author Contributions: Drs Fuchs and Wang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: Fuchs, Doi, Jang, Muro, Satoh, Machado, Sun, Jalal, Shah, Metges, Garrido, Golan, Mandala, Wainberg, Catenacci, Ohtsu, Shitara, Geva, Bleeker, Ko, Ku, Philip, Enzinger, Bang, Levitan, Wang, Rosales, Dalal, Yoon.
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Obtained funding: Sun.
Administrative, technical, or material support: Muro, Satoh, Sun, Garrido, Geva, Ku.
Study supervision: Machado, Jalal, Shah, Garrido, Golan, Wainberg, Enzinger, Bang, Dalal.

Conflict of Interest Disclosures: Dr Fuchs has been a consultant for Eli Lilly, Entrinsic Health, Pfizer, Merck, Sanofi, Roche, Genentech, Merrimack Pharmaceuticals, Dicerna, Bayer, Agios, Gilead Sciences, Five Prime Therapeutics, and Taiho. Dr Fuchs has been a consultant for Celgene and KEW and also serves on the Board of Directors for CytomX Therapeutics; in that capacity, he receives a stipend (starting April 11, 2018) and was awarded unexercised stock options (effective April 23, 2018) but owns no stock. Dr Doi has received personal fees and research funding from Novartis, Merck Sharp & Dohme, Eli Lilly, Chugai Pharma, Kyowa Hakko Kirin, and Daiichi Sankyo; research funding from Taiho, Merck Serono, Astellas Pharma, Janssen, Boehringer Ingelheim, Takeda, Pfizer, Sumitomo Group, Bayer, and Celgene; and personal fees from Amgen. Dr Jang has been a site principal investigator in clinical trials sponsored by AstraZeneca, Merck, Novartis, Lilly, Boston Biomedical, and Bristol-Myers Squibb. Dr Muro has received honoraria from Takeda, Eli Lilly, Merck, Serono, Chugai Pharmaceuticals, Yakult Honsha, and Taiho Pharmaceuticals. Dr Satoh has received honoraria from Chugai Pharmaceuticals, Takeda, Eli Lilly, Merck Serono, Yakult Honsha, Taiho Pharmaceuticals, and Bayer; has been a consultant for Chugai Pharmaceuticals, Eli Lilly, and Ono Pharmaceutical; and has received institutional research funding from Yakult Honsha, Chugai Pharmaceutical, and Ono Pharmaceutical. Dr Sun has been a consultant for Bayer and Taiho and has received institutional research funding from Merck and Bayer. Dr Shah has received institutional research funding from Merck, Roche, and Boston Biomedical. Dr Metges has received honoraria from Eli Lilly, Sanofi, Novartis, and Merck. Dr Garrido has been a consultant to Merck Sharp & Dohme and Eli Lilly. Dr Mandala has received honoraria from and been a consultant for Merck, Bristol-Myers Squibb, Roche, and Novartis. Dr Wainberg has been a consultant for Genentech, ArrayBiopharma, Sirtex, Novartis, and Five Prime Therapeutics. Dr Catenacci has been a consultant for Eli Lilly, Roche/Genentech, Amgen, Taiho, and Five Prime Therapeutics; served on a speakers bureau for Eli Lilly; and received institutional research funding from Amgen and Genentech. Dr Ohtsu has received a grant from Bristol-Myers Squibb. Dr Shitara has received grants from Daiichi Sankyo, Sumitomo Dainippon Pharmaceuticals, Bayer, Yakult Honsha, Chugai Pharmaceuticals, Sanofi, Eli Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, Taiho Pharmaceuticals, and Onoyakuhin and has received personal fees from Bayer, Chugai Pharmaceuticals, Sanofi, Eli Lilly, Novartis, and Takeda. Dr Geva has been a consultant and advisor for Bayer, Novartis, and Merck Sharp & Dohme; has received honoraria from Bristol-Myers Squibb, Eli Lilly, Roche, Novartis, Medison, and Janssen; and has received travel and expense support from Bristol-Myers Squibb and Roche. Dr Bleeker has received travel support from Merck and has served as a consultant for Bristol-Myers Squibb. Dr Ko has received institutional research support from Merck, Bristol-Myers Squibb, Aduro Biotech, Merrimack, Celgene, and Roche and was a consultant for Seattle Genetics and New Beta Innovations. Dr Ku has received grants from Merck, Bristol-Myers Squibb, Arog Pharmaceuticals, and AstraZeneca and has received personal fees from Merck, Eli Lilly, and AstraZeneca. Dr Philip has received grants from Merck, Celgene, Incyte, Halozyme, Advix, Bayer, Boston Biomedical, Momenta, Novartis, and MacroGenics and has received personal fees from Celgene, Roche, Halozyme, Bayer, Merrimack, Caris, Ipsen, Lexicon, and Cornerstone. Dr Enzinger was a consultant for Merck, Five Prime Therapeutics, Sirtex, and Pfizer. Dr Bang has received institutional grant funding from Merck and has served as a consultant to Merck. Dr Yoon has received honoraria (paid to institution) for serving on advisory boards for Eli Lilly, Genentech, Astellas, LSK, and Five Prime Therapeutics and has received research funding (paid to institution) from Eli Lilly and Genentech. Drs Levitan, Wang, Rosales, and Dalal are employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA. No other disclosures were reported.

Funding/Support: This work was supported by Merck & Co, Inc.

Role of the Funder/Sponsor: Academic advisors and representatives of the sponsor, Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, designed the study. The data were collected by the investigators and their site personnel and were analyzed by the authors and by statisticians employed by the sponsor. Authors employed by the study sponsor contributed to the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript, as well as the decision to submit the manuscript for publication.

Additional Contributions: We thank the patients and their families and caregivers for participating in the study. Jared Lunceford, PhD, Mary Savage, PhD, Michael Nebozhyn, PhD, Jia Lu, MS, and Linda Sun, PhD, of Merck & Co, Inc provided biomarker analyses and statistical support. Medical writing and/or editorial assistance was provided by Sarita S. Shaevitz, PhD, of the ApotheCom pembrolizumab team. This assistance was funded by Merck & Co Inc. Principal investigators from the participating centers are listed in eAppendix 2 in Supplement 2. The investigators did not receive compensation for their assistance.

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