Efficacy and safety of anti-PD-1 monotherapy and combination therapy in Chinese advanced Gastric cancer: a real-world study

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Abstract

Purpose: Anti-PD-1 inhibitor, pembrolizumab, has been approved for the treatment of locally advanced or metastatic gastric or gastroesophageal junction cancer (GC/GEJC) patients. Our study aimed to evaluate the efficacy and safety profile of anti-PD-1-based treatment in Chinese advanced or metastatic GC/GEJCs and population with poor clinical conditions in a real-world setting.

Methods: A retrospective cohort study was conducted and 54 patients were identified and included in our analysis, including 19 patients treated with anti-PD-1 monotherapy and 35 patients treated with anti-PD-1 combination therapy. Demographic and clinical information were evaluated. Clinical response, survival outcomes and safety profile were measured and analyzed.

Results: In overall cohort, median overall survival (OS) was 11.10 months (95%CI, 7.05-15.15) and median progression-free survival (PFS) was 3.93 months (95%CI, 2.47-5.39). 16.7% patients reached clinical response and 72.2% patients got disease control. Prolonged OS and PFS and increased clinical response were observed in combination group compared with monotherapy group, although statistical significance was not reached. In subgroups with live metastases or elevated baseline NLR level, combination therapy outperformed anti-PD-1 alone in survival outcomes. 50% and 16.7% of the overall cohort experienced treatment-related adverse events (TRAEs) of any grade and grade 3-5.

Conclusions: Anti-PD-1-based monotherapy and combination therapy showed favorable survival outcomes and manageable safety profile in advanced or metastatic GC/GEJCs. Specific population might benefit from combination therapy. Further study with larger sample size is needed.

Introduction

Gastric cancer (GC) is one of the most frequently diagnosed cancers and leading causes of cancer deaths worldwide¹. It is more prevalent in Eastern Asia and in China, the estimated incidence and mortality of GC in 2015 were 679,100 and 498,000, respectively, ranking the second most common cancer^{2,3}. Most patients are diagnosed at advanced-stage with a 5-year survival of 29%⁴. Currently, the first-line treatment for advanced GC patients are primarily platinum plus fluoropyrimidine or in combination with trastuzumab for HER2-overexpressing tumors^{5,6}. Preferred treatment modalities for second-line or beyond include ramucirumab plus paclitaxel or monotherapy of docetaxel, paclitaxel, irinotecan, or ramucirumab⁵.

Recently, immunotherapy has provided a revolutionizing treatment strategy for advanced cancers. Immune checkpoint blockades (ICBs) including antibodies to Programmed Death Receptor 1 (PD-1) or its ligand (PD-L1) are now standard therapies for a range of solid tumors as approved by the Food and Drug Administration (FDA)⁷. Several clinical trials have shown that some GC patients could benefit from anti-PD-1/PD-L1 antibody therapy, indicating that ICBs are a potential treatment option for GC. For ICBs monotherapy in third-line, pembrolizumab (a humanized anti-PD-1 IgG4 monoclonal antibody) was

