J Gastric Cancer. 2023 Jan;23(1):207-223
https://doi.org/10.5230/jgc.2023.23.e10
pISSN 2093-582X·eISSN 2093-5641

Journal of Gastric Cancer

Review Article

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Recent Progress in Immunotherapy for Gastric Cancer

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OPEN ACCESS

Received: Oct 24, 2022
Revised: Dec 15, 2022
Accepted: Jan 2, 2023
Published online: Jan 31, 2023

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Funding
This article was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (Grant No. 2021R1A2C2007430), the Institute of Smart Healthcare Innovative Medical Sciences, a Brain Korea 21 four program, Seoul National University.

ABSTRACT

Gastric cancer (GC) is the fourth leading cause of cancer-related deaths worldwide. Under the standard of care, patients with advanced GC (AGC) have a median survival time of approximately 12–15 months. With the emergence of immunotherapy as a key therapeutic strategy in medical oncology, relevant changes are expected in the systemic treatment of GC. In the phase III ATTRACTION-2 trial, nivolumab, a monoclonal anti-programmed cell death 1 (PD-1) antibody, as a third- or later-line treatment improved overall survival (OS) compared with placebo in patients with AGC. Furthermore, nivolumab in combination with 5-fluorouracil and platinum as a first-line treatment improved OS in patients with human epidermal growth factor receptor-2 (HER2)-negative AGC in the global phase III CheckMate-649 study. Another anti-PD-1 antibody, pembrolizumab, in combination with trastuzumab and cytotoxic chemotherapy as a first-line treatment, significantly improved the overall response rate in patients with HER2-positive AGC. Therefore, immune checkpoint inhibitors (ICIs) are essential components of the current treatment of GC. Subsequent treatments after ICI combination therapy, such as ICI rechallenge or combination therapy with agents having other modes of action, are being actively investigated to date. On the basis of the success of immunotherapy in the treatment of AGC, various clinical trials are underway to apply this therapeutic strategy in the perioperative and postoperative settings for patients with early GC. This review describes recent progress in immunotherapy and potential immunotherapy biomarkers for GC.

Keywords: Gastric cancer; Immunotherapy; Immune checkpoint inhibitors; Chemotherapy; Biomarkers

INTRODUCTION

Gastric cancer (GC) is the fifth most frequently diagnosed malignant tumor and the fourth leading cause of cancer-related deaths worldwide [1]. The incidence of GC is higher in eastern Asia, including Korea, than in Western countries [1,2]. Curative treatment involves surgical resection followed by adjuvant chemotherapy according to pathologic stage. Although Korea has a high rate of early detection of GC using endoscopy through a national cancer surveillance program [2], some cases are still diagnosed at an advanced stage. Patients

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: Y.J., O.D.Y.; Data curation: Y.J., O.D.Y.; Funding acquisition: O.D.Y.; Supervision: K.T.Y., O.D.Y.; Writing - original draft: Y.J., O.D.Y.; Writing - review & editing: Y.J., K.T.Y., O.D.Y.

with initially unresectable or recurrent GC have a poor prognosis, with an overall survival (OS) time of approximately 12–15 months [3,4]. Thus, patients with advanced GC (AGC) have unmet medical needs.

Immunotherapy is considered an effective therapeutic strategy in medical oncology. Immune checkpoint inhibitors (ICIs), which target pathways involved in immune regulation, help break the cycle of immune tolerance and allow T-cell recognition against tumor cells, thereby increasing the immune response of immune cells to cancer and inhibiting the immune evasion induced by cancer cells [5,6]. GC is a malignancy associated with a high somatic mutational burden [7], which is a potential marker for predicting response to ICIs. Moreover, positive expression of programmed cell death ligand 1 (PD-L1) has been observed in 25%–65% of patients with GC, and genomic alterations and epigenetic regulations of the *PD-L1* gene have also been observed in GC [8,9]. Thus, the application of ICIs is essential to improve survival outcomes in patients with AGC.

ICIs have emerged as "game changers" in the treatment of various cancers [5,10-12]. In GC, ICI monotherapy has been demonstrated to improve survival in the third- or later-line setting, leading to its establishment as a standard treatment [13,14]. Recently, the phase III CheckMate-649 trial showed that nivolumab in combination with cytotoxic chemotherapy improved OS compared with chemotherapy alone as the first-line treatment for human epidermal growth factor receptor-2 (HER2)-negative AGC [15,16]. Furthermore, according to a preplanned interim analysis of the KEYNOTE-811 trial, pembrolizumab in combination with trastuzumab and cytotoxic chemotherapy increased the overall response rate (ORR) in patients with HER2-positive AGC [17,18]. The addition of ICIs to the existing standard first-line treatment has become a new systemic treatment strategy for AGC. Subsequent treatments after ICI combination therapy, such as ICI rechallenge or combination therapy with agents having other modes of action, are being actively investigated to date [19-21]. On the basis of the success of immunotherapy in the treatment of AGC, various clinical trials are underway to apply this therapeutic strategy in the perioperative and postoperative settings for patients with early GC [22,23].

