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Regular Article

Impact of Immune-Related Adverse Events on Prognosis in Advanced or Recurrent Gastric Cancer Patients Receiving Nivolumab Monotherapy as Third-Line or Later Treatment: A Survey Study

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This retrospective study examined patients with advanced or recurrent gastric cancer who received nivolumab monotherapy as a third-line or later treatment at Saitama Cancer Center (Saitama, Japan) between January 2018 and June 2022. The aim was to assess the incidence of immune-related adverse events (irAEs) and explore their association with patient prognosis. Patients who experienced Grade 1 or higher irAEs, as defined by the Common Terminology Criteria for Adverse Events version 5.0, were categorized into the irAE group, whereas those without irAEs comprised the non-irAE group. Among the 134 patients analyzed, 38 (28.4%) developed irAEs, with skin disorders and hypothyroidism being the most common. Overall survival (OS) was significantly longer in the irAE group (median OS: 13.23 months; 95% confidence interval [CI]: 6.94–24.83) than in the non-irAE group (median OS: 4.83 months; 95% CI: 3.76–5.63) ($p < 0.001$). Significant differences were also observed between the two groups in terms of primary tumor resection and disease stage ($p < 0.05$). Multivariate analysis identified the presence of irAEs (hazard ratio [HR]: 0.23) and subsequent treatments after nivolumab (HR: 0.29) as favorable prognostic factors. Conversely, elevated alkaline phosphatase levels were associated with poorer outcomes (HR: 1.64) ($p < 0.001$). These findings suggest that the development of irAEs during nivolumab monotherapy may be linked to improved survival outcomes in patients with advanced or recurrent gastric cancer.

Key words nivolumab, immune checkpoint inhibitor, immune-related adverse events, gastric cancer

INTRODUCTION

Nivolumab is a human IgG4 monoclonal antibody targeting programmed cell death protein 1 (PD-1). By blocking the interaction between PD-1 and its ligand PD-L1, nivolumab reactivates antigen-specific T cells that have become unresponsive to cancer cells, thereby exerting antitumor effects.[1,2] In Japan, it is approved for the treatment of various cancers, including melanoma, non-small cell lung cancer (NSCLC), and gastric cancer, and is considered a cornerstone of current cancer therapy.

Unlike traditional cytotoxic agents, immune checkpoint inhibitors (ICIs) such as nivolumab are less likely to cause typical side effects like nausea, skin disorders, and fatigue; however,, they can lead to immune-related adverse events (irAEs) by activating self-reactive T cells that attack healthy tissues.[3,4] Although the side effects of conventional anticancer drugs often negatively impact prognosis by reducing patients' activities of daily living (ADLs) and quality of life, irAEs present a different clinical challenge.[5-10] Serious irAEs may also impair ADLs and quality of life, making it difficult to decide whether to continue treatment. Nivolumab can be used in three ways depending on the treatment modality: (1) in combination with cytotoxic agents; (2) in combination with other ICIs; and (3) as a single agent. To more clearly evaluate the adverse effects specific to nivolumab, assessing irAEs during monotherapy is preferable, as the absence of other drugs eliminates confounding variables. Notably, irAEs can occur unpredictably in terms of timing and affected organs, and may even arise after discontinuation or previous use of ICIs.[11] Given the limited data on irAEs in gastric cancer compared with other malignancies, we conducted a retrospective study of patients with gastric cancer treated with nivolumab monotherapy and no prior ICI exposure.[12-14] This study aimed to better understand the relationship between irAE occurrence and patient prognosis, and to contribute to the growing body of evidence in this area.

MATERIALS AND METHODS

Patients and Study Design This retrospective study analyzed the medical records of patients with gastric cancer who received nivolumab (OPDIVO®) monotherapy as third-line or

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later-line chemotherapy at Saitama Cancer Center (Saitama, Japan) between January 2018 and June 2022. The aim of this study was to evaluate the incidence of irAEs and their impact on patient prognosis.

Survey Items The following baseline characteristics were collected: age, sex, dates of nivolumab initiation and discontinuation, date of death, line of therapy at nivolumab initiation, presence and onset of irAEs, alkaline phosphatase (ALP) levels, number of metastatic sites, Eastern Cooperative Oncology Group (ECOG) performance status, whether the primary tumor was surgically resected, post-nivolumab treatment stage, and neutrophil-to-lymphocyte ratio (NLR).[15-17] Patients were excluded if they had a history of treatment with other ICIs or investigational agents, or if they were under 18 years of age. irAEs were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0. Events classified as Grade 1 or higher were considered irAEs. The primary endpoints of this study were overall survival (OS) and progression-free survival (PFS), whereas prognostic factors were evaluated as secondary endpoints.