approved by FDA for the treatment of locally advanced or metastatic gastric or gastroesophageal junction cancer (GC/GEJC) patients with PD-L1 positive tumors (Combined Positive Score (CPS) ≥ 1) based on the data of KEYNOTE-059, a single-arm study⁸. In ATTRACTION-2, a phase III clinical trial comparing nivolumab with placebo in Asian patients who were heavily pretreated, nivolumab (a human anti-PD-1 IgG4 monoclonal antibody) led to improved overall survival (OS) and progression-free survival (PFS) and were in general well tolerated⁹. However, in another phase III clinical trial conducted on a global scale (JAVELIN Gastric 300), avelumab (a human anti-PD-L1 IgG1 monoclonal antibody) did not improve OS or PFS compared with chemotherapy in the total population (including 25.4% Asian patients) as third-line treatment¹⁰. For first or second-line treatment, only three single-arm studies showed 7–22% of objective response rate (ORR) from ICBs monotherapy^{11–13} and two phase III trials reported no significant clinical benefit from pembrolizumab monotherapy compared with chemotherapy^{14,15}. In view of the modest benefit from ICBs monotherapy, co-administration with another therapeutic agent provides a potential solution to enhance treatment efficacy. However, in KEYNOTE 062, the only phase III study investigating pembrolizumab plus chemotherapy as first-line treatment of advanced GC/GEJCs, the arm given pembrolizumab plus chemotherapy did not exhibit significantly prolonged OS than those taking chemotherapy alone¹⁵. Several phase I-II studies preliminarily showed that ICBs combined with chemotherapy, targeted, or antiangiogenic agents presented improved ORR^{16–18}. The majority of aforementioned studies were conducted on Caucasian patients, while little is known about how Asian GC/GEJCs patients, either treatment-naïve or previously treated, would respond to ICBs therapy. This represents an unmet medical need particularly when Asians are known to be heavily burdened with GC/GEJCs. Moreover, the populations included in the clinical trials described above are usually highly selected. It remains inconclusive whether patients with an Eastern Cooperative Oncology Group (ECOG) performance score > 1 , patients with brain metastases, or patients over 70 years old, could benefit from ICBs treatment, since they are usually excluded from interventional clinical trials.

In order to explore whether ICBs could bring clinical benefit to Asian GC patients, we conducted a real-world study to examine the safety and anti-tumor activities of anti-PD-1 monotherapy and combination therapy in advanced GC patients in China.

Methods

Patients

We conducted a retrospective analysis to evaluate the efficacy and safety profile of anti-PD-1 treatment in a real-world setting. Consecutive GC/GEJCs patients treated at the Center of Oncology, Chinese PLA General Hospital from May 2015 to May 2021 were reviewed and screened. Inclusion criteria were as follows: 1) pathologically confirmed GC/GEJCs; 2) advanced or metastatic disease, or recurrence after curative surgery; 3) administration of nivolumab or pembrolizumab as monotherapy or combination therapy. The ethics committee of the People's Liberation Army General Hospital approved this study

according to the ethical standards of the Declaration of Helsinki and its subsequent amendments (Ethical approval number: S2020-284-01).

Clinicopathological characteristics were reviewed and collected. Two physicians independently extracted and recorded demographic and clinical information, followed by confirmation by a third physician in case of inconsistency. Data were collected from the following sources: 1) Chinese PLA General Hospital inpatient and outpatient records, including doctors' notes, radiographic reports and biopsy results; 2) patient or family interview. Complete blood cell counts of eligible patients, covering neutrophils, lymphocytes, thrombocytes and erythrocytes, were also collected. NLR was defined as absolute neutrophil count divided by absolute lymphocyte count in peripheral blood collected before the initiation of anti-PD-1 treatment. PLR was defined as absolute thrombocyte count divided by absolute lymphocytes count. Median NLR and PLR were adopted as cutoff in our analysis.

Outcome and assessments

The primary endpoint was overall survival (OS), defined as the time from the first dose of anti-PD-1 to death from any cause. Secondary endpoints included progression-free survival (PFS), defined as the time from treatment initiation to the first documented disease progression, objective response rate (ORR), defined as the proportion of patients with confirmed complete response or partial response, disease control rate (DCR), defined as the proportion of patients with confirmed complete response, partial response or stable disease, duration of response (DOR) and the maximum percentage change from baseline in the sum of diameters of target lesions. All endpoints were evaluated according to RECIST version 1.1 guidelines¹⁹. Follow-up imaging reports were reviewed by two radiologists independently. Any discrepancy was further verified by the director of the imaging center. Data for patients without disease progression or death events were censored at the time of last follow-up. Adverse events (AE) were evaluated and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0)²⁰. Treatment-related adverse events (TRAEs) and immune-related AEs were graded and recorded respectively. All patients were followed up until May 2021 or death.

