THERAPEUTIC ADVANCES in
Medical Oncology

Original Research

Investigating the role of immunotherapy for real-world patients with HER2-negative advanced gastric cancer between 2011 and 2023

Ther Adv Med Oncol

2025, Vol. 17: 1–12

DOI: 10.1177/17588359251322670

Keitaro Shimozaki, Akira Ooki, Koichiro Yoshino, Mikako Tamba, Shohei Udagawa, Hiroki Osumi, Shota Fukuoka, Izuma Nakayama, Takeru Wakatsuki, Mariko Ogura, Daisuke Takahari, Eiji Shinozaki, Keisho Chin and Kensei Yamaguchi

Abstract

Background: Although the emergence of immunotherapy has benefited patients with advanced gastric cancer (AGC), the magnitude of the benefit among real-world patients with HER2-negative AGC remains unclear.

Objectives: The current study aimed to evaluate the treatment features across various immunotherapy approval periods and investigate the utility of immunotherapy for patients with HER2-negative AGC in daily practice.

Design: Retrospective observational study.

Methods: We retrospectively evaluated the clinical outcomes of patients with HER2-negative AGC who received first-line platinum-based chemotherapy between 2011 and 2023 across different periods of immunotherapy approval in Japan: Group A (pre-immunotherapy approval): 2011–2017; Group B (approved for third-line treatment or later): 2018–2021; and Group C (approved for first-line treatment): 2022–2023.

Results: A total of 949 patients were enrolled ($n = 477$, 344, and 128 for Groups A, B, and C, respectively). Patient characteristics were comparable between the three groups, except for the proportion of those aged ⩾75 years ($p = 0.002$), prior gastrectomy ($p = 0.03$), and liver metastases ($p = 0.0005$). The median overall survival (OS) was 16.2, 15.2, and 21.3 months in Groups A, B, and C, respectively, with no significant difference between the groups (log-rank $p = 0.50$). Patients who received first-line immunotherapy plus chemotherapy ($n = 173$) showed significantly better OS than did those who did not receive any immunotherapy-containing treatment from 2011 to 2017 ($n = 382$; hazard ratio (HR), 0.78; 95% confidence interval (CI), 0.61–0.99; $p = 0.04$). Multivariate analysis showed that the use of first-line immunotherapy was not significantly associated with worse OS, whereas the use of any-line immunotherapy was significantly associated with prognosis (HR, 0.54; 95% CI, 0.47–0.63; $p < 0.0001$). The proportion of patients receiving any second-line treatment was comparable between the groups: 76%, 80%, and 71%, respectively.

Conclusion: Our study suggests that immunotherapy has a moderate impact on improving the survival of real-world patients with HER2-negative AGC, highlighting the need for appropriate treatment strategies, including efforts to identify biomarkers and the development of other agents.

Keywords: gastric cancer, gastroesophageal junction cancer, immunotherapy

Received: 18 December 2024; revised manuscript accepted: 4 February 2025.

Correspondence to:
Akira Ooki
Department of Gastroenterological Chemotherapy, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan
akira.oki@jfcr.or.jp

Keitaro Shimozaki
Department of Gastroenterological Chemotherapy, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Keio Cancer Center, Keio University School of Medicine, Tokyo, Japan

Koichiro Yoshino
Mikako Tamba
Shohei Udagawa
Hiroki Osumi
Shota Fukuoka
Takeru Wakatsuki
Mariko Ogura
Eiji Shinozaki
Keisho Chin
Kensei Yamaguchi
Department of Gastroenterological Chemotherapy, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Izuma Nakayama
Department of Gastroenterological Chemotherapy, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Daisuke Takahari
Department of Gastroenterological Chemotherapy, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Division of Medical Oncology, Department of Internal Medicine, Gunma University Graduate School of Medicine, Gunma, Japan

Introduction

Despite the accelerated advances in therapies for advanced gastric cancer (AGC), the overall survival (OS) from this disease still has room for further improvement. After platinum-based chemotherapy had been established as a standard first-line treatment for AGC,[1] the development of therapies for HER2-negative AGC had stagnated for years despite attempts to combine molecular-targeted agents with cytotoxic agents. Various studies have shown that several therapeutics, including vascular endothelial growth factor (VEGF)/VEGF receptor inhibitors (bevacizumab, AVAGAST trial[2]; ramucirumab, RAINFALL trial[3]), anti-epidermal growth factor receptor antibody (cetuximab, EXPAND trial[4]; panitumumab, REAL-3 trial[5]), and MET inhibitor (onartuzumab, METGastric trial[6]; rilotumumab, RILOMET-1 trial[7]), did not promote superior survival over chemotherapy alone in first-line settings.

Following the success of immunotherapy in melanoma and lung cancer, the ATTRACTION-2 trial[8] showed that the anti-programmed cell death 1 (PD-1) antibody nivolumab demonstrated superior survival benefits compared to best supportive care for heavily pretreated AGC, with a median OS of 5.26 and 4.14 months (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.51–0.78). These results led to the approval of nivolumab for third- or later-line treatment of AGC throughout Japan in September 2017. Furthermore, the CheckMate 649 and ATTRACTION-4 trials, which compared nivolumab plus chemotherapy to chemotherapy alone in HER2-negative AGC, confirmed the efficacy of adding anti-PD-1 antibody to first-line chemotherapy.[9,10] Since November 2021, nivolumab plus chemotherapy has been available in Japan as first-line treatment for HER2-negative AGC, regardless of programmed cell death 1 ligand-1 (PD-L1) expression status. The results of KEYNOTE-859[11] also indicated that pembrolizumab plus chemotherapy could be another option for the first-line treatment of HER2-negative AGC. Similarly, the combination of anti-PD-1 antibody and chemotherapy, following the results of RATIONALE-305[12] and ORIENT-16 trials,[13] has now become an established standard of care for first-line treatment of HER2-negative AGC worldwide.