Ethics This study was approved by the Institutional Review Board of Saitama Cancer Center (Approval No. 1761; approved on January 24, 2024).

Statistical Analysis All statistical analyses were conducted using JMP Student Edition 18 (SAS Institute, Cary, NC, USA). Fisher's exact test was used to compare baseline characteristics between the irAE and non-irAE groups. OS was analyzed using the Kaplan–Meier method, and differences were assessed with the log-rank test. Cox proportional hazards regression analysis was used to identify prognostic factors. p-values < 0.05 were used to indicate statistical significance.

RESULTS

Baseline Clinical Characteristics Among the 134 patients included in the analysis, 38 (28.4%) experienced irAEs, whereas 96 did not. Fisher's exact test revealed significant differences between the irAE and non-irAE groups in terms of primary tumor resection status and disease stage or recurrence (Table 1).

Characteristics of irAEs Details of irAEs are summarized in Table 2. A total of 47 irAEs were observed in 38 out of 134 patients. The most frequently reported irAEs were skin disorders (17 cases), followed by hypothyroidism (11 cases) and interstitial lung disease (5 cases). Severe irAEs (Grade 3 or higher) occurred in 14 patients. Notably, patients continued nivolumab treatment even after the onset of irAEs.

OS and PFS Figure 1 shows the OS curves for the irAE and non-irAE groups. The median OS was significantly longer in the irAE group at 13.23 months (95% confidence interval [CI]: 6.94–24.83), compared with 4.83 months in the non-irAE group (95% CI: 3.76–5.63) ($p < 0.001$). Similarly, as shown in Figure 2, the median PFS was 4.86 months (95% CI: 2.93–9.90) in the irAE group and 1.60 months (95% CI: 1.20–1.83) in the non-irAE group, with the irAE group demonstrating significantly prolonged PFS ($p < 0.001$).

Prognosis Factors Cox proportional hazards analysis identified the occurrence of irAEs (HR: 0.30) and subsequent treatments after nivolumab (HR: 0.33) as factors associated with improved OS. Conversely, elevated ALP was linked to poorer prognosis (HR: 1.75). NLR, with a cutoff value of 5, was not a significant predictor of OS in this study (Table 3).

Table 1. Clinical Characteristics of Patients in the irAE and Non-irAE Groups

	Total (n = 134)	irAE group (n = 38)	Non-irAE group (n = 96)	p-value
Age, years, n (%)				0.054
<65	69 (51.5)	7 (18.4)	34 (35.4)	
≥65	65 (48.5)	31 (81.6)	62 (64.6)	
Sex, n (%)				0.182
Male	101 (75.3)	32 (84.2)	69 (71.9)	
Female	33 (24.7)	6 (15.8)	27 (28.1)	
ECOG PS, n (%)				0.041
0	42 (31.3)	17 (44.7)	25 (26.0)	
≥1	92 (68.7)	21 (55.3)	71 (74.0)	
Number of metastases, n (%)				0.126
<2	68 (50.7)	15 (39.5)	53 (55.2)	
≥2	66 (49.3)	23 (60.5)	43 (44.8)	
Resection of the primary lesion, n (%)				0.049
Yes	84 (62.7)	20 (52.6)	64 (66.7)	
No	66 (49.3)	18 (47.4)	32 (33.3)	
Stage, n (%)				0.031
IV	106 (79.1)	25 (65.8)	81 (84.4)	
Relapse	28 (20.9)	13 (34.2)	15 (15.6)	
ALP, n (%)				0.565
Low (<ULN)	79 (59.0)	24 (63.2)	55 (57.3)	
High (≥ULN)	55 (41.0)	14 (36.8)	41 (42.7)	
Post-treatment				0.848
Yes	55 (41.0)	15 (39.5)	40 (41.7)	
No	79 (59.0)	23 (60.5)	56 (58.3)	

All data are reported as medians (min–max ranges) or n (%)
ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; irAE, immune-related adverse event; PS, performance status; ULN, upper limit normal.

Table 2. Symptoms in Patients with irAEs, Including Duplicates

	Total number of cases	≥Grade 3	Treatment continuation
Skin disorders	17	1	14
Hypothyroidism	11	1	8
Pneumonitis	5	2	2
ALP increased	3	2	0
Hypopituitarism	2	1	2
Type 1 diabetes mellitus	2	2	0
Arthritis	2	1	1
Esophagitis	1	1	1
Creatinine increased	1	1	0
Myocarditis	1	1	0
Adrenal insufficiency	1	1	1
Diarrhea	1	0	0

ALP, alkaline phosphatase; irAE, immune-related adverse event.

