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Cancer Therapy: Clinical

Clinical Cancer Research

Efficacy of Sequential Ipilimumab Monotherapy versus Best Supportive Care for Unresectable Locally Advanced/Metastatic Gastric or Gastroesophageal Junction Cancer

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Abstract

Purpose: Ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte–associated protein-4 interactions, enhances T-cell activation and promotes tumor immunity. This phase II study evaluated the safety and efficacy of ipilimumab monotherapy versus best supportive care (BSC) among patients with advanced/metastatic gastric or gastroesophageal junction cancer who achieved at least stable disease with first-line chemotherapy.

Experimental Design: Eligible patients were randomized to ipilimumab 10 mg/kg every 3 weeks for four doses, then 10 mg/kg every 12 weeks for up to 3 years, or BSC, which could include continuation of fluoropyrimidine until progression or toxicity. The primary endpoint was immune-related progression-free survival (irPFS); secondary endpoints included PFS by modified World Health Organization criteria and overall survival (OS).

Results: Of 143 patients screened, 57 were randomized to each arm. irPFS with ipilimumab versus BSC was not improved [2.92 months, 95% confidence interval (CI), 1.61–5.16 vs. 4.90 months, 95% CI, 3.45–6.54, HR = 1.44; 80% CI, 1.09–1.91; $P = 0.097$], resulting in study cessation. At study closeout, which occurred 8 months after the interim analysis, the median OS durations were 12.7 months (95% CI, 10.5–18.9) and 12.1 months (95% CI, 9.3–not estimable), respectively. Grade 3/4 treatment-related adverse events occurred in 23% of ipilimumab-treated patients, in whom diarrhea (9%) and fatigue (5%) were most frequent, and in 9% of active BSC-treated patients.

Conclusions: Although ipilimumab at 10 mg/kg was manageable, it did not improve irPFS versus BSC. However, comparable median OS of approximately 1 year and a favorable safety profile support the investigation of ipilimumab in combination with other therapies for advanced gastric cancer. *Clin Cancer Res; 23(19); 5671–8. ©2017 AACR.*

Introduction

Gastric cancer is the fifth most common cancer globally and represents the third most common cause of cancer-related deaths (1). Although the introduction of nationwide screening programs has improved the detection of gastric cancer in some countries, particularly in Korea and Japan, many cases are diagnosed at an advanced stage globally (2). Although several therapies are used in the first-line treatment of advanced gastric cancer, there is no universally preferred treatment or maintenance regimen, and the prognosis for these patients remains poor. In phase III clinical trials of patients with advanced gastric cancer, the median overall survival (OS) in patients treated in the first-line setting was approximately 8 to 14 months (3–10). Median OS in the second-line setting is reported to range between 4.0 and 9.6 months compared with 2.4 and 4.3 months with current best supportive care (BSC; refs. 11–14).

Ipilimumab is a fully human monoclonal antibody (IgG1) that blocks cytotoxic T-lymphocyte–associated protein-4 (CTLA-4), an immune checkpoint protein that negatively regulates T-cell effector responses. By blocking the interaction between CTLA-4 and its ligands, ipilimumab promotes antitumor responses through T-cell activation and tumor infiltration (15, 16). Ipilimumab has demonstrated clinical efficacy in metastatic melanoma with a significant OS benefit in two pivotal phase III clinical trials (17, 18), as well as in a number of other tumor types (19–22). This study evaluated the efficacy of ipilimumab monotherapy versus BSC as maintenance therapy in patients with unresectable locally advanced/metastatic gastric or gastroesophageal junction (GEJ) cancer who achieved at least stable disease (SD) following first-line