Patients with AGC have apparently benefited considerably from the emergence of immunotherapy; however, the magnitude of the impact of immunotherapy has yet to be thoroughly investigated, especially for patients in clinical practice. Real-world patients tend to be heterogeneous, including those with more advanced diseases or elderly patients who may not be candidates for intensive chemotherapy; however, immunotherapy with or without chemotherapy could also be considered for these patients in clinical practice.

Although several studies have performed cross-period comparisons for the treatment of AGC in Japan, their results in terms of improvement in survival have been inconsistent,[14,15] which might have been influenced by the subgroup of patients with HER2-positive AGC. Kadono et al.[16] suggested that the approval of third- or later-line nivolumab for AGC could prolong survival; however, only a few studies have evaluated the clinical significance of immunotherapy, including first-line treatment for patients with AGC. Although quantitatively estimating the impact of immunotherapy for AGC seems difficult based on current clinical practice where multiple treatment options are available, investigating how the advent of immunotherapy has influenced the treatment of real-world patients with AGC can be meaningful. Thus, the current study aimed to evaluate the treatment features across various immunotherapy approval periods and investigate the utility of immunotherapy for patients with HER2-negative AGC in daily practice.

Materials and methods

Patients

This retrospective study was conducted at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (JFCR). The following inclusion criteria were used to select patients for this study: (1) unresectable or metastatic gastric or gastroesophageal junction cancer, (2) histologically or cytologically confirmed HER2-negative adenocarcinoma, and (3) receiving platinum-based chemotherapy as a first-line treatment between January 2011 and December 2023. The exclusion criteria were as follows: (1) receiving palliative chemotherapy at another hospital; (2) adjuvant chemotherapy after R0 metastasectomy; (3) receiving fluoropyrimidine monotherapy for systemic disease; (4) the presence of other advanced cancers; and (5) cases in which the attending physician determined that combination therapy with immunotherapy was not an appropriate first-line treatment because of a history of interstitial lung disease or other

factors. The calendar period was segmented into three groups (Group A: 2011–2017; Group B, 2018–2021; and Group C, 2022–2023) for analysis, based on the year in which immunotherapy had been approved as mentioned above.

Reporting statement

The reporting of this study conforms to the STROBE statement,[17] which is available in the Supplemental Material.

Statistical analyses

OS was defined as the duration from first-line platinum-based chemotherapy initiation to death from any cause. Progression-free survival (PFS) was defined as the duration from first-line chemotherapy initiation to disease progression or death from any cause. Time to treatment failure (TTF) was defined as the duration from chemotherapy initiation in each treatment line to disease progression, treatment discontinuation, or death from any cause. Post-progression survival (PPS) was defined as the duration for which patients survived following progressive disease during first-line treatment. OS, PFS, TTF, and PPS were calculated using the Kaplan–Meier method. The Cox proportional hazard regression model with time-dependent covariates was used to calculate HRs for the use of immunotherapy at any line. The neutrophil-to-lymphocyte ratio (NLR) was determined by dividing the neutrophil count by the lymphocyte count. Comparisons between groups were conducted using analysis of variance and Pearson's Chi-square test for continuous and categorical variables, respectively. Univariate and multivariate analyses of OS and PFS were performed using the Cox proportional regression model. All p values were based on a two-sided hypothesis, with values less than 0.05 indicating statistical significance. All statistical analyses were performed using JMP version 17.0.0 (SAS Institute, Cary, NC, USA) and EZR version 1.42 (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[18] a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Among the 949 consecutive patients (median age, 65 years; range, 26–84 years, with 14% being ⩾75 years) who received platinum-based chemotherapy at the JFCR between 2011 and 2023 ($n = 477$, 344, and 128 for Groups A, B, and C, respectively; Figure 1), 585 (61%) were male; 308 (32%) received gastrectomy prior to chemotherapy; and 560 (59%) and 389 (41%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 and ⩾1, respectively. Moreover, 301 (32%) patients had ⩾2 metastatic sites; 701 (74%) had a diffuse-type Lauren classification; and 210 patients (22%) had an NLR of ⩾4 at baseline. Details regarding the patient's characteristics are described in Table 1. Generally, all groups had comparable characteristics, except for the proportion of elderly patients (defined as ⩾75 years of age; A: 10%, B: 17%, and C: 21%; $p = 0.002$), the proportion of patients who did not receive prior gastrectomy (A: 66%, B: 72%, C: 60%; $p = 0.03$), the presence of peritoneal metastases (A: 53%, B: 63%, C: 59%; $p = 0.0005$), and the presence of liver metastases (A: 20%, B: 21%, C: 13%; $p = 0.0005$).

Survival among the groups

At the cutoff period for data collection (August 1, 2024), the median follow-up duration was 46.3 months (53.2, 51.1, and 14.9 months for Groups A, B, and C, respectively), with 721 (76%) patients succumbing to their disease. Overall, the median OS, PFS, and TTF for second-line treatment were 16.0 months (95% CI, 14.9–17.2), 6.9 months (95% CI, 6.5–7.3), and 3.4 months (95% CI, 3.2–3.7), whereas the PPS after progression to first-line treatment was 6.9 months (95% CI, 6.4–7.4), respectively.

