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ORIGINAL ARTICLE

Retrospective analysis for the efficacy and safety of nivolumab in advanced gastric cancer patients according to ascites burden

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Abstract

Background Nivolumab is a standard later-line therapy for advanced gastric cancer (AGC). However, few reports exist about its efficacy and safety in patients with massive ascites.

Methods We retrospectively collected clinical data from 72 AGC patients who received nivolumab administration at least once from Oct 2017 to Feb 2019 and studied their clinical outcomes dividing into two groups: 50 patients with no or localized ascites in the pelvic cavity or liver surface (LAB: low ascites burden) and 22 patients with massive ascites (HAB: high ascites burden).

Results Median overall survival (OS) was 5.3 months (95% CI 3.4–7.3) in the LAB group and 2.5 months (95% CI 0.0–5.0) in the HAB group. Multivariate Cox regression analysis for OS revealed blood neutrophil-to-lymphocyte ratio (hazard ratio 0.40, 95% CI 0.20–0.83, $p = 0.013$) as an independent prognostic factor. Response rates in the patients with measurable lesions were 16% (7/43) and 8% (1/12) in the LAB and HAB groups, respectively. Ascites decreased or disappeared in 6 HAB patients (27%) and these responders had a prolonged OS of median 9.7 months (95% CI 3.6–15.8). The median time to ascites response was 1.3 months (95% CI 0.8–1.9). These responders have lower neutrophil-to-lymphocyte ratios than 5.0 at the start of nivolumab. Immune-related adverse events occurred in 23% of HAB and 18% of LAB patients.

Conclusions Nivolumab could improve massive ascites and confer survival benefit for some AGC patients. Considering a similar incidence of immune-related adverse events, it would be a recommended treatment option for AGC with massive ascites.

Keywords Gastric cancer · Nivolumab · Ascites

Introduction

Peritoneal metastasis is the most frequent metastasis in advanced gastric or gastroesophageal junction cancer (AGC) [1]. Despite recent advances in systemic chemotherapy, the prognosis of gastric cancer with peritoneal metastasis is poor [2–6]. Approximately, 40% of patients with peritoneal metastasis have malignant ascites accompanying clinical symptoms such as abdominal pain, vomiting, and difficulty with ingestion that worsen performance status (PS) and complicate chemotherapy [7, 8].

Worldwide, the standard chemotherapy for AGC is first oral fluoropyrimidine plus platinum [with trastuzumab for human epidermal growth factor receptor (HER) 2-positive disease] followed by paclitaxel plus ramucirumab and finally nivolumab or irinotecan. However, oral fluoropyrimidine is often unstable and contraindicated in patients with massive ascites due to the aforementioned complications. In these cases, 5-Fluorouracil (5-FU), paclitaxel monotherapy, or the combination with oxaliplatin (FOLFOX: 5-FU/leucovorin/oxaliplatin) is often used [9–11]. Recently, the results of a randomized study of FLTAX (5-FU/leucovorin/paclitaxel) versus 5-FU/leucovorin in AGC patients with severe peritoneal metastasis were reported but remained poor; median

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progression-free survival (PFS) for FLTAX and 5-FU/leucovorin was 5.4 and 1.9 months, while median overall survival (OS) was 7.3 and 6.1 months, respectively [9]. Outside of these treatments there are few chemotherapy options except for nivolumab.

Nivolumab, a fully human, IgG4 monoclonal antibody against programmed death 1 (PD-1), is recommended as third- or later-line therapy for AGC based on the results of the ATTRACTION-2 study, which demonstrated survival prolongation with nivolumab compared with placebo [12]. The median OS was 5.2 and 4.1 months (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.51–0.78; $p < 0.001$) in the nivolumab and placebo groups, respectively. However, substantial evidence for the efficacy and safety of nivolumab for AGC with massive ascites is lacking as these patients are often excluded from clinical trials due to poor general condition. In this study, we retrospectively evaluated the efficacy and safety of nivolumab monotherapy for such patients.