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Overall survival (OS) for patients with advanced gastric cancer is approximately 8 to 14 months in the first-line setting and approximately 4 to 5 months in the second-line setting. Ipilimumab, a fully human anti–CTLA-4 IgG1 antibody, is an immune checkpoint inhibitor with antitumor activity in solid tumors. Here, ipilimumab monotherapy was compared with the current best standard of care (including continuation of first-line fluoropyrimidine chemotherapy) in a phase II proof-of-concept study designed to investigate safety and efficacy in patients with gastric and gastroesophageal junction cancer. At final analysis, immune-related progression-free survival was similar between arms, as was median OS of ≈1 year. Ipilimumab-related adverse events were manageable, and no new safety signals were identified. Based on the safety profile observed in this study and preliminary results from the combination of ipilimumab 3 mg/kg with nivolumab 1 mg/kg—which showed an encouraging median OS of 6.9 months and a 12-month OS rate of 34% in chemotherapy-refractory patients with gastroesophageal cancer (25)—these data support the investigation of ipilimumab in combination with other therapies in gastric cancer.

treatment with combination platinum-fluoropyrimidine chemotherapy. Importantly, BSC could include continuation of first-line fluoropyrimidine chemotherapy as maintenance (active BSC) or no active maintenance treatment. The results of the analysis described herein are based on a preplanned interim analysis (database lock in June 2014), which became the final analysis upon trial cessation. The study closed 8 months later, and updated OS results from that analysis are reported herein.

Materials and Methods

Patients

In this randomized, phase II, open-label study (NCT01585987), patients with histologically confirmed, unresectable locally advanced or metastatic gastric or GEJ adenocarcinoma were eligible if they were ≥18 years of age, had Eastern Cooperative Oncology Group performance status of 0 or 1, had a life expectancy of >12 weeks, and had received a platinum and fluoropyrimidine-based chemotherapy regimen as lead-in chemotherapy in the first-line setting consisting of either oxaliplatin + 5-fluorouracil every 14 days; oxaliplatin + capecitabine every 21 days; cisplatin + capecitabine every 21 days; cisplatin + 5-fluorouracil every 21 days; or cisplatin + S1 every 5 weeks. Eligible patients needed to have radiological evidence of clinical benefit [either complete response (CR), partial response (PR), or SD] by modified World Health Organization (mWHO) criteria (Supplementary Table S1) following the last dose of first-line chemotherapy and were required to have at least one measurable lesion (except for those patients who had a CR); previous irradiation of the measurable lesion was not allowed. Toxicities related to prior cancer therapy (chemotherapy, radiotherapy, or surgery) must have returned to grade 1 or baseline. Patients were excluded if they had known human epidermal growth factor receptor 2–positive status or radiological evidence of brain metastasis, documented history of severe autoimmune disease or immune-mediated symptomatic disease requiring prolonged systemic immunosuppressive treatment for >2 months, or a history of HIV infection or active hepatitis B or C infection.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Institutional Review Board/independent ethics committee approval of the protocol was obtained before initiating the trial. All participating patients (or their legal representatives) gave written informed consent.

Treatment and monitoring

Patients were randomly assigned 1:1 to receive either intravenous ipilimumab 10 mg/kg, every 3 weeks for four doses during the induction phase and then 10 mg/kg every 12 weeks for up to 3 years during the maintenance phase, or BSC. BSC could have included the same fluoropyrimidine the patient received during first-line chemotherapy as maintenance but no other systemic anticancer therapy. Randomization was stratified by (1) geographic region (Asia vs. rest of the world) and (2) prior best response to first-line chemotherapy (CR/PR vs. SD by mWHO criteria). Treatment was to be given until confirmed immune-related progressive disease or unacceptable toxicity, or for up to 3 years from the first dose of ipilimumab or withdrawal of consent. Crossover between treatment arms was not allowed.

The primary endpoint of the study was immune-related progression-free survival (irPFS) per assessment of a blinded independent review committee. Secondary endpoints were PFS by mWHO criteria, OS, and immune-related best overall response rate (irBORR), and exploratory endpoints included the safety profile of patients in each treatment arm, duration of response, and immune-related time to progression. Safety analysis was performed in all treated patients using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Tumor assessments were performed at screening and every 6 weeks ± 1 week starting from randomization until documented and confirmed disease progression per immune-related response criteria and subsequent systemic therapy. Any patient who developed an objective tumor response or disease progression by immune-related response criteria was required to undergo confirmatory scans within 4 weeks of the prior scan to verify the radiological finding.