Table 3. Multivariate Analysis of Risk Factors and Their Relationships with Overall Survival

	Hazard Ratio	95% CI	*p*-value
irAE (+/-)	0.30	0.18–0.49	<0.001
Number of metastases (≥2/<2)	0.61	0.41–0.92	0.017
ECOG PS (≥1/0)	1.40	0.96–2.06	0.079
Resection of the primary lesion (+/-)	0.84	0.51–1.38	0.492
ALP (≥ULN/<ULN)	1.76	1.20–2.57	0.003
Post-treatment (+/-)	0.33	0.22–0.49	<0.001
NLR (>5/5)	0.98	0.60–1.57	0.943

Logistic regression analysis (*$p < 0.05$).
ALP, alkaline phosphatase; ULN, upper limit normal; ECOG, Eastern Cooperative Oncology Group; irAE, immune-related adverse event; NLR, neutrophil-to-lymphocyte ratio; PS, performance status; CI, confidence interval.

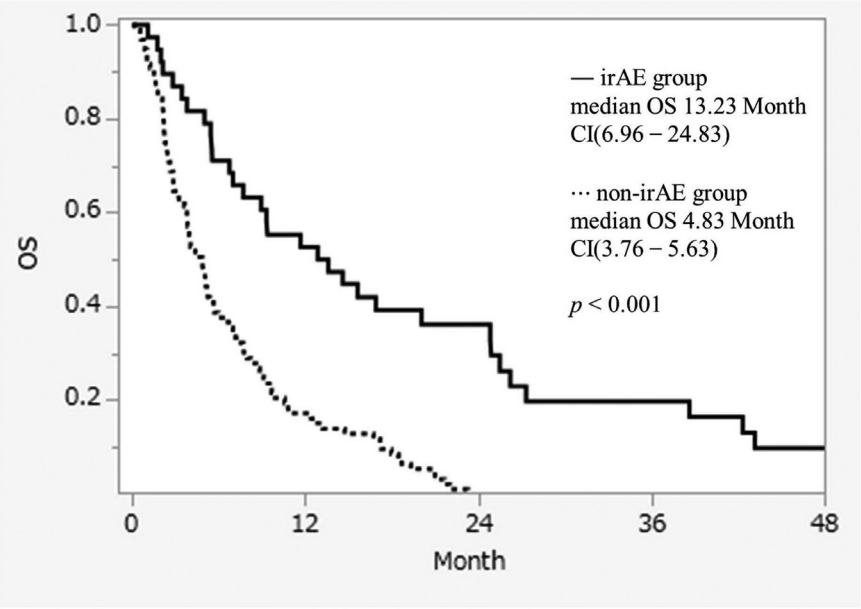

Fig. 1. Kaplan–Meier Curve of the Overall Survival (OS) for the Immune-Related Adverse Event (irAE) and Non-irAE Groups. CI, confidence interval.

DISCUSSION

Unlike the side effects of cytotoxic agents, irAEs are unpredictable in both timing and affected organs, and they can occasionally be severe.[7] In this study, 38 of the 134 patients experienced irAEs, reaffirming the need for clinical vigilance and preparedness, as a notable proportion of patients will develop these events. Although irAEs occurred in 38 patients, treatment was continued in 25 of them. Prior research has shown that approximately 28.8% of patients who resumed treatment after discontinuation due to irAEs experienced recurrence of similar adverse events, highlighting the need for caution in treatment continuation.[18] The most frequent site of irAE onset in this cohort was the skin (17 cases), but only one was Grade 3 or higher. Treatment was continued in 14 of these 17 patients, suggesting that most skin-related irAEs were mild and manageable. Conversely, irAEs such as hepatic dysfunction, Type 1 diabetes mellitus, renal impairment, myocarditis, and diarrhea were less common but more severe (Grade 3 or higher), often necessitating discontinuation of therapy. On the other hand, previous reports indicate no correlation between the type of irAE and prognosis. Furthermore, favorable safety profiles and efficacy have been reported even in patients who received ICI re-treatment after developing severe immune-related adverse events.[19] Therefore, if appropriate immune-related adverse event management is possible, sustained treatment efficacy can be expected.