The median OS in Groups A, B, and C was 16.2, 15.2 (HR for Group A, 1.01; 95% CI, 0.87–1.18), and 21.3 months (HR, 0.84; 95% CI, 0.62–1.14), respectively (Figure 2(a)). The median PFS in Groups A, B, and C was 7.3, 6.0 (HR, 1.11; 95% CI, 0.96–1.29), and 7.3 months (HR, 0.77; 95% CI, 0.60–1.004), respectively (Figure 2(b)). The adjusted HRs for OS stratified according to age (<65 vs ⩾65 years), prior gastrectomy (yes vs no), and a number of metastases (0–1 vs ⩾2) were calculated to compare the OS between each group. Consequently, no significant differences in OS were observed between Groups A and B (adjusted HR, 1.01; 95% CI, 0.87–1.18) and Groups A and C (adjusted HR, 0.87; 95% CI, 0.64–1.18). Among the patients who received second-line treatment, the median

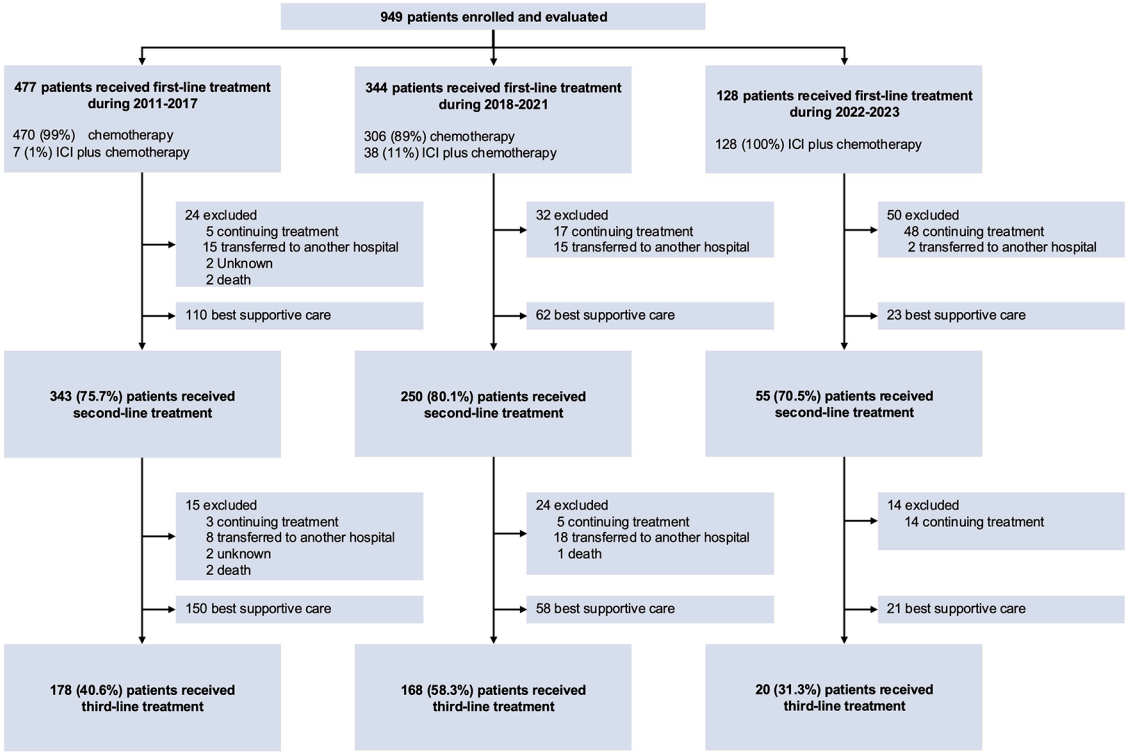

Figure 1. Flow chart for patient selection.
ICI, immunotherapy.

TTF for second-line treatment in Groups A, B, and C was 3.4, 3.4 (HR, 1.03; 95% CI, 0.86–1.22), and 3.0 months (HR, 1.09; 95% CI, 0.78–1.51), respectively (Figure 2(c)). Among those whose disease had progressed to first-line treatment, the median PPS in Groups A, B, and C was 15.7, 13.6 (HR, 1.03; 95% CI, 0.88–1.21), and 11.3 months (HR, 1.30; 95% CI, 0.95–1.77), respectively (Figure 2(d)). Among the subgroups with intestinal-type histology, those in Group C showed a numerically longer OS than those in Group A (HR, 0.32; 95% CI, 0.1–0.89; Supplemental Figure 1(A)). Meanwhile, among the subgroups with diffuse-type histology, those in Groups B and C did not show improved OS when compared to those in Group A (Supplemental Figure 2(B)). Subgroups according to age (<75, ⩾75 years) did not show trends toward improvement of OS (Supplemental Figure 1(C) and (D)).

To determine the magnitude of the efficacy of third- or later-line anti-PD-1 antibody treatment, patients in Group A who received any third- or later-line treatments other than immunotherapy at the cutoff period for data collection ($n = 89$) were compared with those in Group B who received third- or later-line immunotherapy ($n = 129$). Notably, we found that Groups A and B had a median OS of 19.6 months (95% CI, 16.9–21.3) and 19.0 months (95% CI, 17.0–22.6; HR, 1.01; 95% CI, 0.87–1.18; $p = 0.82$), respectively (Figure 3(a)). The adjusted HR for OS was 0.96 (95% CI, 0.72–1.30; $p = 0.83$). The 1-, 2-, and 3-year OS rates for Groups A and B were 84.2% (76.7%–91.8%) and 75.8% (95% CI, 68.4%–83.2%), 35.2% (25.1%–45.2%) and 38.1% (29.6%–46.7%), and 11.3% (4.4%–18.2%) and 23.2% (15.5%–29.6%), respectively.