Statistical analysis

Efficacy endpoints were analyzed on an intent-to-treat basis. The study was powered for the primary endpoint, irPFS. Using the assumption that the irPFS of each arm follows an exponential distribution and the true HR for irPFS was 0.64 between the ipilimumab versus BSC arm, 91 irPFS events were required for a two-sided stratified log-rank test with $\alpha = 0.2$ to have 80% power. The study was not powered for an analysis of differences in OS.

The distributions of irPFS, PFS per mWHO, and OS were compared between treatment arms using a two-sided log-rank test stratified by geographic region and prior response to first-line chemotherapy. irPFS, PFS per mWHO, and OS for each treatment arm were estimated and plotted using the Kaplan–Meier product-limit method. The estimates of medians and two-sided 95% CIs

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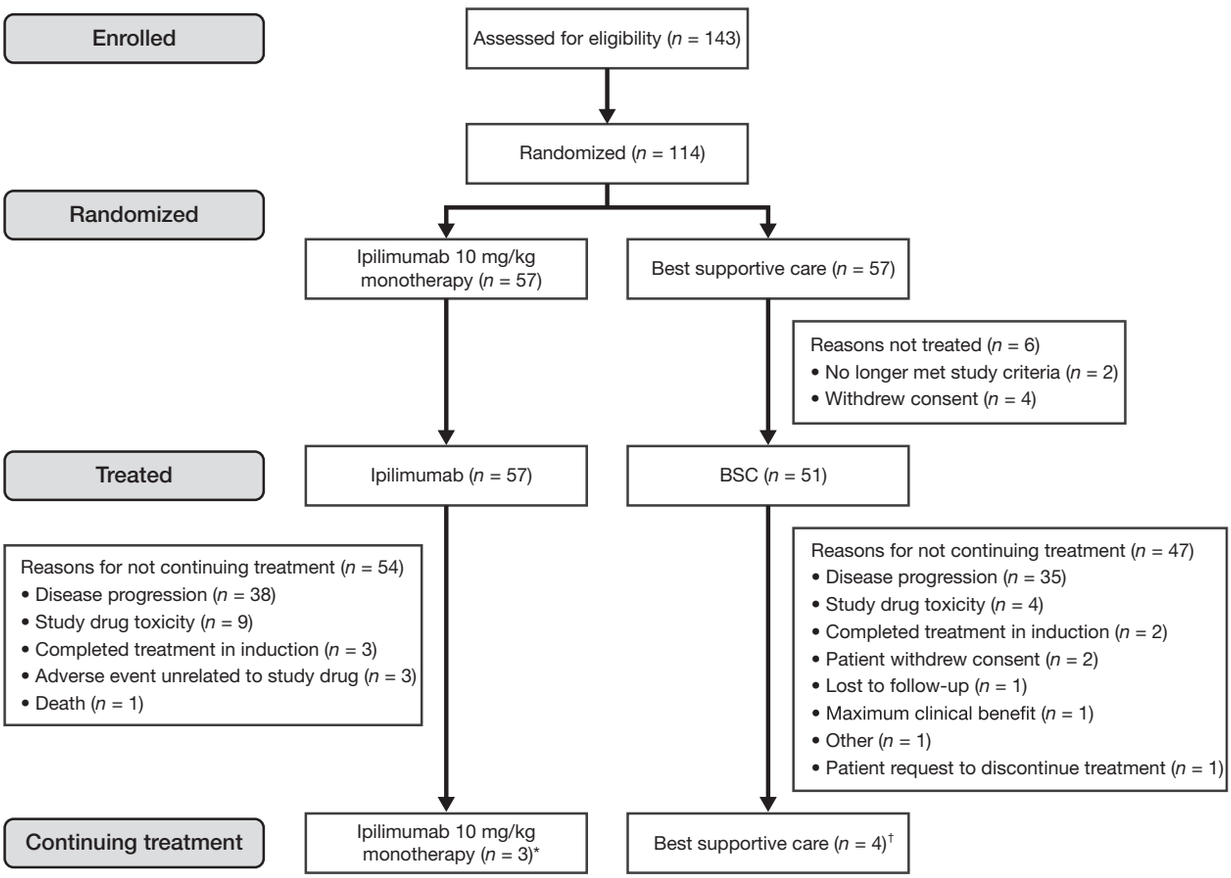