Methods

Patients

We retrospectively collected the clinical data of patients with AGC who received nivolumab administration at least once from Oct 2017 to Feb 2019 at three hospitals in Japan. Data, including age, gender, history of gastrectomy, tumor status (metastatic or recurrence), Eastern Cooperative Oncology Group (ECOG) PS, number of metastatic organs, number of previous chemotherapy, previous treatment with ramucirumab, histological type, tumor HER2 status, blood neutrophil-to-lymphocyte ratio (NLR) before nivolumab treatment (on the day of first nivolumab administration), serum tumor markers of CEA and CA19-9, serum C-reactive protein (CRP) and albumin levels, immune-related adverse events (irAEs), and the efficacy outcomes (response, PFS, and OS) were extracted from medical records. We defined the presence of ascites as peritoneal dissemination.

Treatment

The patients received nivolumab intravenously every two weeks. The dosage of nivolumab was 3 mg/kg in the early phase of this study but after the revision of approved dosages by Japanese authorities on 21 August 2018, the dosage of nivolumab was fixed at 240 mg/body. The patients received treatment until disease progression, unacceptable toxicity, or withdrawal of consent. Interruption of treatment was performed by each physician according to the criteria of a reported clinical trial [12].

Study design

This retrospective study was conducted according to Japanese ethical guidelines with the approval of the ethics review committee of each hospital. The requirement for informed consent was waived owing to the retrospective nature of the study.

We evaluated the amount of ascites by computed tomographic (CT) scans and scored them as follows: massive (extending throughout the abdominal cavity), moderate (neither mild nor massive), mild (localized at pelvic cavity or liver surface), or no ascites (ascites not detected). We classified moderate or massive ascites as high ascites burden (HAB) and mild or no ascites as low ascites burden (LAB) [9] then evaluated the efficacy and safety of nivolumab in patients with HAB or LAB. Tumor responses were evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The best ascites responses in the HAB group were defined as follows: disappeared (disappearance of ascites), decreased (from moderate to mild or from massive to moderate/mild), or increased (from moderate to massive) [13]. Adverse events (AEs) were evaluated by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical analysis

Comparisons of patient backgrounds between groups were conducted by Mann–Whitney U testing for continuous variables and Fisher's exact test for categorical variables. PFS was defined as the time from the date of nivolumab initiation to the date of disease progression or death from any cause. OS was defined as the time from the date of nivolumab initiation to the date of death from any cause. Patients without PFS and/or OS events were censored on the day of their last visits. PFS and OS were estimated by the Kaplan–Meier method and compared between groups using a log-rank test. Cox proportional hazard analyses were performed to examine the association of patient background factors with survival before selecting those factors with p values ≤ 0.2 for multivariate regression analysis. The characteristics of ascites responders were evaluated in the HAB group. Two-sided p values of < 0.05 were considered statistically significant. Statistical analyses were performed using IBM® SPSS® Statistics software, version 26 (SPSS Inc., Chicago, IL, USA).

Results

Patients

Clinical data were collected from 72 AGC patients treated with nivolumab (22 HAB, 50 LAB). The HAB group

had less prior gastrectomy ($p = 0.02$), worse ECOG PS ($p < 0.001$), more frequent pathologically diffuse type ($p = 0.02$), and lower serum albumin level ($p < 0.001$) than the LAB group (Table 1). 10 of 15 and 1 of 2 patients with HER2-positive tumors in the LAB and HAB groups were treated with trastuzumab, respectively. 43 patients in the LAB group and 12 patients in the HAB group had the measurable lesions.

Efficacy

The median duration of survival follow-up in all patients was 4.8 months (0.5–22.5 months) and Kaplan–Meier survival curves are shown in Fig. 1. CT scans were performed approximately every 8 weeks in each patient. The median PFS was 1.5 (95% CI 1.0–2.0) months in the LAB group and 1.0 (95% CI 0.9–1.1) month in the HAB group (HR 0.73, 95% CI 0.43–1.23). The median OS was 5.3 (95% CI 3.4–7.3) months in the LAB group and 2.5 (95% CI 0.0–5.0) months in the HAB group (HR 0.51, 95% CI