Statistical analysis

Categorical characteristics and objective response were compared between treatment groups with chi-square test or Fisher's exact test. Continuous variables were compared using the Mann Whitney U test. OS and PFS were evaluated with Kaplan-Meier survival analysis and compared between groups with Log-rank test. Hazard Ratio was estimated by means of Cox proportional hazard model. Variables with P value < 0.10 in the univariate Cox regression or acting as clinically relevant factors were adjusted in the multivariate Cox regression model. All P values are two-tailed and P value < 0.05 was considered statistically significant. The SPSS statistical package (SPSS 20, SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

Patients' characteristics and treatment

Fifty-four patients who received anti-PD-1 based therapy during their course of disease were identified and included in our analysis, including 19 patients treated with anti-PD-1 monotherapy and 35 patients treated with anti-PD-1 combined with chemotherapy, targeted therapy or anti-CTLA-4. Patients' clinicopathological characteristics were summarized in Table 1. The median age of the recruited patients was 58 years old in the monotherapy group and 59 years old in the combination therapy group, where 2 (10.5%) and 9 (25.7%) patients received immunotherapy at the age of over 65 in the two groups respectively. Eleven patients (57.9%) and 7 patients (20.0%) in two groups had an ECOG performance score of 2-4. Less patients in the monotherapy group received anti-PD-1 as first-line treatment than in the combination group (5.3% vs 37.1%, $P=0.01$), while more patients in the monotherapy groups were treated with anti-PD-1 as 4th line or later therapy (36.8% vs 11.4%, $P=0.04$).

Treatment outcome

As of data cut-off on May 31, 2021, the median follow-up was 8.4 months, ranging from 0.8 to 43.8 months. 44 (81.5%) progression events and 37 (68.5%) deaths occurred during the follow-up period. In the overall cohort, the median OS was 11.10 months (95%CI, 7.05-15.15) and the median PFS was 3.93 months (95%CI, 2.47-5.39). Prolonged median OS was observed in the patients receiving combination therapy (11.10 months; 95%CI, 7.18-15.03) over those taking anti-PD-1 alone (5.40 months; 95%CI, 2.64-8.17). However, the difference in OS between the two groups was not statistically significant potentially due to the small sample size (HR 0.70, 95%CI 0.36-1.35, $P=0.29$) (Figure 1). Likewise, the median PFS of the combination group 4.07 months (95%CI, 1.83-6.03) was non-significantly longer than that of the monotherapy group 2.93 months (95%CI, 0.85-5.01) (HR 0.69, 95%CI 0.37-1.26, $P=0.22$) (Figure 2).

In the overall population, for patients who took anti-PD-1-based therapy as first or second-line treatment, the median OS and PFS were 11.10 months (95%CI 6.36-15.85) and 3.43 months (95%CI 2.20-4.66). In patients treated with anti-PD-1 based-therapy in third line or beyond, the median OS and PFS were 9.13 months (95%CI 2.22-16.04) and 4.20 months (95%CI 1.60-6.80). There was no statistical difference between the monotherapy and the combination groups with regard to OS or PFS upon stratification by treatment lines (Supplementary Figure 1-4). Duration of treatment and outcomes for each patient were specified in Figure 3.

Response rates of the overall population, the monotherapy group and the combination arm were summarized in Table 2. ORR and DCR were 16.7% (95%CI 6.4-26.9%) and 72.2% (95%CI 59.9-84.6%) in the overall cohort. ORR tended to be higher in the combination group (20.0%, 95%CI 8.4-36.9%) than in the monotherapy group (10.5%, 95%CI 1.9-29.6%), but the difference was not statistically significant ($P=0.47$) with limited sample size. DCR were 63.2% and 77.1% in the monotherapy and the combination group ($P=0.35$). With respect to the best overall responses, 36.8% (7/19) of the patients given monotherapy and 40.0% (14/35) of the patients on combination treatment achieved a decrease from baseline in the sum of their target lesions (Figure 4).