Figure 1.
CONSORT flow diagram. * By the time of study closeout, all 3 patients discontinued; reasons: 1 disease progression, 1 withdrew consent, 1 other. †By the time of study closeout, all 4 patients discontinued; reasons: 1 disease progression, 1 study drug toxicity, 1 poor/noncompliance, and 1 other.

were calculated by the Brookmeyer and Crowley method. Exact two-sided 95% CIs for irBORR rates were computed using the method of Clopper and Pearson. For the comparison of irBORR between treatment arms, a Cochran–Mantel–Haenszel test with an associated OR estimate and exact 80% CI, stratified by randomization stratification factors, was used. For duration of

Table 1. Demographics and baseline disease characteristics

	Ipilimumab ($n = 57$)	BSC ($n = 57$)	Total ($n = 114$)
Median age (range), y	65 (34–86)	62 (32–80)	64 (32–86)
Male, *n* (%)	36 (63.2)	41 (71.9)	77 (67.5)
Race, *n* (%)			
White	24 (42.1)	27 (47.4)	51 (44.7)
Asian	31 (54.4)	30 (52.6)	61 (53.5)
Other	2 (3.6)	0 (0.0)	2 (1.8)
ECOG performance status, *n* (%)			
0	32 (56.1)	24 (42.1)	56 (49.1)
1	25 (43.9)	33 (57.9)	58 (50.9)
Baseline tumor type, *n* (%)			
Gastric	48 (84.2)	47 (82.5)	95 (83.3)
Gastroesophageal junction	9 (15.8)	10 (17.5)	19 (16.7)
History of *Helicobacter pylori*, *n* (%)	13 (22.8)	7 (12.3)	20 (17.5)
Extent of disease, *n* (%)			
Locally advanced	7 (12.3)	7 (12.3)	14 (12.3)
Metastatic	50 (87.7)	50 (87.7)	100 (87.7)
Prior response[a] to first-line chemotherapy, *n* (%)			
CR/PR	33 (57.9)	33 (57.9)	66 (57.9)
SD	24 (42.1)	24 (42.1)	48 (42.1)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]Per modified WHO criteria and as reported by the interactive voice response system.

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response and time to progression, the event-free probabilities for each treatment arm were estimated and plotted using the Kaplan–Meier product-limit method. The estimates of medians and two-sided 95% CIs were calculated by the Brookmeyer and Crowley method.

Results

Patients

Between July 2012 and July 2014, a total of 143 patients with gastric or GEJ cancer from 12 countries across Asia, Europe, and North America who did not show evidence of disease progression following completion of initial fluoropyrimidine/platinum doublet first-line chemotherapy were screened for eligibility. Of these patients, 114 were randomized in a 1:1 ratio to receive ipilimumab 10 mg/kg or BSC (Fig. 1). Baseline patient disposition and disease characteristics were generally balanced across treatment arms (Table 1). At baseline, 83% of patients had gastric cancer and 17% had GEJ cancer. In both treatment arms, 88% of patients had metastatic cancer and 12% had locally advanced cancer.