Table 1 Patient characteristics

	No or low ascites burden[a] ($n = 50$)	High ascites burden ($n = 22$)	*P* value*
Age (median (IQR), years)	70 (66–77)	62 (54–74)	0.08
Gender (male/female)	43/7	14/8	0.06
Gastrectomy [Yes, *n* (%)]	32 (64)	7 (32)	0.02
Tumor status (synchronous/metachronous)	25/25	15/7	0.20
ECOG PS (0/1/2/3)	16/29/4/1	0/16/6/0	< 0.001
Metastatic sites (1/2/3/4)	17/23/10/0	8/11/2/1	0.38
Previous treatments [> 3, *n* (%)]	50 (100)	22 (100)	
Yes, *n* (%)	43 (86)	18 (82)	0.73
Histological type (intestinal/diffuse)	29/21	6/16	0.02
HER2 status [positive, *n* (%)]	15 (30)	2 (9)	0.07
NLR [median (IQR)]	2.6 (1.6–4.1)	3.1 (1.4–7.4)	0.59
CEA (ng/ml) [median (IQR)]	7 (4.2–128)	6.9 (3.9–19)	0.38
CA19-9 (U/ml) [median (IQR)]	40 (7.4–725)	204 (15–915)	0.23
Alb (g/dl) [median (IQR)]	3.4 (3.0–3.7)	2.6 (2.4–3.0)	< 0.001
CRP (mg/dl) [median (IQR)]	0.5 (0.2–1.7)	0.7 (0.3–3.5)	0.45

ECOG PS Eastern Cooperative Oncology Group performance status, *NLR* blood neutrophil-to-lymphocyte ratio

[a]Low ascites burden means localized ascites in the pelvic cavity or hepatic surface

*Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables

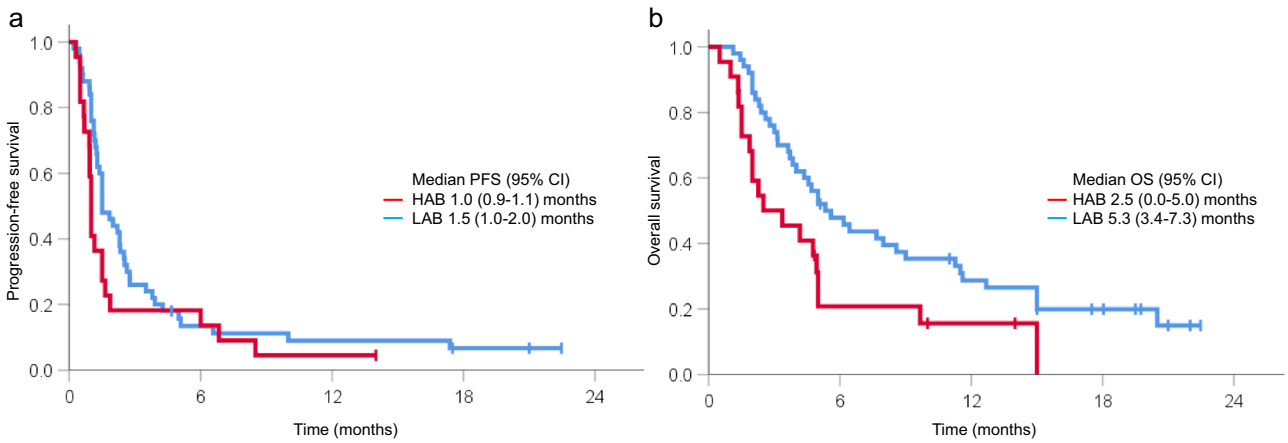

Fig. 1 Kaplan–Meier curve of progression-free survival (**a**) and overall survival (**b**) by ascites groups. LAB, low ascites burden; HAB, high ascites burden

0.30–0.88). Multivariate analyses for OS showed NLR (HR 0.40, 95% CI 0.20–0.83, $p=0.013$) was an independent prognostic factor (Table 2). The objective response rate was 16% in the LAB group and 8% in the HAB group (Table 3).