Potential biomarkers for predicting the efficacy of ICIs have been discussed, including Epstein–Barr virus (EBV) positivity, microsatellite instability (MSI), and PD-L1 expression. Patients with MSI-high or EBV-positive GC are known to respond well to ICIs [24-26]. Another well-known biomarker, PD-L1, positively correlates with the response to pembrolizumab in AGC [14,27]. In addition, according to the CheckMate-649 trial, patients with higher PD-L1 expression gain better clinical benefits from nivolumab [15].

In this review, we focus on recent updates on immunotherapy for GC and potential predictive biomarkers that reflect the efficacy of ICIs in the treatment of AGC.

APPLICATION OF IMMUNOTHERAPY IN GC

Table 1 summarizes the major clinical trials on immunotherapy in patients with AGC. Six trials evaluated ICI monotherapy; 9 trials, ICIs in combination with cytotoxic chemotherapy; 3 trials, ICIs in combination with HER2-targeted agents; 2 trials, dual ICI combination therapy; and 2 trials, ICIs in combination with anti-angiogenic agents.

https://doi.org/10.5230/jgc.2023.23.e10

Table 1. Pivotal clinical trials on immunotherapy for gastric cancer

Line	Target	Trial	Reference	Phase	Patient selection	Arms	Primary endpoint	Results	OS			PFS			ORR	
									Median	HR	P-value	Median	HR	P-value	%	P-value
Monotherapy																
3rd or later	PD-1	ATTRACTION-02	[13]	III	All	Nivolumab	OS	Positive	5.26	0.63	<0.0001	1.61	0.60	<0.0001	11.2	-
		(NCT02267343)				Placebo			4.14			1.45			0.0	
3rd or later	PD-1	KEYNOTE-059	[14]	II	All	Pembrolizumab	ORR (all/CPS ≥1)	Positive	5.60	-	-	2.00	-	-	11.6	-
		(NCT02335411)			CPS ≥1	Pembrolizumab			5.80	-	-	2.10	-	-	15.5	-
3rd	PD-L1	JAVELIN Gastric 300	[28]	III	All	Avelumab	OS	Negative	4.60	1.10	0.81	1.40	1.73	>0.99	2.2	-
		(NCT02625623)				TPC			5.00			2.70			4.3	
2nd	PD-1	KEYNOTE-061	[27]	III	CPS ≥1	Pembrolizumab	OS/PFS	Negative	9.10	0.82	0.0421	1.50	1.27	-	16.0	-
		(NCT02370498)				Paclitaxel			8.30			4.10			14.0	
1st	PD-1	KEYNOTE-062	[29]	III	CPS ≥1	Pembrolizumab	OS (CPS ≥1, 10)	Negative	10.60	0.91	-	2.00	1.66	-	14.8	-
		(NCT02494583)				FP/XP	PFS (CPS ≥1)		11.10			6.40			37.2	
					CPS ≥10	Pembrolizumab			17.40	0.69	-	2.90	1.10	-	25.0	-
						FP/XP			10.80			6.10			37.8	
1st maintenance	CTLA-4	CA184-162	[36]	II	All	Ipilimumab	Immune-related PFS	Negative	12.70	-	-	2.72	1.59	0.034	-	-
		(NCT01585987)				Best supportive care (allowed to continue chemotherapy)			12.10			4.90			-	
1st maintenance	PD-L1	JAVELIN Gastric 100	[37]	III	HER2 (–)	FOLFOX/CAPOX → avelumab	OS	Negative	10.40	0.91	0.1779	3.20	1.04	-	13.3	-
		(NCT02625610)				FOLFOX/CAPOX			10.90			4.40			14.4	
Chemotherapy combination																
1st	PD-1	KEYNOTE-062	[29]	III	CPS ≥1	FP/XP + pembrolizumab	OS (CPS ≥1, 10)	Negative	12.50	0.85	0.05	6.90	0.84	0.04	48.6	-
		(NCT02494583)				FP/XP	PFS (CPS ≥1)		11.10			6.40			37.2	
					CPS ≥10	FP/XP + pembrolizumab			12.30	0.85	0.16	5.70	0.73	-	53.0	-
						FP/XP			10.80			6.10			38.0	
1st	PD-1	ATTRACTION-04	[30]	III	HER2 (–)	CAPOX/SOX + nivolumab	OS/PFS	Positive	17.45	0.90	0.26	10.45	0.68	0.0007	57.0	-
		(NCT02746796)				CAPOX/SOX + placebo			17.15			8.34			48.0	
1st	PD-1	CheckMate-649	[15]	III	All	FOLFOX/CAPOX + nivolumab	OS/PFS (CPS ≥5)	Positive	13.80	0.80	0.0002	7.70	0.77	-	58.0	-
		(NCT02872116)				FOLFOX/CAPOX			11.60			6.90			46.0	
					CPS ≥1	FOLFOX/CAPOX + nivolumab			14.00	0.77	<0.0001	7.50	0.74	-	60.0	-
						FOLFOX/CAPOX			11.30			6.90			46.0	
					CPS ≥5	FOLFOX/CAPOX + nivolumab			14.40	0.71	<0.0001	7.70	0.68	<0.0001	60.0	-
						FOLFOX/CAPOX			11.10			6.05			45.0	
1st	PD-1	RATIONALE-305	[31]	III	HER2 (–)	FP/CAPOX + tislelizumab	OS/PFS	Ongoing	-	-	-	-	-	-	-	-
		(NCT03777657)				FP/CAPOX + placebo			-			-			-	
1st	PD-1	KEYNOTE-859	[32]	III	HER2 (–)	FP/CAPOX + pembrolizumab	OS	Ongoing	-	-	-	-	-	-	-	-
		(NCT03675737)				FP/CAPOX + placebo			-			-			-	
Adjuvant	PD-1	ATTRACTION-05	[39]	III	All	S-1 or CAPOX + nivolumab	RFS	Ongoing	-	-	-	-	-	-	-	-
		(NCT03006705)				S-1 or CAPOX + placebo			-			-			-	
Perioperative	PD-1	KEYNOTE-585	[22]	III	All	XP/FP/FLOT + pembrolizumab	OS/EFS/pCR	Ongoing	-	-	-	-	-	-	-	-
		(NCT03221426)				XP/FP/FLOT + placebo			-			-			-	
Perioperative	PD-1	MATTERHORN	[40]	III	All	FLOT + durvalumab	EFS	Ongoing	-	-	-	-	-	-	-	-
		(NCT04592913)				FLOT + placebo			-			-			-	