The primary outcome, OS, was notably longer in the irAE group (median OS: 13.23 months, 95% CI: 6.96–24.83) compared to the non-irAE group (median OS: 4.86 months, 95% CI: 3.76–5.63), as shown in Fig. 1. This OS in the irAE group surpasses that reported in the ATTRACTION-2 trial (5.26 months),[20] which may be attributable to the availability of newer post-treatment options such as trifluridine/tipiracil and trastuzumab deruxtecan, not included in the earlier study.[21,22] PFS also showed significant improvement in the irAE group (Fig. 2). Although irAEs are adverse events, a growing body of evidence suggests a positive correlation between their occurrence and better prognosis in gastric cancer, as well as in NSCLC and melanoma. In our multivariate analysis, both the presence of irAEs and the administration of post-nivolumab treatment were favorable prognostic indicators for patients undergoing third-line or later treatment. Conversely, elevated ALP ≥Upper Limit Normal (ULN) and the presence

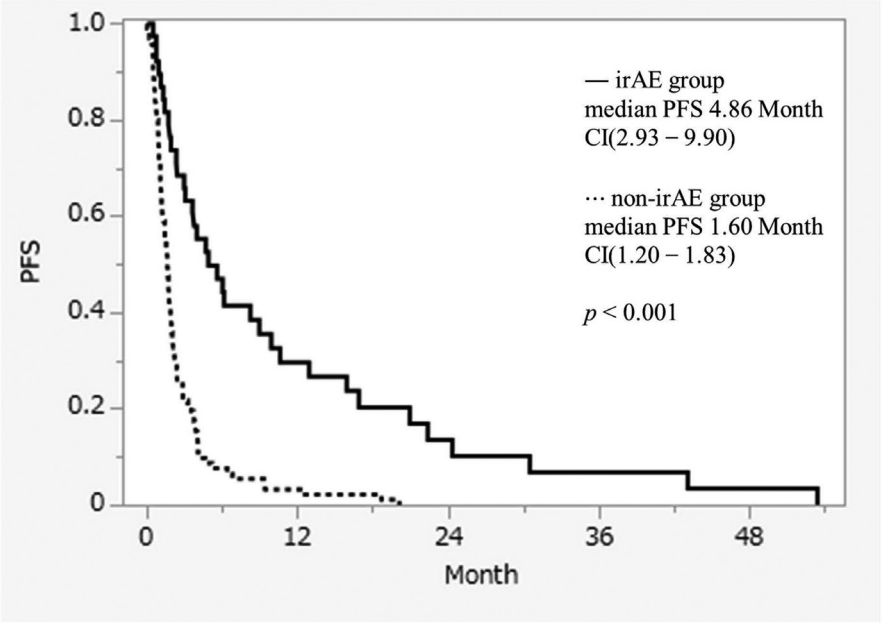

Fig. 2. Kaplan–Meier Curve of the Progression-Free Survival (PFS) for the Immune-Related Adverse Event (irAE) and Non-irAE Groups. CI, confidence interval.

of two or more metastatic sites were associated with poorer outcomes. Notably, NLR, with a cutoff value of 5, was not associated with improved prognosis in our study.[15,23,24] Prior research suggests that it is a marker for the severity of irAEs rather than survival.[17] Another key consideration is the availability of post-treatment options following nivolumab therapy. Access to subsequent therapies appears to be closely linked to prolonged OS. However, a limitation of this study is the inability to determine whether patients' eligibility for post-treatment was influenced solely by clinical indications or also by broader physical, social, and economic factors, such as performance status (PS), financial constraints, or access to healthcare facilities. As of August 2025, the approval of zolbetuximab for patients with claudin-18 isoform 2-positive recurrent or advanced gastric cancer presents additional promise for improved outcomes.[25-27] In line with previous findings, high ALP was again confirmed as a negative prognostic marker, reinforcing its clinical utility in evaluating patients with advanced gastric cancer.[16]

The strengths of this study include the accumulation of valuable data on the correlation between nivolumab monotherapy and irAE occurrence specifically in gastric cancer patients receiving third-line or later treatment—an area where limited research exists.[13,28,29] Furthermore, this study focused solely on patients treated with nivolumab alone, excluding those with prior ICI use, allowing for a clearer evaluation of irAEs without confounding from combination therapies. These methodological decisions strengthen the reliability of our findings.

irAEs are believed to stem from excessive autoimmune responses triggered by the activation of normal immune cells.[3,4] Consequently, their occurrence may signal immune system engagement and, to some extent, antitumor efficacy. However, moderate to severe irAEs can lead to significant declines in organ function, quality of life, and may even be life-threatening. Early recognition and appropriate management are therefore essential. Considering the variable clinical presentations and severity of irAEs depending on the affected organ and grade, timely diagnosis through both routine examinations and patient-reported symptoms is critical. Encouraging patients to understand and communicate the onset of specific symptoms can facilitate earlier detection and intervention. As treatment options for gastric cancer continue to expand, further accumulation of clinical data will be crucial for optimizing outcomes and ensuring safe, effective care.

Conflict of interest The authors declare no conflict of interest.

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