Similarly, to investigate the potential therapeutic impact of first-line immunotherapy plus chemotherapy, we evaluated 382 patients in Group A who did not receive any-line immunotherapy and 173 patients who received first-line immunotherapy plus chemotherapy. Accordingly, we found that such patients had a median OS of 14.1 months (95% CI, 13.9–15.7) and 17.6 months (95% CI, 14.4–22.5; HR, 0.78; 95% CI, 0.61–0.99; $p = 0.04$; Figure 3(b)), respectively. The 1-, 2-, and 3-year OS rates for Group A and patients who received

Table 1. Patient characteristics.

Characteristics	Overall (*N* = 949)	2011–2017 (*n* = 477)	2018–2021 (*n* = 344)	2022–2023 (*n* = 128)	*p* Value
Age, median (range)	65 (26–84)	63 (26–84)	66 (26–83)	66 (27–83)	0.055
⩾75	135 (14%)	50 (10%)	58 (17%)	27 (21%)	0.002*
Sex, male	585 (62%)	289 (61%)	225 (65%)	71 (55%)	0.11
ECOG PS					
0	560 (59%)	279 (58%)	207 (60%)	74 (58%)	0.85
⩾1	389 (41%)	198 (42%)	137 (40%)	54 (42%)	
Primary location					
EGJ	776 (82%)	391 (82%)	278 (81%)	108 (84%)	0.67
Stomach	169 (18%)	86 (18%)	63 (18%)	20 (16%)	
Prior gastrectomy					
No	641 (68%)	316 (66%)	248 (72%)	77 (60%)	0.03*
Histological type					
Diffuse type	701 (74%)	349 (73%)	247 (72%)	105 (82%)	0.07
Metastatic site					
Peritoneum	544 (57%)	254 (53%)	215 (63%)	75 (59%)	0.21
Liver	185 (19%)	97 (20%)	71 (21%)	17 (13%)	0.0005*
Lymph node	338 (36%)	151 (32%)	126 (37%)	61 (48%)	0.053
Number of metastases					
0–1	648 (68%)	341 (71%)	221 (64%)	86 (67%)	0.08
⩾2	301 (32%)	136 (29%)	123 (36%)	42 (33%)	
ALP, U/L median (range)	230 (23–7724)	234 (100–7724)	233 (23–5389)	222 (41–3914)	0.93
NLR, median (range)	3.08 (0.28–92.4)	2.92 (0.48–47.0)	3.45 (0.61–92.4)	2.86 (0.28–37.6)	0.21
First-line immunotherapy	173 (18%)	7 (1%)	38 (11%)	128 (100%)	
Second- or later-line immunotherapy	391 (41%)	89 (19%)	129 (38%)	2 (2%)	

*$p < 0.05$.
ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; EGJ, esophagogastric junction; NLR, neutrophil-to-lymphocyte ratio; PS, performance status.

first-line immunotherapy plus chemotherapy were 57.7% (52.6%–62.8%) and 64.7% (56.9%–72.5%), 25.7% (21.2%–30.2%) and 35.9% (26.1%–45.7%), and 13.7% (10.0%–17.4%) and 24.6% (13.6%–35.6%), respectively. Although no significant difference in PFS was observed between the two subgroups (median 7.3 vs 7.6 months; HR, 0.83; 95% CI, 0.66–1.03; $p = 0.09$; Supplemental Figure 2(A)), a durable response was observed in patients who received first-line immunotherapy plus chemotherapy, with 1-, 2-, and 3-year PFS rates of 28.5% (23.7%–33.2%) versus 31.7% (23.7%–39.6%), 9.6% (6.2%–12.8%) versus 17.0% (9.1%–24.9%), and 5.8% (3.2%–8.4%) versus 17.0% (9.1%–24.9%), respectively. In addition, compared to Group B