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https://doi.org/10.5230/jgc.2023.23.e10

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Table 1. (Continued) Pivotal clinical trials on immunotherapy for gastric cancer

Line	Target	Trial	Reference	Phase	Patient selection	Arms	Primary endpoint	Results	OS			PFS			ORR	
									Median	HR	P-value	Median	HR	P-value	%	P-value
HER2-targeted agent combination																
1st	PD-1	KEYNOTE-811	[18]	III	HER2 (+)	FP/CAPOX + trastuzumab + pembrolizumab	OS/PFS	Ongoing	-	-	-	-	-	-	74.4	0.00006
		(NCT03615326)				FP/CAPOX + trastuzumab			-			-			51.9	
1st	PD-1	HERIZON-GEA-01	[34]	III	HER2 (+)	FP/CAPOX + zanidatamab + tislelizumab	OS/PFS	Ongoing	-	-	-	-	-	-	-	-
		(NCT05152147)				FP/CAPOX + zanidatamab			-			-			-	
						FP/CAPOX + trastuzumab			-			-			-	
1st	PD-1/ LAG-3	MAHOGANY (NCT04082364)	[33,35]	II/III	HER2 (+) CPS ≥1	Margetuximab + retifanlimab	ORR	Ongoing	NR	-	-	6.40	-	-	53.0	-
Dual immunotherapy combination																
1st	PD-1/ CTLA-4	CheckMate-649 (NCT02872116)	[16]	III	All	Nivolumab + ipilimumab	OS/PFS (CPS ≥5)	Negative	11.70	0.91	-	2.80	1.66	-	23.0	-
						FOLFOX/CAPOX			11.80			7.10			47.0	
					CPS ≥5	Nivolumab + ipilimumab			11.20	0.89	0.2302	2.80	1.42	-	27.0	-
						FOLFOX/CAPOX			11.60			6.30			47.0	
1st	PD-1/ CTLA-4	ATTRACTION-06 (NCT05144854)	[41]	III	HER2 (–)	SOX/CAPOX + nivolumab + ipilimumab	OS	Ongoing	-	-	-	-	-	-	-	-
						SOX/CAPOX			-			-			-	
Anti-angiogenic inhibitor combination																
3rd or later	PD-1	LEAP-005 (NCT03797326)	[20]	II	All	Pembrolizumab + lenvatinib	ORR	Ongoing	5.90	-	-	2.50	-	-	10.0	-
1st maintenance	PD-1	LEAP-015	[38]	III	HER2 (–)	FOLFOX/CAPOX + pembrolizumab + lenvatinib	OS/PFS (all/CPS ≥1)	Ongoing	-	-	-	-	-	-	-	-
		(NCT04662710)				FOLFOX/CAPOX			-			-			-	

PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand 1; CTLA-4 = cytotoxic T lymphocyte- associated protein 4; CPS = combined positivity score; HER2 = human epidermal growth factor receptor-2; TPC = treating physician's choice; FP = 5-fluorouracil/cisplatin; XP = capecitabine/cisplatin; FOLFOX = 5-fluorouracil/oxaliplatin; CAPOX = capecitabine/oxaliplatin; SOX = S-1/ oxaliplatin; FLOT = 5-fluorouracil/docetaxel/oxaliplatin; OS = overall survival; PFS = progression-free survival; ORR = overall response rate; RFS = relapse-free survival; EFS = event-free survival; pCR = pathologic complete response; HR = hazard ratio; NR = not reached.

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https://doi.org/10.5230/jgc.2023.23.e10

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ICI monotherapy

The ATTRACTION-2 trial was the first randomized, double-blind, placebo-controlled, phase III study to demonstrate the efficacy and safety of nivolumab, a humanized anti-PD-1 monoclonal antibody, as a third- or later-line treatment for patients with AGC [13]. In this study, 439 patients from Korea, Japan, and Taiwan were enrolled without selection based on PD-L1 status and randomly assigned to receive either nivolumab or placebo in a 2:1 ratio. Nivolumab provided an improvement in OS compared with placebo (median OS, 5.26 vs. 4.14 months, hazard ratio [HR] 0.63, P<0.001) [13]. In addition, an OS benefit was observed regardless of tumor PD-L1 expression [42]. The median OS of patients who showed complete or partial response to nivolumab was 26.7 months (95% confidence interval [CI], 21.65–38.57), indicating a durable response [42,43]. In the long-term follow-up in ATTRACTION-2, the benefit was well maintained among the responders. In this population, the OS rate at 1, 2, and 3 years was 87.1%, 61.3%, and 35.5%, respectively [42,43]. In terms of progression-free survival (PFS), nivolumab demonstrated efficacy compared with placebo (median PFS, 1.61 vs. 1.45 months, HR, 0.60, P<0.001), and the ORR was 11.2% in the nivolumab group and 0% in the placebo group [13]. On the basis of these results, nivolumab has been approved for the treatment of AGC in later-line settings in Asian countries.

The KEYNOTE-059 study was an open-label, nonrandomized, 3-cohort, phase II trial in which 259 patients were enrolled in cohort 1 to investigate pembrolizumab monotherapy as a third- or later-line treatment for patients with AGC [14]. Pembrolizumab showed similar efficacy to nivolumab (ORR, 11.6%; median OS, 5.60 months [95% CI, 4.3–6.9]; median PFS, 2.00 months [95% CI, 2.0–2.1]) [14]. In this study, PD-L1 positivity was defined as a PD-L1 combined positivity score (CPS) of ≥1, as evaluated using the 22C3 immunohistochemistry assay. In a subgroup analysis, the median OS of PD-L1-positive and PD-L1-negative populations was 5.80 months (95% CI, 4.5–7.9) and 4.90 months (95% CI, 3.4–6.5), respectively. Moreover, the ORR of PD-L1-positive and PD-L1-negative patients who received pembrolizumab was 15.5% (95% CI, 10.1–22.4) and 6.4% (95% CI, 2.6–12.8), respectively. These findings suggest that pembrolizumab is more effective in patients with PD-L1-positive AGC and PD-L1 CPS is a potential predictive marker for selecting patients who are likely to respond well to pembrolizumab [14]. The most common treatment-related adverse events associated with nivolumab and pembrolizumab are pruritus (9.0% and 8.9%), skin rash (6.0% and 8.5%), fatigue (5.0% and 18.9%), and hypothyroidism (3.0% and 7.7%) [13,14].