We also did subgroup analysis to compare the survival outcomes of monotherapy and combination therapy according to different stratifications (Table 3). In patients with liver metastases or elevated NLR levels (NLR above the median), anti-PD-1 administered in conjunction with other medications led to a more favorable median OS compared to those on monotherapy (HR in the subgroup with liver metastases 0.33, 95% CI 0.11-1.00, P=0.05; HR in the subgroup with elevated NLR 0.38, 95%CI 0.14-1.00).

In combination group, 5 patients accepted anti-PD-1 combined with apatinib, a small molecular anti-angiogenic agent. All 5 patients got durable stable disease, ranging from 4.20 to 9.37 months, although no objective response was observed.

Association between clinicopathological characteristics and survival outcomes

In univariate analyses with Cox regression model, ECOG 0-1 was associated with better OS outcome (HR 0.28, 95%CI 0.11-0.56) (Supplementary Table 1). While patients with ascites, elevated NLR or elevated PLR were at higher risk of death (HR for ascites 3.27, 95%CI 1.61-6.65, P=0.001; HR for elevated NLR 2.19, 95%CI 1.18-4.05, P=0.01; HR for elevated PLR 2.49, 95%CI 1.33-4.65, P=0.004). In light of the results from univariate analyses, we selected ECOG performance score, ascites, NLR and PLR for multivariate analyses. ECOG performance score and ascites were independent risk factors associated with OS outcome in patients treated with anti-PD-1-based therapy. NLR and PLR didn't reach statistical significance in multivariate analysis.

Treatment-related adverse events (TRAEs) of any grade occurred in 27 patients (50%) in the overall cohort (Table 4). All-grade TRAEs observed in 5% or more of patients of the overall cohort included decreased neutrophil count, nausea, vomiting, increased alanine aminotransferase and increased alkaline phosphatase levels. Patients treated with anti-PD-1 monotherapy (n=5, 26.3%) had less TRAEs than those in the combination group (n=22, 62.9%). There were also less patients with TRAEs of grade 3 to 5 with monotherapy (n=2, 10.5%) than with combination therapy (n= 7, 20.0%). Grade 3 to 5 events were reported in 9 patients (16.7%), including mucositis oral (n=1, 5.3%) and obstruction gastric (n=1, 5.3%) in anti-PD-1 monotherapy group, and decreased neutrophil count (n=4, 11.4%), gastric perforation (n=1, 2.9%), lung infection (n=1, 2.9%) and pneumonitis (n=1, 2.9%) in combination group. Only one death was attributed to treatment in the combination group (one patient with gastric perforation). No death related to study treatment occurred in the monotherapy group. Pneumonitis was the only potentially immune-related adverse event reported in our cohort, which was observed in 3 patients (1 with monotherapy and 2 with combination therapy).

Discussion

To our knowledge, this is the one of the first real-world studies that evaluated the performance of anti-PD-1-based treatment regimen in Chinese GC/GEJC population. Anti-PD-1 monotherapy and combination therapy showed favorable survival outcomes and manageable safety profiles in advanced or metastatic GC/GEJCs. The median OSs were 11.10 months (95%CI, 7.05-15.15), 5.40 months (95%CI, 2.64-8.17) and 11.1 months (95%CI, 7.17-15.03) in overall population, the monotherapy group and the combination