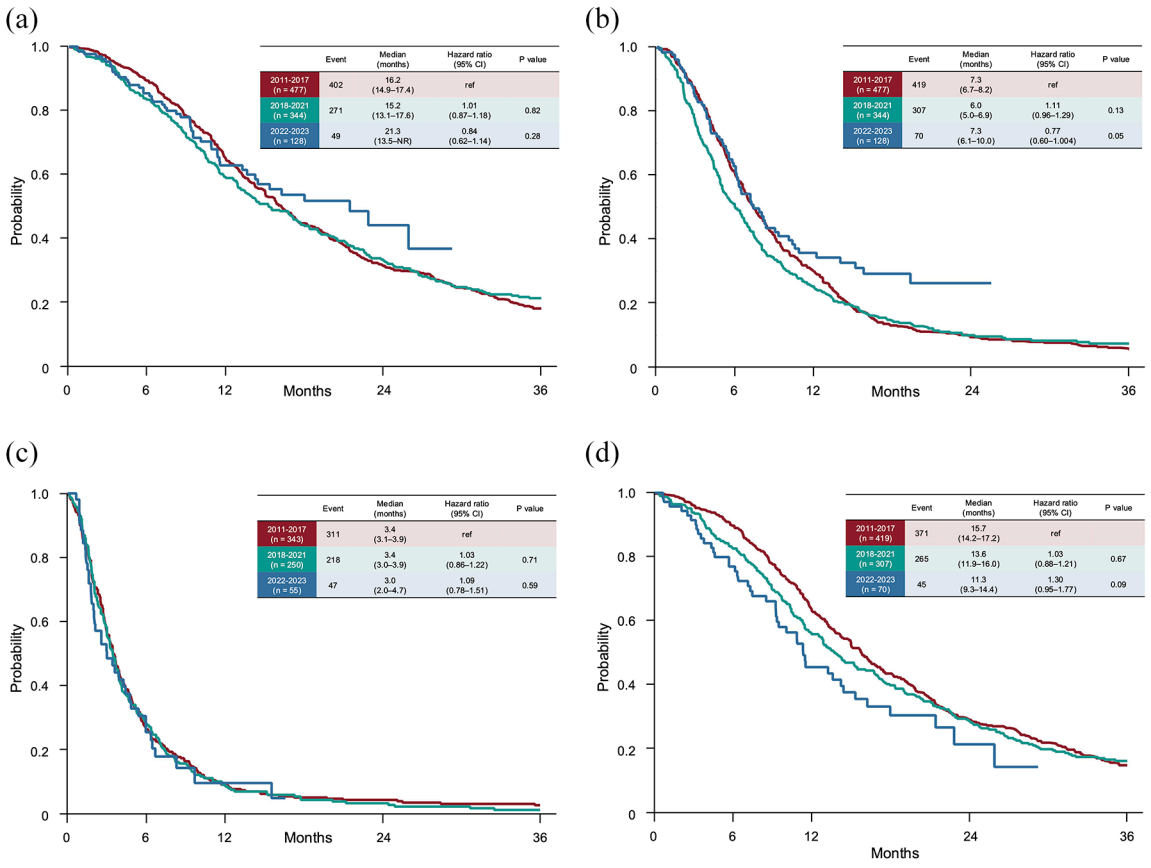

Figure 2. Kaplan–Meier estimates of (a) overall survival, (b) progression-free survival, (c) time to treatment failure of second-line treatment, and (d) post-progression survival after first-line treatment in Groups A (2011–2017), B (2018–2021), and C (2022–2023).
CI, confidence interval; Ref, reference.

excluding patients who received first-line immunotherapy plus chemotherapy ($n=306$), and those who received first-line immunotherapy plus chemotherapy ($n=173$), the OS rates were comparable between the subgroups (median, 14.5 vs 17.6 months; HR, 0.88; 95% CI, 0.68–1.13; $p=0.33$; Figure 3(c)). Overall, patients who received any-line immunotherapy ($n=391$) had significantly better OS than did those who did not receive immunotherapy-containing treatment ($n=558$; median, 21.0 vs 13.1 months; HR with time-dependent covariates, 0.54; 95% CI, 0.47–0.633; $p<0.0001$; Figure 3(d)).

Univariate and multivariate Cox regression analyses for OS and PFS

Table 2 summarizes the results of univariate and multivariate Cox regression analyses for OS using baseline characteristics and laboratory tests. The following factors were independently associated with poor prognosis in this cohort: ECOG PS ⩾1 (HR, 1.68; 95% CI, 1.43–1.98; $p<0.0001$), diffuse-type (HR, 1.38; 95% CI, 1.14–1.67; $p=0.0008$), absence of gastrectomy (HR, 1.32; 95% CI, 1.03–1.68; $p=0.02$), ⩾2 metastases (HR, 1.20; 95% CI, 1.01–1.43; $p=0.03$), presence of peritoneal metastases (HR, 1.38; 95% CI, 1.16–1.65; $p=0.0002$), high alkaline phosphatase (ALP) level (HR, 1.39; 95% CI, 1.15–1.69; $p=0.0006$), and NLR ⩾4 (HR, 1.56; 95% CI, 1.31–1.85; $p<0.0001$). Treatment period (Group A vs Group B or C) and use of first-line immunotherapy were not associated with OS.

The results of univariate and multivariate Cox regression analyses for PFS are summarized in Supplemental Table 1. Overall, ECOG PS ⩾1 (HR, 1.39; 95% CI, 1.18–1.63; $p<0.0001$), absence of gastrectomy (HR, 1.34; 95% CI, 1.05–1.72; $p=0.01$), ⩾2 metastases (HR, 1.31; 95% CI, 1.10–1.57; $p=0.002$), high serum ALP