In the HAB group, ascites response rate was 27% (95% CI 11–50) (Table 3). The median time to ascites response was 1.3 months (95% CI 0.8–1.9). NLRs were lower (median 1.3 vs. 4.3; $p=0.04$) and irAEs incidence was higher (67% vs. 6%, $p=0.001$) in ascites responders than non-responders (Table 4). Three of 6 (50%) ascites responders and 3 of 16 (19%) ascites non-responders had histologically verified intestinal-type tumors ($p=0.28$). Patients with tumor response, ascites response, and irAEs appeared to have a longer survival (Fig. 2). Among 11 patients with HAB who received nivolumab for six or more weeks, four patients showed irAE, and all of them exhibited ascites response. On the other hand, there are only two ascites responders in the remaining seven patients without irAE. A representative case of ascites responder with HAB is shown in Fig. 3. The relationship between OS and NLR in the HAB group according to ascites response is shown in Fig. 4. Patients with NLR > 5.0 (32%, $n=7/22$) were unlikely to respond to nivolumab treatment and had a short OS.

The median duration and number of courses of nivolumab treatment were 5.9 (2.0–97.7) weeks and 4 (1–43) courses in the LAB group and 2.4 (2.0–60.1) weeks and 2 (1–20) courses in the HAB group, respectively. Subsequent chemotherapies after nivolumab were done in 23 (46%) patients in the LAB group and 7 (32%) patients in the HAB group. Eleven patients failed the nivolumab treatment within 2 courses and moved to the best supportive care alone.

Table 3 Response evaluation

	No or low ascites burden[a] ($n=50$)	High ascites burden ($n=22$)
Measurable lesion	$n=43$	$n=12$
Tumor response in measurable lesions (RECIST Ver. 1.1)		
Complete response	1	0
Partial response	6	1
Stable disease	5	1
Progressive disease	30	10
Not evaluable	1	0
Response rate (95% CI)	16% (5–27)	8% (0–39)
Ascites response		
Disappeared	–	4
Decreased	–	2
No change or increased	–	16
Response rate (95% CI)	–	27% (11–50)

RECIST Response evaluation criteria in solid tumors

[a]Low ascites burden means localized ascites in the pelvic cavity or hepatic surface

Safety

IrAEs of any grade occurred in 23% of the HAB group and 18% of the LAB group (Table 5). Grade 3 or higher adverse events relating to the treatment were not observed except for immune-related myocarditis (grade 5) in one LAB patient. Unacceptable toxicities which reached interruption of nivolumab were grade 2 hypopituitarism and

Table 2 Cox proportional hazard model and regression analyses for overall survival

	Univariate analyses		Multivariate analyses	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (< 65 vs. ≥ 65 years)	1.24 (0.71–2.14)	0.45		
Sex (female vs. male)	2.17 (1.19–3.93)	0.011	1.38 (0.68–2.79)	0.37
Gastrectomy (no vs. yes)	1.56 (0.95–2.57)	0.082	1.08 (0.60–1.95)	0.79
Metastasis (synchronous vs. metachronous)	1.14 (0.69–1.88)	0.61		
Ascites amount (high vs. no/low)	1.96 (1.13–3.37)	0.016	1.57 (0.80–3.11)	0.19
ECOG PS ≥ 1 versus 0	2.34 (1.24–4.42)	0.009	1.53 (0.74–3.17)	0.26
Metastasis organs ≥ 2 versus 1	1.45 (0.84–2.48)	0.18	1.20 (0.68–2.11)	0.53
Prior ramucirumab (yes vs. no)	1.01 (0.47–2.15)	0.99		
NLR (≥ 5 vs. < 5)	3.08 (1.71–5.57)	< 0.001	2.48 (1.21–5.10)	0.013
CEA [≥ 5 vs. < 5 (ng/ml)]	1.12 (0.67–1.89)	0.67		
CA19-9 [< 37 vs. ≥ 37 (U/ml)]	1.01 (0.61–1.66)	0.98		
HER2-expression (negative vs. positive)	1.16 (0.64–2.10)	0.62		
Histological type (diffuse vs. intestinal)	1.52 (0.92–2.51)	0.10	1.33 (0.77–2.30)	0.31

ECOG PS Eastern Cooperative Oncology Group performance status, *NLR* blood neutrophil-to-lymphocyte ratio, *HER-2* human epidermal growth factor receptor 2

Table 4 Characteristics of patients with high ascites burden according to ascites response