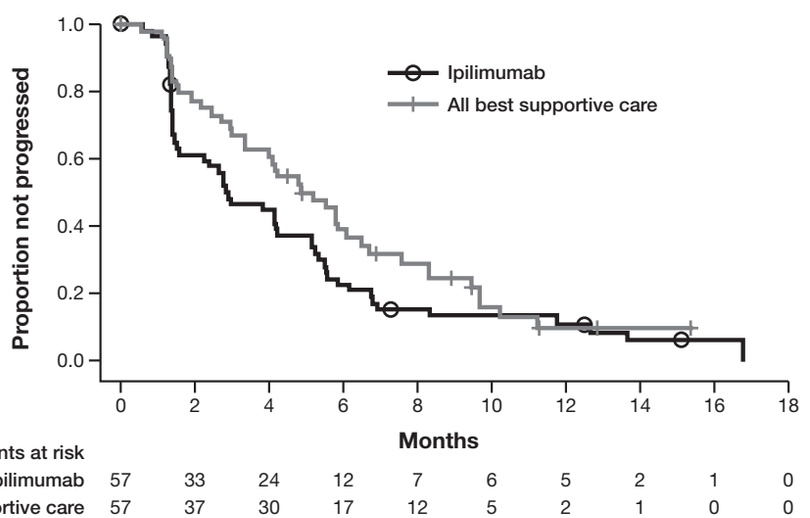
The median number of doses received by patients in the ipilimumab arm was four (range, 1–10; Supplementary Table S2). Fifty-eight percent of patients treated with ipilimumab received four or more ipilimumab doses, and the median time on study treatment was 9 weeks. Most patients in the BSC arm received active treatment (45/57; 79%), which included capecitabine ($n = 26$), 5-fluorouracil ($n = 15$), and S-1 ($n = 4$); the median time on study treatment for patients receiving active treatment was 12 weeks. At the time of the final analysis, 3 patients (5.3%) in the ipilimumab arm and 4 patients (7.8%) in the BSC arm were still on treatment; by study closeout, all of these patients had discontinued (Fig. 1). The primary reason for discontinuation in both study arms was disease progression. Nine patients (15.8%) in the ipilimumab arm discontinued due to study drug toxicity. Among those receiving active BSC, 4 patients (7.8%) discontinued due to study drug toxicity. One death (aspiration pneumonia, which resulted from accidental choking) was reported as a reason for discontinuation in the ipilimumab and was determined to be unrelated to study treatment. Forty-one (72%) patients in the ipilimumab arm and 36 (63%) patients in the BSC arm went on to receive subsequent therapy (Supplementary Table S3).

Clinical outcomes

The median irPFS was 2.92 months (95% CI, 1.61–5.16) in the ipilimumab arm and 4.90 months (95% CI, 3.45–6.54) in the BSC arm (Fig. 2). The study did not demonstrate irPFS improvement with ipilimumab versus BSC (HR, 1.44; 80% CI, 1.09–1.91; $P = 0.097$). The irPFS rates in the ipilimumab 10 mg/kg and BSC arms were 22.3% versus 38.5% at 6 months and 10.6% versus 9.3% at 12 months, respectively. PFS findings (per mWHO criteria) were consistent with irPFS: improvement with ipilimumab versus BSC (HR, 1.59; 80% CI, 1.20–2.10; $P = 0.034$) was not observed (Supplementary Fig. S1). Median PFS in the ipilimumab and BSC arms was 2.72 months and 4.90 months, respectively. The PFS rates (per mWHO) in the ipilimumab and BSC arms were 18.3% versus 38.5% at 6 months and 8.4% versus 16.1% at 12 months, respectively. For both irPFS and PFS in the initial 6 weeks, progression was more frequent in the ipilimumab arm relative to the BSC arm; however, after 6 weeks, the rate of progression appeared similar in the two study arms (Fig. 2 and Supplementary Fig. S1).