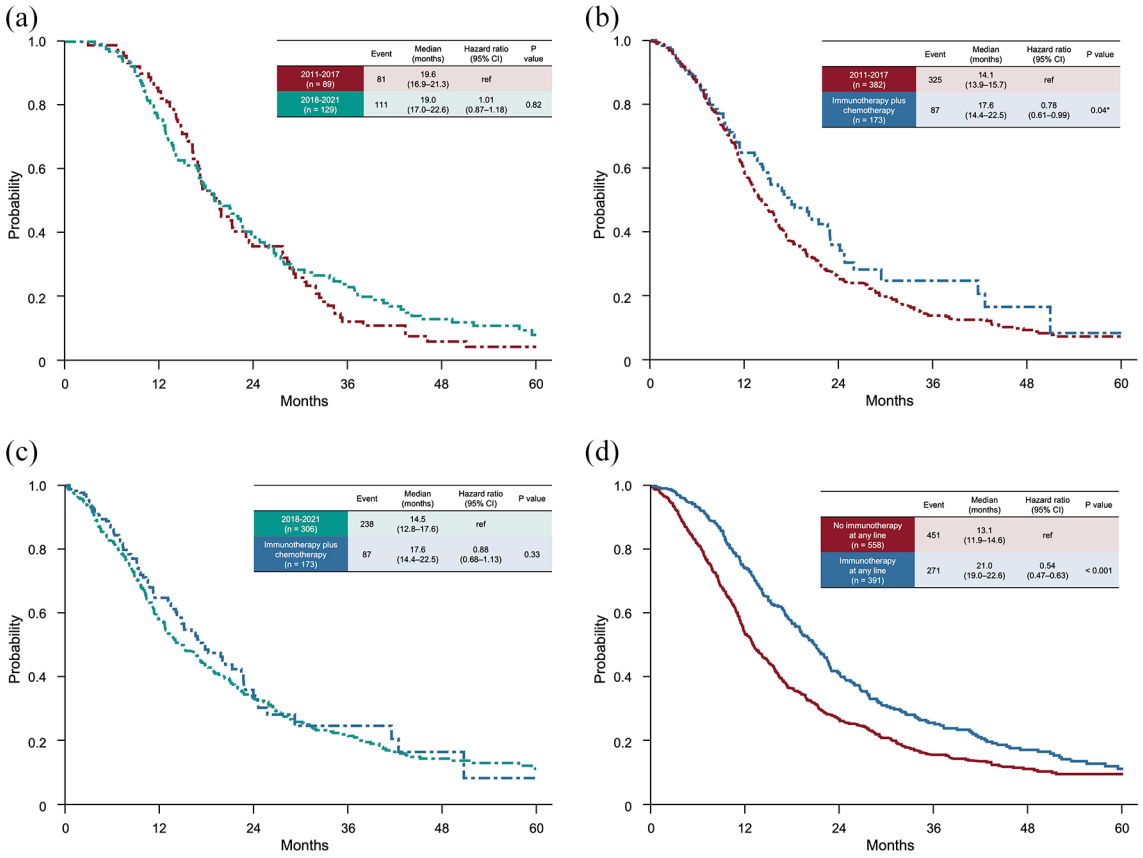

Figure 3. Kaplan–Meier estimates of overall survival in the subgroup of (a) patients in Group A who had received any third-line treatment other than immunotherapy or continued first- or second-line treatment after cutoff point for data collection and patients in Group B who received immunotherapy as third- or later-line treatment or continued first- or second-line treatment after cutoff point for data collection; (b) patients in Group A who did not receive any-line immunotherapy and those who had received first-line immunotherapy plus chemotherapy; (c) patients in Group B excluding those who had received first-line immunotherapy plus chemotherapy and first-line immunotherapy plus chemotherapy; and (d) patients who did and did not receive any-line immunotherapy.
CI, confidence interval; Ref, reference.

(HR, 1.35; 95% CI, 1.03–1.552; $p=0.03$), NLR ⩾4 (HR, 1.35; 95% CI, 1.14–1.61; $p=0.0005$), and the use of immunotherapy for first-line treatment (HR, 0.79; 95% CI, 0.64–0.98; $p=0.03$) were associated with PFS.

Patterns of subsequent treatment

At the cutoff point for data collection, 796 (84%) patients had discontinued first-line treatment. Among them, 343 (76%), 250 (80%), and 55 (71%) in Groups A, B, and C received second-line treatment, respectively (Supplemental Figure 3(A)). After discontinuing second-line treatment, 178 (41%), 168 (58%), and 20 (31%) in Groups A, B, and C received any third-line treatment, with the rate of receiving third-line treatment being significantly higher in Group B than in Group A ($p=0.0001$) and Group C ($p<0.0001$).

Details regarding subsequent treatment agents in each line according to the groups are described in Supplemental Figure 3(B). The majority of the patients received taxane-based chemotherapy as second-line treatment, whereas irinotecan (46%), immunotherapy (73%), and trifluridine/tipiracil (FTD/TPI) (70%) were the most commonly provided third-line treatment in Groups A, B, and C, respectively. Among those aged ⩾75 years, those in Group had a significantly lower rate of receiving second- or third-line treatment than did those in Group B (Supplemental Figure 3(C)).

Table 2. Univariate and multivariate analyses for survival.

Variables	Category (Ref)	Univariate			Multivariate		
		HR	95% CI	*p*	HR	95% CI	*p*
Age	⩾75 vs <75 (Ref)	0.97	0.78–1.20	0.81			
Sex	Female vs male	1.12	0.96–1.30	0.12			
ECOG PS	⩾1 vs 0	1.86	1.60–2.15	<0.0001*	1.68	1.43–1.98	<0.0001*
Histological type	Diffuse vs intestinal	1.46	1.23–1.73	<0.0001*	1.38	1.14–1.67	0.0008*
Tumor status	Metastatic vs recurrent	1.29	1.08–1.55	0.005*	0.91	0.69–1.19	0.50
Gastrectomy	No vs yes	1.36	1.16–1.60	0.0001*	1.32	1.03–1.68	0.02*
Number of meta	⩾2 vs 0–1	1.33	1.14–1.55	0.0002*	1.20	1.01–1.43	0.03*
Peritoneum	Yes vs no	1.50	1.27–1.78	<0.0001*	1.38	1.16–1.65	0.0002*
Liver	Yes vs no	1.03	0.85–1.24	0.72			
Lymph node	Yes vs no	1.04	0.88–1.22	0.60			
ALP	⩾ULN vs <ULN	1.57	1.33–1.86	<0.0001*	1.39	1.15–1.69	0.0006*
NLR	⩾4 vs <4	1.88	1.62–2.19	<0.0001*	1.56	1.31–1.85	<0.0001
ICI for first line	Yes vs no	0.91	0.72–1.14	0.43			
Period	2011–2017 (Ref)	Ref			Ref		
	2018–2021	1.01	0.87–1.18	0.82	1.05	0.89–1.24	0.51
	2022–2023	0.84	0.62–1.14	0.28	0.92	0.67–1.25	0.60

*$p < 0.05$.
ALP, alkaline phosphatase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICI, immunotherapy; NLR, neutrophil-to-lymphocyte ratio; PS, performance status; Ref, reference; ULN, upper limit of normal.