group, respectively, while the median PFSs were 3.93 months (95%CI, 2.47-5.39), 2.93 months (95%CI, 0.85-5.01) and 4.07 months (95%CI, 1.83-6.03). Prolonged OS and PFS were observed in the combination group compared with the monotherapy group, although statistical significance was not reached. Objective response was achieved in 16.7%, 10.5% and 20.0% patients in the overall population, monotherapy and combination group. In the overall cohort, 72.2% of the patients achieved tumor regression or disease control (95%CI 59.9-84.6%). In patients treated with anti-PD-1/L1 monotherapy as third-line treatment, the median OS and PFS were reported to be 4.6-5.6 months and 1.4-2.0 months⁸⁻¹⁰. Among the patients treated as third-line and beyond treatment in our cohort, the median OS was 6.3 months (95%CI 0-18.43) and the median PFS was 4.13 months (95%CI 0.86-7.40). In a phase II clinical trial, anti-PD-1 as first-line treatment showed a median OS of 13.8 months (95% CI 8.6-not evaluable) in the monotherapy cohort and 20.7 months (95% CI 9.2-20.7) in the combination cohort²¹. Fourteen patients in our cohort received anti-PD-1 based regimen as first-line treatment with a median OS of 11.10 months (95%CI not evaluable). Among these 14 patients, 4 (28.6%) had an ECOG performance score > 1. That might explain the relatively inferior survival outcome compared with previous report. In a phase Ib/II clinical trial, 18 Chinese metastatic GC patients received anti-PD-1 plus chemotherapy as first-line treatment and 58 patients received anti-PD-1 monotherapy as second-line treatment. In the former cohort, median OS was not reached and the median PFS was 5.8 months, while in the latter cohort the median OS was 4.8 months and the median PFS was 1.9 months²². In our cohort, 13 patients received anti-PD-1-based combination therapy as first-line treatment with median OS not reached and median PFS of 5.2 months. 18 patients who progressed after at least one systematic chemotherapy were treated with anti-PD-1 monotherapy whose median OS of 6.3 months (95%CI 0-15.54) and median PFS of 2.87 (95%CI 0-5.91). Overall, our study showed results comparable to previously published interventional studies.

In a recent phase 1a/b clinical trial, 41 GC/GEJC patients whose disease progressed after one or two lines of systemic therapy were treated with pembrolizumab plus ramucirumab (an IgG1 VEGFR-2 monoclonal antibody). Twenty-one (51%) patients achieved disease control, including 3 (7%) partial response and 18 (44%) stable disease²³. In our cohort, five patients were given anti-PD-1 (3 with pembrolizumab and 2 with nivolumab) combined with apatinib, an antiangiogenic agent, and all the 5 patients obtained clinical benefit with durable disease control. De-novo or acquired resistance to immune checkpoint inhibitors is complex and could be attributed to a number of factors such as immunosuppressive tumor microenvironment, paucity of PD-L1 expression and T-cell exclusion²⁴⁻²⁶. Anti-angiogenesis therapy could prevent immunotherapy resistance by increasing T cell trafficking, migration cross vascular endothelium and infiltrating into tumor tissue²⁷. Further studies with larger sample sizes are needed to verify the synergistic effects of anti-angiogenesis therapy with ICBs.

Patients recruited into randomized clinical trials are usually highly selected. Inclusion criteria typically include an ECOG performance score of < 2 and no symptomatic brain metastases or other unfavorable physical conditions^{28,29}. Randomized clinical trials provide an optimal way to evaluate the efficacy and safety of a specific treatment, however such studies are intrinsically less amenable to extrapolation. An ECOG performance score of >1 was previously reported as an independent risk factor for unfavorable

survival upon treatment with immune checkpoint inhibitors in real-world studies^{30,31}. In our cohort, there were 18 patients with a baseline ECOG performance score of 2-4, only 5.6% (95% CI 0-17.3%) of which obtained clinical response. In contrast, for patients with a baseline ECOG 0-1, the ORR was 22.2% (95% CI 8.0-36.5%) and the median PFS was 5.20 months (95%CI 2.03-8.37). Patients with ECOG 2-4 also had worse overall survival compared with patients with ECOG 0-1 (median OS 4.80 months versus 13.23 months; HR 3.54, 95%CI 1.80-6.97). Consistent with previous studies, ECOG performance score was validated to be an independent risk factor of OS (Table 4). Patients with brain metastases are usually excluded from randomized studies^{9,23}. In our cohort, 4 patients had brain metastases at the onset of anti-PD-1 therapy, their median PFS was 1.30 months (95%CI 1.05-1.56) and median OS was 8.37 months (95%CI 0.98-15.75). In addition to the special subpopulations mentioned above, there were 9 patients in our study aged ≥ 70 , among whom 10% responded to the treatment and their median PFS and OS were 3.07 months (95%CI 2.66-3.48) and 5.17 months (95%CI 4.58-5.75). Collectively, in populations which usually don't meet inclusion criteria of randomized studies, anti-PD-1-based therapy also showed favorable survival outcomes.