At study closeout, which occurred 8 months after the interim analysis, there were 36 deaths in the ipilimumab arm and 30 deaths in the BSC arm; the median OS durations were 12.7 months (95% CI, 10.5–18.9) and 12.1 months (95% CI, 9.3–not estimable), respectively (Fig. 3). Subgroup analyses of OS by the baseline demographics and disease characteristics are shown in Supplementary Fig. S2.

The irBORR was 1.8% ($n = 1/57$) in the ipilimumab arm and 7.0% ($n = 4/57$) in the BSC arm (Table 2). SD was the best overall response for 31.6% ($n = 18/57$) and 40.4% ($n = 23/57$) of patients in the ipilimumab and BSC arms, respectively. The median duration of response was not estimable for either study arm.



Group	No. of events/no. of patients	Median (95% CI)
Ipilimumab	51/57	2.92 (1.61–5.16)
All best supportive care	40/57	4.90 (3.45–6.54)

Figure 2.
Immune-related progression-free survival. CI, confidence interval.

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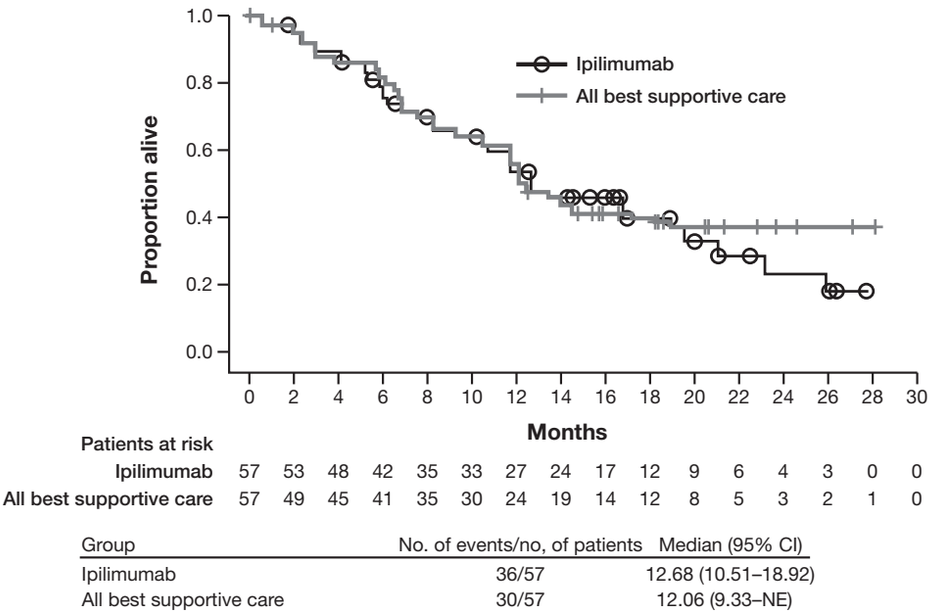

Group	No. of events/no, of patients	Median (95% CI)
Ipilimumab	36/57	12.68 (10.51–18.92)
All best supportive care	30/57	12.06 (9.33–NE)

Figure 3.
Overall survival. CI, confidence interval; NE, not estimable.

Safety

A total of 41 patients (71.9%) who received ipilimumab had at least one treatment-related adverse event (TRAE) and 13 (22.8%) of these patients experienced at least one grade 3/4 TRAE (Table 3). The most frequent TRAEs of any grade (reported in at least 10% of patients) in the ipilimumab arm were pruritus (31.6%), diarrhea (24.6%), fatigue (22.8%), and rash (17.5%). The most frequent grade 3/4 TRAEs (reported in at least 5% patients) in the ipilimumab arm were fatigue (8.8%) and rash (5.3%). Among patients who received active BSC therapy, the most frequent TRAEs of any grade were asthenia (17.8%) and palmar-plantar erythrodysesthesia (15.6%); the latter was the most common grade 3/4 TRAE (4.4%). The most common treatment-related serious adverse events (SAE) reported for patients in the ipilimumab treatment arm were diarrhea (12.3%) and colitis (5.3%). No treatment-related SAEs were reported for patients receiving BSC. On-study TRAEs resulting in discontinuation of study drug were reported in 10 patients (17.5%) receiving ipilimumab and in 4 (8.9%) receiving active BSC; ipilimumab-related adverse events leading to discontinuation of study drug were gastrointestinal disorders ($n = 6$), asthenia ($n = 2$), fatigue ($n = 1$), and acute hepatitis ($n = 1$). In both the ipilimumab and BSC arms, there were no deaths considered related to study therapy.