Discussion

After evaluating 949 real-world patients with HER2-negative AGC, our findings suggested that the introduction of immunotherapy might have impacted the treatment landscape and contributed to the improvement of survival in this population. To the best of our knowledge, the current study has been the first to evaluate the clinical utility of immunotherapy in real-world patients with HER2-negative AGC, including both later-line immunotherapy and first-line chemotherapy plus immunotherapy.

The current large-scale cohort study showed no clear improvements in survival outcomes across treatment periods following the approval of immunotherapy. Immunotherapy had initially been approved in 2017 for third- or later-line treatment and then as first-line treatment in combination with chemotherapy in 2021. Exploratory analyses, however, indicated trends favoring the initiation of immunotherapy earlier during the treatment course. The OS of patients receiving third- or later-line immunotherapy monotherapy, who primarily belonged to Group B, did not significantly differ from that of patients who did not receive any-line immunotherapy. This lack of improvement could partly have been attributed to the fact that patients in Group A had received third-line treatments, such as irinotecan or other agents, which could have influenced the comparison of OS between Groups A and B. Although irinotecan did not demonstrate any OS benefits as a third- or later-line treatment, the WJOG4007 trial showed that it offers therapeutic efficacy comparable to that

of paclitaxel in the second-line setting.[19] Consequently, irinotecan has also been considered a viable option for third-line treatment, particularly for patients in Group A. It is worth noting that approximately 80% of patients in the ATTRACTION-2 trial had received more than three prior treatments before starting nivolumab monotherapy, and approximately 30% of patients subsequently underwent additional pharmacotherapy.[8] While the introduction of immunotherapy as a third-line treatment in clinical practice has expanded therapeutic options for AGC patients, particularly those previously ineligible for later-line treatments in Group B, detecting a clear difference in OS between patients receiving third-line immunotherapy monotherapy and those receiving non-immunotherapy pharmacotherapy in clinical practice remains challenging.

Patients who received first-line immunotherapy plus chemotherapy demonstrated improved survival when compared to those in Group A who rarely had the opportunity to receive any-line immunotherapy. However, no significant difference in OS was found between patients receiving first-line immunotherapy plus chemotherapy and those in Group B. These apparently inconsistent results mirror those presented in the CheckMate-649 and ATTRACTION-4 trials, both of which demonstrated prolonged PFS but only the CheckMate-649 trial showed an improvement in OS. Only 13% of the patients in Group A received third- or later-line immunotherapy, whereas 42% of those in Group B received the same. Therefore, the proportion of patients who received any-line immunotherapy could influence survival outcomes, which may explain the difference between the results of the CheckMate-649 and ATTRATION-4 trials. Following the results of the TAGS trial, the approval of FTD/TPI in Japan in 2019 influenced subsequent treatment options for HER2-negative AGC[20] (Supplemental Figure 4). Although nivolumab monotherapy has generally been the preferred third-line treatment option given its moderate and manageable toxicity profile compared to cytotoxic agents, as well as its potential to achieve durable responses in selected cases, FTD/TPI has played a significant role in improving the outcomes of fourth-line or later treatments. In Group B, this treatment approach also slightly improved OS, narrowing the OS gap between Groups B and C. After considering the time-dependent covariate of any-line immunotherapy, our results further suggest favorable OS for patients receiving any-line immunotherapy, indicating that certain patients might benefit from immunotherapy regardless of treatment lines. Given the potential risk of missing out on opportunities for immunotherapy, initiating immunotherapy as part of first-line treatment in combination with chemotherapy is quite reasonable.

As described in previous reports,[14] our study revealed slight shifts in the characteristics of real-world patients, suggesting the broadening of broadened for platinum-based chemotherapy, especially for elderly patients. This trend may become even more pronounced with the approval of immunotherapy for first-line treatment. In addition, increasing opportunities for surgical intervention of metastatic gastric cancer, including surgeries with curative intent (2% vs 3% vs 7%), and greater participation in clinical trials should be considered when interpreting the results of the current study, which did not clearly show improvements in survival across treatment periods. However, the changing patient population across treatment periods might be viewed favorably, given that it reflects an expanding indication for chemotherapy among those with AGC in clinical practice.

Further discussions are needed to clarify predictive biomarkers of the treatment efficacy of immunotherapy with or without chemotherapy. Although mismatch repair deficiency/microsatellite instability-high is a robust predictive biomarker for immunotherapy in gastric cancer,[21] the validity of PD-L1 expression as a predictive biomarker of immunotherapy in gastric cancer remains controversial.[8] Requirements for the approval of nivolumab or pembrolizumab in combination with chemotherapy differ according to the regulatory authorities. Thus, further research is needed to identify the optimal subgroup of patients who would benefit most from initiating immunotherapy-based treatments, including identifying biomarkers for precisely predicting immunotherapy efficacy, such as not only PD-L1 expression or mismatch repair deficiency/microsatellite instability but also other novel biomarkers.[22] Moreover, the appearance of targetable biomarkers, including claudin 18 isoform 2[23,24] and fibroblast growth factor 2 isoform IIIb,[25] can improve the survival of patients with HER2-negative AGC who do not respond to current agents and help deliver immunotherapy plus chemotherapy for appropriate patients with AGC.

Several limitations inherent to the retrospective nature of the current study are important to note. First, the follow-up period was shorter for Group C than for the other groups, which may have limited the number of PFS or OS events. This difference could hinder the interpretation of the results according to treatment periods, underscoring the need for further observation in this subgroup. Hence, we plan to conduct further analyses with longer follow-up data, which could help in clarifying the robust efficacy of immunotherapy in the treatment of real-world patients with HER2-negative AGC. Second, the study only included patients who received platinum-containing treatment and excluded those who received fluoropyrimidine monotherapy as first-line treatment, which might have created an imbalance in patients' characteristics between the groups. As noted earlier, the heterogeneity of patients across groups due to various factors may introduce potential bias, emphasizing the need for caution when interpreting our results. Although these limitations may affect the generalizability of our findings, we believe that real-world patients with AGC stand to benefit from the therapeutic advances in immunotherapy. Our findings underscore the need for ongoing improvement in AGC treatment and exploration of the optimal indications for immunotherapy within this population.