	Ascites non-responder ($n=16$)	Ascites responder ($n=6$)	P value
Age (median (IQR), years)	58 (48–70)	70 (62–76)	0.14
Gender (male/female)	8/8	6/0	0.05
Gastrectomy [Yes, *n* (%)]	6 (38)	5 (83)	0.15
Metastasis (synchronous/metachronous)	10/6	5/1	0.62
ECOG PS (0/1/2/3)	0/10/6/0	0/6/0/0	0.13
Metastatic site (1/2/3/4)	7/8/0/1	1/3/2/0	0.12
Previous ramucirumab [Yes, *n* (%)]	12 (75)	6 (100)	0.54
Histological type (intestinal/diffuse)	3/13	3/3	0.28
HER2 status [positive, *n* (%)]	1 (6)	1 (17)	0.46
NLR [median (IQR)]	4.3 (2.0–8.8)	1.3 (0.9–3.5)	0.04
CEA (ng/ml) [median (IQR)]	6.9 (3.5–11)	6.9 (3.7–88)	0.71
CA19-9 (U/ml) [median (IQR)]	309 (25–786)	86 (6–5935)	0.54
Alb (g/dl) [median (IQR)]	2.7 (2.4–3.2)	2.6 (2.5–2.8)	0.60
CRP (mg/dl) [median (IQR)]	0.8 (0.2–4.9)	0.4 (0.3–0.7)	0.27
Immune-related adverse events [Yes, *n* (%)]	1 (6)	4 (67)	0.001

ECOG PS Eastern Cooperative Oncology Group performance status, *NLR* blood neutrophil-to-lymphocyte ratio

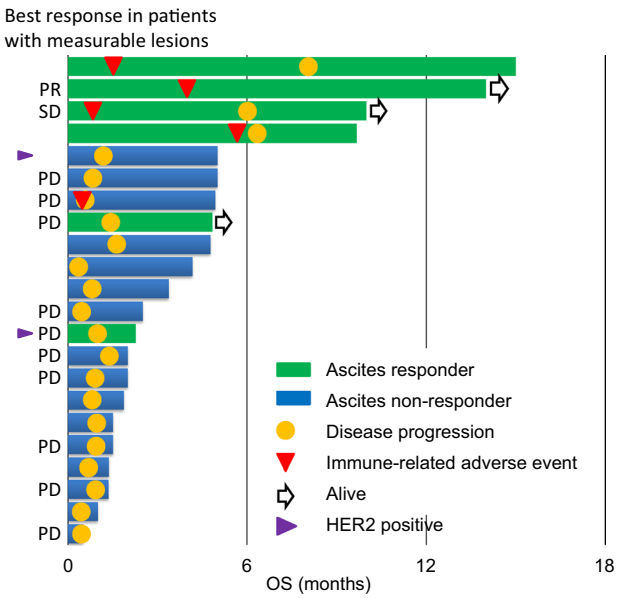

Fig. 2 Overall survival, best tumor/ascites responses and immune-related adverse events for 22 patients with high ascites burden. Each bar represents one patient. PR, partial response; SD, stable disease; PD, progressive disease

grade 5 myocarditis in each one patient with LAB, and were not observed in the patients with HAB. The major reason for discontinuation of treatment was disease progression (both groups > 90%).

Discussion

This study focused on the efficacy and safety of nivolumab monotherapy for AGC with massive ascites and revealed that nivolumab carries a survival benefit (with similar irAEs risk) in some HAB and LAB patients. Although treatment and management for AGC with HAB is complicated by a short OS (median 2.5 months), ascites burden improved in 27% of patients with HAB and OS was substantially prolonged with nivolumab. In addition, we found two clinical factors (NLR and irAEs) associated with the efficacy of nivolumab. These findings present nivolumab as a hopeful option for the management for AGC with HAB.

Interestingly, NLR was an independent prognostic factor and responsive patients in the HAB group had low NLR scores in line with reports that baseline NLR before start of immune checkpoint inhibitors is a predictive factor for OS and PFS in various cancers [14–18]. In our study, none of the patients with high NLR (> 5.0) responded to nivolumab in the HAB group. This finding hints at the ability to screen non-responders to nivolumab but there were a considerable number of patients who did not respond to nivolumab despite having low NLR. NLR may thus be insufficient in some comorbid cases as it is a simple inflammatory biomarker influenced by bacterial infection and disease progression. Further studies are needed for the clinical use of NLR as a response predictor to nivolumab.