Various responses to checkpoint inhibitors by different tumors types mainly arise from the diversity of tumor immune microenvironment^{32,33}. One of the well investigated and commonly used biomarkers for systemic inflammatory response is circulating white blood cell, including neutrophils and lymphocytes^{34,35}. Recent studies investigated the predictive value of NLR (neutrophil-to-lymphocyte ratio) and PLR (platelet-to-lymphocyte ratio) for the treatment of checkpoint inhibitors. Low baseline NLR levels were associated with prolonged PFS and OS in metastatic melanomas following treatment with ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4)³⁶. In non-small cell lung cancers treated with anti-PD-1 inhibitors, low NLR and PLR levels were also reported to be associated with better PFS, OS and response rate^{37,38}. In our cohort, elevated NLR and PLR were predictive markers for OS in univariate analyses, but not in multivariate analyses when taking clinical factors into consideration. This could have been explained in part by the small sample size which might limit the statistical power.

In our cohort, in patients with liver metastases and elevated baseline NLR levels, combination therapy presented better survival outcomes compared with anti-PD-1 monotherapy. Following adjustment according to clinical characteristics, the differences in PFS and OS between the treatment groups were no longer significant. In a recent update on the phase 3 study KEYNOTE 062, pembrolizumab combined with chemotherapy in gastric cancers as first-line therapy didn't improve PFS or OS compared with pembrolizumab alone¹⁵. In non-small cell lung cancer patients, anti-PD-1/L1 combined with chemotherapy showed better survival benefit than anti-PD-1/L1 alone^{39,40}. Tumor PD-L1 expression and tumor immune microenvironment were previously reported to be affected by cytotoxic agents, which could explain the synergistic effects of the combination of anti-PD-1/L1 inhibitors and chemotherapy^{41,42}. However, in gastric cancer population, the synergistic effects of combination therapy were relatively modest. Significant spatial heterogeneity of genomic alterations and tumor immune

microenvironment in gastric cancer might account for inconsistent results and should be taken into consideration in future clinical trial designs^{43,44}.

There are several limitations of our study. Firstly, the sample size was limited. However, to our knowledge, this is one of the first real world study to explore the effectiveness and safety of anti-PD-1/L1 inhibitors monotherapy and combination therapy as first-line or second-line treatment in GC especially in Asian patients. Second, this is a retrospective cohort study and could have been potentially biased, however, a retrospective real-world cohort allows us to investigate whether patients with higher ECOG scores or more advanced GC could benefit from immunotherapies which is usually not feasible with prospective trials. Moreover, patients were recruited consecutively with an effort to minimize bias and comprehensive clinicopathological information was collected to enable adjustment in multivariate regression analyses. Third, the combination regimens were heterogeneous and a specific combination regimen should be considered when designing prospective studies in the future.

Anti-PD-1 monotherapy and combination therapy showed promising survival outcome and manageable safety profile in advanced or metastatic GC/GEJCs in a real-world setting. Prolonged OS and PFS and increased ORR were observed in the combination group compared with the monotherapy group, although statistical significance was not reached. In some subgroups, such as patients with live metastases or elevated baseline NLR levels, combination therapy outperformed anti-PD-1 alone in terms of survival outcomes. Treatment regimens involving anti-PD-1 in GC warrant further prospective investigations with larger sample sizes.

Declarations

Ethics approval and consent to participate

All participants in this study signed informed consent forms. The ethics committee of the People's Liberation Army General Hospital approved this study according to the ethical standards of the Declaration of Helsinki and its subsequent amendments (Ethical approval number: S2020-284-01).