Conclusion

The current study highlighted the clinical significance of immunotherapy across each treatment period and treatment lines. Notably, our results suggest that immunotherapy might have partially improved the survival of real-world patients with HER2-negative AGC, underscoring the need for further appropriate treatment strategies including efforts to identify biomarkers and the development of other agents.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Cancer Institute Hospital of JFCR (Tokyo, Japan; approval date: July 2022; registry number: 2021-GB-095). Given the retrospective nature of the study, informed consent was waived with the opportunity to opt out from the research. All procedures were conducted in accordance with the Helsinki Declaration of 1964 and later versions. Given the retrospective nature of this study, informed consent was waived with the opportunity to opt out from participation. *Consent to participate*: Informed consent was waived with the opportunity to opt out from the research.

Consent for publication

Not applicable.

Author contributions

Keitaro Shimozaki: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Writing – original draft.

Akira Ooki: Conceptualization; Project administration; Supervision; Writing – review & editing.

Koichiro Yoshino: Resources; Writing – review & editing.

Mikako Tamba: Resources; Writing – review & editing.

Shohei Udagawa: Resources; Writing – review & editing.

Hiroki Osumi: Resources; Writing – review & editing.

Shota Fukuoka: Resources; Writing – review & editing.

Izuma Nakayama: Resources; Writing – review & editing.

Takeru Wakatsuki: Resources; Writing – review & editing.

Mariko Ogura: Resources; Writing – review & editing.

Daisuke Takahari: Resources; Writing – review & editing.

Eiji Shinozaki: Resources; Writing – review & editing.

Keisho Chin: Resources; Writing – review & editing.

Kensei Yamaguchi: Project administration; Writing – review & editing.

Acknowledgements

The authors thank the patients, as well as their families and caregivers, for participating in this study.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID iDs
Keitaro Shimozaki https://orcid.org/0000-0002-4559-5699

Akira Ooki https://orcid.org/0000-0001-7618-5775

Mikako Tamba https://orcid.org/0009-0006-1380-4325

Hiroki Osumi https://orcid.org/0000-0002-4742-0446

Supplemental material
Supplemental material for this article is available online.

References

1. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; 9: 215–221.
2. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; 29: 3968–3976.
3. Fuchs CS, Shitara K, Di Bartolomeo M, et al. Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; 20: 420–435.
4. Lordick F, Kang YK, Chung HC, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; 14: 490–499.
5. Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; 14: 481–489.
6. Shah MA, Bang YJ, Lordick F, et al. Effect of fluorouracil, leucovorin, and oxaliplatin with or without Onartuzumab in HER2-negative, MET-positive gastroesophageal adenocarcinoma: the METGastric randomized clinical trial. *JAMA Oncol* 2017; 3: 620–627.
7. Catenacci DVT, Tebbutt NC, Davidenko I, et al. Rilotumumab plus epirubicin, cisplatin, and capecitabine as first-line therapy in advanced MET-positive gastric or gastro-oesophageal junction cancer (RILOMET-1): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; 18: 1467–1482.
8. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; 390: 2461–2471.
9. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021; 398: 27–40.
10. Kang YK, Chen LT, Ryu MH, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2022; 23: 234–247.
11. Rha SY, Oh DY, Yañez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2023; 24: 1181–1195.
12. Xu J, Jiang H, Pan Y, et al. Sintilimab plus chemotherapy for unresectable gastric or gastroesophageal junction cancer: the ORIENT-16 randomized clinical trial. *JAMA* 2023; 330: 2064–2074.

13. Qiu MZ, Oh DY, Kato K, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial. *BMJ* 2024; 385: e078876.

14. Nakayama I, Takahari D, Shimozaki K, et al. Clinical progress in inoperable or recurrent advanced gastric cancer treatment from 1004 single institute experiences between 2007 and 2018. *Oncologist* 2022; 27: e506–e517.

15. Ogata T, Narita Y, Oze I, et al. Chronological improvement of survival in patients with advanced gastric cancer over 15 years. *Ther Adv Med Oncol* 2024; 16: 17588359241229428.

16. Kadono T, Iwasa S, Hirose T, et al. Impact of immune checkpoint inhibitors on survival outcomes in advanced gastric cancer in Japan: a real-world analysis. *Cancer Med* 2024; 13: e7401.

17. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61: 344–349.

18. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant* 2013; 48: 452–458.

19. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol* 2013; 31: 4438–4444.

20. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2018; 19: 1437–1448.

21. Chao J, Fuchs CS, Shitara K, et al. Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials. *JAMA Oncol* 2021; 7: 895–902.

22. Kang YK, Morita S, Satoh T, et al. Exploration of predictors of benefit from nivolumab monotherapy for patients with pretreated advanced gastric and gastroesophageal junction cancer: post hoc subanalysis from the ATTRACTION-2 study. *Gastric Cancer* 2022; 25: 207–217.

23. Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med* 2023; 29: 2133–2141.

24. Shitara K, Lordick F, Bang Y-J, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. *Lancet* 2023; 401: 1655–1668.

25. Wainberg ZA, Enzinger PC, Kang Y-K, et al. Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Oncol* 2022; 23: 1430–1440.