Next, ascites responders showed a higher incidence of irAEs than non-responders. The incidence of overall irAEs was not significantly different between the HAB and LAB groups and were comparable to those of the ATTRAC

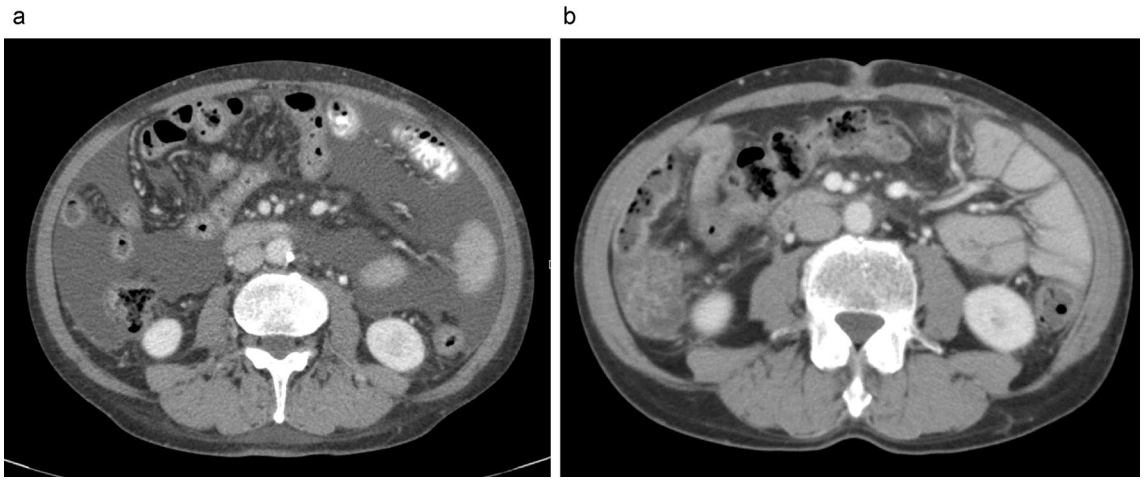

Fig. 3 Representative radiological findings of effective case in a patient with HAB. A 66-year-old man treated with nivolumab as third-line therapy for advanced gastric cancer with massive ascites. **a** Before nivolumab treatment. **b** After 3 courses of nivolumab

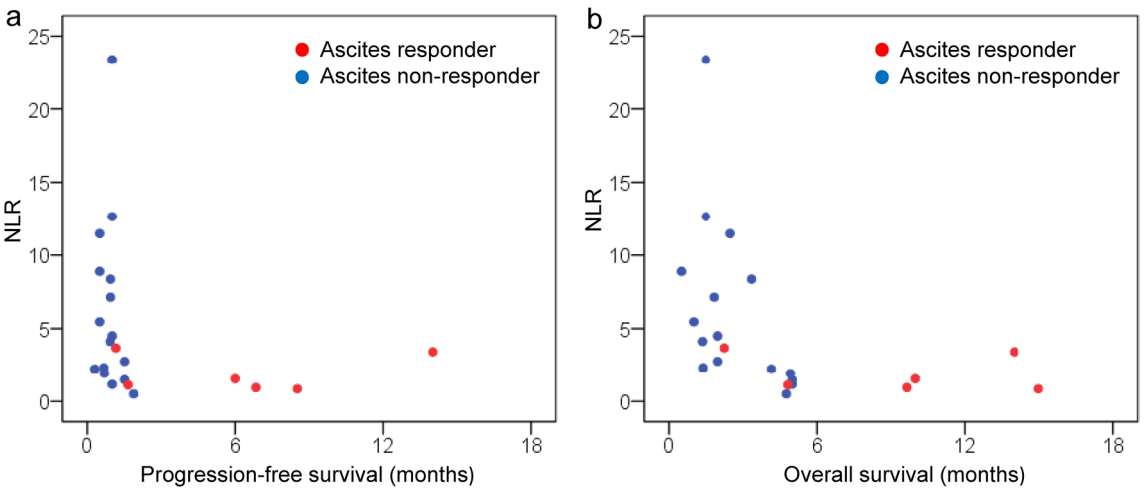

Fig. 4 Relationship between survival and blood neutrophil-to-lymphocyte ratio (NLR) in patients with high ascites burden by ascites response. **a** Progression-free survival and NLR. **b** Overall survival and NLR

TION-2, although a grade 5 myocarditis event was observed in one patient with LAB. Several studies have shown a close correlation between the development of irAEs and better treatment efficacy of PD-1 inhibitors in various cancers, including AGC [19–21]. This indicates that patient symptoms associated with cancer progression from irAEs are important and special attention must be paid to irAEs and tumor response to nivolumab.