Discussion

This report represents the first investigation of ipilimumab 10 mg/kg in patients with gastric or GEJ cancer and the first randomized clinical trial of an immune checkpoint inhibitor in this patient population. More than half (57.9%) of ipilimumab-treated patients received at least four ipilimumab induction doses, and nearly one-fifth (19.3%) of the patients received ipilimumab maintenance dosing. Exposure to ipilimumab in this study was similar to that observed in other studies evaluating the 10 mg/kg dose of ipilimumab. TRAEs in the ipilimumab arm were reported at a rate consistent with those reported for other ipilimumab-treated patient populations, and no new safety signals were identified. This important observation supports the continuing investigation of ipilimumab in

Table 2. Clinical activity among patients in the ipilimumab and BSC treatment arms

	Ipilimumab 10 mg/kg ($n = 57$)	**BSC ($n = 57$)**
Best overall response,[a] *n* (%)		
CR	0 (0.0)	0 (0.0)
PR	1 (1.8)	4 (7.0)
SD	18 (31.6)	23 (40.4)
PD	23 (40.4)	11 (19.3)
Unknown	15 (26.3)	19 (33.3)
Overall response rate, *n*/*N* (%; 95% CI)	1/57 (1.8; 0.91–1.00)	4/57 (7.0; 0.83–0.98)
Time to progression, months		
Number of events/number of patients, *n*/*N* (%)	37/57 (64.9)	25/57 (43.9)
Median	2.86 (1.41–4.24)	5.19 (4.07–9.69)
Duration of response, mo		
Number of responders, *n* (%)	1 (1.8)	4 (7.0)
Median (95% CI)	NE (NE–NE)	NE (8.3–NE)

Abbreviations: CI, confidence interval; NE, not estimable.

[a]Determined by independent review committee.

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Table 3. Treatment-related adverse events

	Ipilimumab ($n = 57$)		Active BSC ($n = 45$)	
Event	**Any, *n* (%)**	**Grade 3/4, *n* (%)**	**Any, *n* (%)**	**Grade 3/4, *n* (%)**
Any TRAE	41 (71.9)	13 (22.8)	25 (55.6)	4 (8.9)
TRAEs reported in ≥10% of patients				
Pruritus	18 (31.6)	0 (0.0)	1 (2.2)	0 (0.0)
Diarrhea	14 (24.6)	5 (8.8)	3 (6.7)	0 (0.0)
Fatigue	13 (22.8)	3 (5.3)	3 (6.7)	0 (0.0)
Rash	10 (17.5)	0 (0.0)	2 (4.4)	0 (0.0)
Nausea	7 (12.3)	0 (0.0)	8 (17.8)	0 (0.0)
Asthenia	6 (10.5)	2 (3.5)	1 (2.2)	1 (2.2)
Hypothyroidism	6 (10.5)	2 (3.5)	0 (0.0)	0 (0.0)
Vomiting	6 (10.5)	0 (0.0)	1 (2.2)	0 (0.0)
Palmar-plantar erythrodysesthesia syndrome	3 (5.3)	0 (0.0)	7 (15.6)	2 (4.4)
Any treatment-related SAE	17 (29.8)	13 (22.8)	0 (0.0)	0 (0.0)
Diarrhea	7 (12.3)	5 (8.8)	0 (0.0)	0 (0.0)
Colitis	3 (5.3)	3 (5.3)	0 (0.0)	0 (0.0)
Fatigue	2 (3.5)	2 (3.5)	0 (0.0)	0 (0.0)
Hypothyroidism	2 (3.5)	2 (3.5)	0 (0.0)	0 (0.0)
Acute hepatitis	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
Asthenia	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
Decreased appetite	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
Dehydration	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
Endocrine disorder	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Hypopituitarism	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
Myalgia	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Performance status decreased	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)