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article (and its supplementary information files).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Tao Li, Tingting Liu, Lei Zhao, served as co-first authors, with primary contribution to the manuscript. Tao Li, Tingting Liu, Lei Zhao, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

All authors contributed to study concept and design.

All authors contributed to acquisition, analysis, and interpretation of data.

All authors took responsibilities on manuscript drafting and revising.

Critical revision of the manuscript for important intellectual content: Yi Hu.

Statistical analysis: Tao Li, Lu Liu.

Study supervision: Yi Hu, Fan Zhang.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors read and approved the final manuscript.

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Tables

Table 1. Baseline demographic and clinical characteristics of GC/GEJC patients

	Monotherapy	Combination therapy	
	(n=19)	(n=35)	P value
Gender			1.00
Male	11(57.9%)	21(60.0%)	
Female	8(42.1%)	14(40.4%)	
Age			0.29
Median (range), years	58(34-81)	59(24-86)	
<65	17(89.5%)	26(74.3%)	
≥65	2(10.5%)	9(25.7%)	
ECOG performance status			0.01
0	2(10.5%)	21(60.9%)	
1	6(31.6%)	7(20.0%)	
2	6(31.6%)	5(14.3%)	
3	4(21.1%)	2(5.7%)	
4	1(5.3%)	0	
TNM stage			0.61
III	2(10.5%)	2(5.71%)	
IV	17(89.5%)	33(94.3%)	
Tumor site			0.54
Gastric	19(100%)	32(91.4%)	
Gastro-oesophageal junction	0	3(8.6%)	
Organs with metastases			0.25
≤2	7(36.8%)	20(57.1%)	
>2	12(63.2%)	15(42.9%)	
Site of metastases			
Lymph node	18(94.7%)	29(82.9%)	1.00
Peritoneum	13(68.4%)	18(52.9%)	0.26
Liver	5(26.3%)	22(64.7%)	0.02
Bone	4(21.1%)	8(23.5%)	1.00

Lung	3(15.8%)	4(11.4%)	0.68
Adrenal	1(5.3%)	3(8.8%)	1.00
Previous anticancer therapies for locally advanced/metastatic disease			
0	1(5.3%)	13(37.1%)	0.01
1	7(36.8%)	14(40.0%)	1.00
2	4(21.1%)	4(11.4%)	0.43
≥3	7(36.8%)	4(11.4%)	0.04
Previous gastrectomy			0.01
Yes	15(78.9%)	7(20.0%)	
No	4(21.1%)	28(80.0%)	
Combined use			
Combined with chemotherapy		24(68.6%)	
Combined with target therapy		4(11.4%)	
Combined with chemotherapy and target therapy		5(14.3%)	
Combined with ipilimumab		2(5.7%)	
Data are number of patients (%) unless specified otherwise.			
ECOG, Eastern Cooperative Oncology Group.			

Table 2 Objective tumor response

	Overall population	Monotherapy	Combination therapy
Tumor response data	(n=54)	(n=19)	(n=35)
Complete response	0	0	0
Partial response	9(16.7%)	2(10.5%)	7(20.0%)
Stable disease	30(55.6%)	10(52.6%)	20(57.1%)
Progressive disease	15(27.8%)	7(36.8%)	8(22.9%)
Objective response rate, 95%CI	9(16.7%; 6.4-26.9)	2(10.5%; 1.9-29.6)	7(20.0%; 8.4-36.9)
Disease control	39(72.2%; 59.9-84.6)	12(63.2%; 38.4-83.7)	26(74.3%; 56.7-87.5)

Data are n (%) or n (%; 95% CI).