Chemotherapy is not indicated for patients with PS 2, massive ascites, and inadequate oral intake [9]. The patients with HAB easily shift to such a state during the treatment. In our study, half of the patients with HAB failed the nivolumab treatment within two courses (4 weeks) and chose best supportive care thereafter. On the other hand, among seven patients who could receive subsequent chemotherapies, six patients were ascites responders. These results suggested that there were few chances for the next chemotherapy in patients with HAB, unless some response to nivolumab was obtained. Once they responded to nivolumab, the efficacy continued for a relatively long term, and the chance for subsequent chemotherapy was expected. Recently, it has been reported that the subsequent chemotherapy after immune checkpoint inhibitors may be more effective because of the sensitized immune system [22]. These ascites responders might have a further survival benefit from the subsequent chemotherapy.

With regard to other characteristics, ascites responders appeared to have intestinal-type tumors more frequently than non-responders in the HAB group (50% vs. 19%), although these differences were not statistically

Table 5 Immune-related adverse events

	No or low ascites burden[a] ($n=50$)		High ascites burden ($n=22$)	
	All grades	Grade ≥3	All grades	Grade ≥3
Hyperthyroidism	1	0	1	0
Hypothyroidism	2	0	1	0
Hypopituitarism	1	0	1	0
Interstitial lung disease	1	0	0	0
Infusion Reaction	1	0	1	0
Rash	1	0	0	0
Arthritis	0	0	1	0
Asthma	1	0	0	0
Myocarditis	1	1[b]	0	0
Total, *n* (%)	9 (18)		5 (23)	

[a]Low ascites burden means localized ascites in the pelvic cavity or hepatic surface

[b]Grade 5

significant. In the sub-analyses of the ATTRACTION-2 study, nivolumab demonstrated a favorable trend of OS for patients with intestinal-type AGC (HR: 0.59) compared to diffuse-type AGC (HR: 0.82) [12]. According to The Cancer Genome Atlas, genomic alterations are less recognized in the diffuse than intestinal type [23, 24]. Thus, PD-1 inhibitors would benefit patients whose tumors have high mutational burdens encoding potential neoantigens [25]. A previous study also reported that high microsatellite instability (MSI) was more common in intestinal-type than diffuse-type tumors [26]. These data may suggest an association between response to nivolumab and the histological type of AGC.

Our study had some limitations. First, the study was retrospective and had a small sample size but our real-world data reliability was supported as our response rate and median OS (16% and 5.3 months) in the LAB group were comparable to those (11% and 5.2 months) in the nivolumab arm of the ATTRACTION-2 study. Second, our study did not assess histological features, such as PD ligand-1 expression, Epstein-Barr virus positivity, and MSI, which were reported to be associated with response to PD-1 inhibitors [27, 28]. Further studies including these features will be needed. Third, we used 5.0 as the NLR cut-off value in this study. The cut-off values for NLR in patients who received nivolumab ranged from 3.0 to 5.0 in previous studies [29–31] and the optimal cut-off value of NLR has not yet been determined. A large-scale investigation should be planned to address these issues.

Conclusion

AGC patients with massive ascites generally have poor prognosis compared to those without ascites, reflecting poorer PS. However, nivolumab demonstrated a durable response in some patients with massive ascites. Considering clinically acceptable toxicities, nivolumab would be a recommended option for these patients.

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Compliance with ethical standards

Conflict of interest HS, TY, AS, SU, YY and TM declare that they have no conflict of interest. IH reports grants and personal fees from Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb Co., personal fees from Eli Lilly Japan K.K., Asahi Kasei Pharma Corp., and grants from Takeda Pharmaceutical Co., Ltd., unrelated to the present study.

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