gastric cancer in combination with other immunotherapies, given that the known safety profile of ipilimumab includes gastrointestinal adverse events (23). The observed rate of grade 3/4 diarrhea (<10%) was considered acceptable for a 10 mg/kg dose of ipilimumab. No episodes of gastrointestinal perforations or hepatotoxicity were reported.

Ipilimumab did not improve irPFS or PFS defined by mWHO criteria compared with BSC. In the ipilimumab arm, the rate of progression was higher in the first 6 weeks relative to the BSC arm, but then converged thereafter such that the rates of progression were similar in both arms. One possible explanation for this observation is that the first-line active chemotherapy was controlling the disease in some patients (in both arms) at study entry, and removal of the active chemotherapy (in the ipilimumab arm) may have enabled disease progression to recommence. Importantly, immunotherapies such as ipilimumab are known to have a delayed onset of effect (24, 25). Based on PFS/irPFS results, there is limited clinical activity of single-agent ipilimumab as sequential or maintenance therapy for this aggressive disease, and combination therapies with either multiple checkpoint inhibitors or standard-of-care therapies may be needed. Combination therapy using multiple checkpoint inhibitors is showing promising results in other patient populations.

Information on long-term survival among patients is limited. Nevertheless, some patients who received active treatment were followed for as long as 2 years; this included 3 patients treated with ipilimumab who were alive at 2 years. This suggests that ipilimumab may show activity and affect long-term survival in a subset of patients.

Although preliminary biomarker analyses such as serum soluble factors, blood candidate gene expression, peripheral blood mononuclear cell T-cell subsets, and Tregs were performed, limited tumor tissue was available for analyses because collection was not required at study initiation. The results of our analyses were consistent with previous observations that ipilimumab treatment increased levels of circulating activated $CD4^+$ T cells. Changes in other blood-based biomarkers were modest, and no robust association was observed between biomarkers and treatment.

Although the study did not achieve its primary endpoint, the safety profile of ipilimumab in this patient population established a foundation for potential future use in combination therapy. Given that the median OS in both treatment arms was approximately 1 year and the safety profile of ipilimumab was consistent with that seen in other patient populations, combination therapy (ipilimumab plus a second immunotherapy or ipilimumab plus chemotherapy) may be a viable approach to treating patients with advanced/metastatic gastric or GEJ cancer. In subgroup analyses of OS according to the baseline demographics and disease characteristics (Supplementary Fig. S2), it is important to note that outcomes by race and region were similar. Ipilimumab is currently being investigated in combination with nivolumab in a phase I/II trial of patients with advanced gastroesophageal cancer refractory to ≥1 prior chemotherapies for the treatment of metastatic or locally advanced disease (26). Preliminary results of this ongoing trial reported an ORR of 26% (12 of 46 patients) with the combination of nivolumab 1 mg/kg and ipilimumab 3 mg/kg. At this interim analysis, a median OS of 6.9 months and a 12-month OS rate of 34% were observed. The safety profile was consistent with those previously reported. These results suggest that nivolumab and ipilimumab might act in a synergistic manner and further support the clinical development of checkpoint inhibitors in the treatment of gastric cancer.

Disclosure of Potential Conflicts of Interest

Y.-J. Bang is a consultant/advisory board member for Bristol-Myers Squibb. Y.H. Kim reports receiving commercial research grants from

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y.-J. Bang, Y.H. Kim, J.W. Kim, M. Di Bartolomeo, J.A. Ajani, K. Yamaguchi, M. Moehler
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