Table 3. Subgroup analysis of overall survival by monotherapy and combination therapy groups

		Monotherapy (n=19)	Combination therapy (n=35)	Hazard ratio(95%CI)	P value
	No. of patients				
Overall	54			0.70(0.36-1.35)	0.29
Gender					
Male	32	11	21	0.87(0.36-2.11)	0.75
Female	22	8	14	0.53(0.19-1.59)	0.24
Age					
<65	43	17	26	0.57(0.28-1.18)	0.13
≥65	11	2	9	1.40(0.16-12.05)	0.76
ECOG performance status					
0-1	36	8	28	0.80(0.31-2.11)	0.66
2-4	18	11	7	1.60(0.57-4.45)	0.37
Organs with metastases					
≤2	26	19	7	0.61(0.21-1.75)	0.36
>2	27	15	28	0.76(0.29-1.94)	0.56
Lymph node positive	47	18	29	0.79(0.39-1.60)	0.51
Peritoneum metastases					
Yes	31	13	18	1.12(0.42-2.30)	0.81
No	23	6	17	0.46(0.15-1.39)	0.17
Liver metastases					
Yes	27	5	22	0.33(0.11-1.00)	0.05
No	27	14	13	1.36(0.57-	0.48

Ascites					
Yes	25	10	15	1.00(0.40-2.00)	0.99
No	29	9	20	0.61(0.21-1.74)	0.35
Previous anticancer therapies for locally advanced/metastatic disease					
0-1	35	8	27	0.68(0.26-1.78)	0.43
≥2	19	11	8	0.60(0.20-1.79)	0.36
Previous gastrectomy					
Yes	22	15	7	0.59(0.16-2.12)	0.42
No	32	4	28	0.09(0.02-0.35)	0.00
Elevated LDH					
Yes	8	4	4	0.49(0.09-2.68)	0.41
No	46	15	31	0.76(0.36-1.62)	0.48
Elevated NLR					
Yes	26	9	17	0.38(0.14-1.00)	0.05
No	27	9	18	0.80(0.31-2.06)	0.64
Elevated PLR					
Yes	26	10	16	0.42(0.17-1.04)	0.06
No	27	8	19	0.84(0.29-2.44)	0.75
HER2 positive					
Yes	10	5	5	1.97(0.32-12.31)	0.74
No	27	11	16	0.72(0.29-1.79)	0.48

ECOG, Eastern Cooperative Oncology Group.

LDH, lactate dehydrogenase

NLR, neutrophil to lymphocyte ratio

PLR, Platelet to lymphocyte ratio

Table 4. Treatment-related adverse events

	Monotherapy(n=19)		Combination(n=35)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAEs*				
Neutrophil count decreased	0	0	11(31.4%)	4(11.4%)
Nausea	0	0	7(20.0%)	0
Vomiting	0	0	4(11.4%)	0
ALT increased	1(5.3%)	0	4(11.4%)	0
AST increased	1(5.3%)	0	3(8.6%)	0
Alopecia			2(5.7%)	0
Mucositis oral	1(5.3%)	1(5.3%)	0	0
Blood bilirubin increased	1(5.3%)	0	0	0
Anemia	1(5.3%)	0	0	0
Diarrhea	1(5.3%)	0	0	0
Obstruction gastric	1(5.3%)	1(5.3%)		
Gastric perforation	0	0	1(2.9%)	1(2.9%)
Lung infection	0	0	1(2.9%)	1(2.9%)
Additional TRAEs of special interest				
Pneumonitis	1(5.3%)	0	2(5.7%)	1(2.9%)

Data are number of patients (% of total patients). *TRAEs=treatment-related adverse events.
ALT=alanine aminotransferase. AST=alkaline phosphatase.

Figures

Median overall survival
 Monotherapy group 5.4 months
 Combination group 11.1 months
 HR 0.70 (95%CI 0.36-1.35)

Figure 1

Kaplan-Meier plot of overall survival

Median progression-free survival
 Monotherapy group 2.93 months
 Combination group 4.07 months
 HR 0.69 (95%CI 0.37-1.26)

Figure 2

Kaplan-Meier plot of progression-free survival

Figure 3

Duration of follow-up and outcome for each patient in monotherapy group (A) and combination group (B).

Figure 4

Regression of target lesions from baseline in each patient in monotherapy group (A) and combination group (B). PD=progressive disease. PR=partial response. SD=stable disease.

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