Immuno-monotherapy vs. cytotoxic chemotherapy

Most studies comparing ICI monotherapy with cytotoxic chemotherapy have not demonstrated the superiority of ICI monotherapy. The JAVELIN Gastric 300 trial was a randomized, open-label, phase III trial that compared avelumab, an anti-PD-L1 monoclonal antibody, with the physician's choice of chemotherapy (e.g., paclitaxel and irinotecan) [28]. A total of 371 patients in the third-line setting were enrolled, and 185 and 186 patients were randomly assigned to the avelumab and chemotherapy arms, respectively. Avelumab failed to improve OS (median OS, 4.60 vs. 5.00 months, HR, 1.1 [95% CI, 0.9–1.4]) and PFS (median PFS, 1.40 vs. 2.70 months, HR, 1.73 [95% CI, 1.4–2.2]) compared with cytotoxic chemotherapy [28]. In a subgroup analysis of OS according to tumor PD-L1 expression, no significant differences were observed between the avelumab and chemotherapy arms [28]. In contrast, the PFS subgroup analysis consistently favored the chemotherapy arm [28].

https://doi.org/10.5230/jgc.2023.23.e10

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In the KEYNOTE-061 trial, a randomized, open-label, phase III study that selected PD-L1-positive patients (PD-L1 CPS ≥1), pembrolizumab did not significantly improve OS compared with paclitaxel as the second-line treatment for AGC (median OS, 9.10 months with pembrolizumab vs. 8.30 months with paclitaxel, HR, 0.82 [95% CI, 0.66–1.03], P=0.042). Pembrolizumab also did not improve PFS compared with paclitaxel (median PFS, 1.50 vs. 4.10 months, HR, 1.27 [95% CI, 1.03–1.57]) [27]. The paclitaxel arm outperformed the pembrolizumab arm at the beginning of treatment. However, the Kaplan-Meier curve for OS crossed at 8 months after randomization. After this crossing of survival curves, the separation in favor of pembrolizumab was sustained, which means that the responses to pembrolizumab were more durable than those to paclitaxel (ORR, 16% vs. 14%; median duration of response, 18.0 months in the pembrolizumab arm [95% CI, 8.3–not estimable] vs. 5.2 months in the paclitaxel arm [95% CI, 3.2–15.3]) [27]. Notably, in a post-hoc subgroup analysis of patients with a PD-L1 CPS of ≥10, pembrolizumab had a more potent efficacy than paclitaxel (HR, 0.64 [95% CI, 0.73–1.32]; median OS, 10.4 months with pembrolizumab vs. 8.0 months with paclitaxel) [27].

The KEYNOTE-062 trial was a randomized, partially blinded, phase III study that investigated pembrolizumab monotherapy or pembrolizumab plus chemotherapy as a first-line treatment for patients with AGC [29]. Patients with HER2-negative AGC with a PD-L1 CPS of ≥1 were enrolled and randomly allocated to pembrolizumab monotherapy, pembrolizumab plus chemotherapy, or placebo plus chemotherapy in a 1:1:1 ratio. Chemotherapy with cisplatin plus 5-fluorouracil and cisplatin plus capecitabine was chosen by the treating physician. When pembrolizumab monotherapy was compared with chemotherapy alone, pembrolizumab was noninferior but not superior to chemotherapy in terms of OS in patients with a PD-L1 CPS of ≥1 (median OS, 10.6 months with pembrolizumab vs. 11.1 months with chemotherapy, HR, 0.91 [99.2% CI, 0.69–1.18; noninferiority margin, 1.2]) [29]. Crossing of the OS curves was observed, as in the KEYNOTE-061 trial. Also similar to the KEYNOTE-061 trial, higher cutoff values of PD-L1 CPS tended to result in better responses to pembrolizumab in the first-line setting of AGC (CPS ≥1: median OS, 10.6 vs. 11.1 months; CPS ≥10: median OS, 17.4 vs. 10.8 months) [29].

Immunotherapy plus chemotherapy vs. cytotoxic chemotherapy

To increase the response to immunotherapy in many cancer types, a combination strategy using cytotoxic agents has been investigated [19,44]. Preclinical studies have demonstrated that many chemotherapeutic agents exert immunomodulatory effects through the following mechanisms: 1) enhanced tumor antigen expression and presentation, 2) downregulation of co-inhibitory molecules and upregulation of co-stimulatory molecules expressed on the surface of tumor cells, and 3) granzyme- and perforin-dependent mechanisms that increase T-cell-facilitated tumor cell lysis [45,46]. In GC, chemotherapy modulates T-cell populations within the tumor microenvironment and transforms the tumor microenvironment toward an immune-responsive state [47].

Recently, the results of pivotal clinical trials that investigated the addition of ICIs to cytotoxic chemotherapy have led to a change in the current standard of care for patients with HER2-negative AGC [15,29,30]. In the KEYNOTE-062 trial, pembrolizumab plus chemotherapy failed to achieve statistically significant improvement in OS and PFS compared with chemotherapy alone (median OS, 12.5 vs. 11.1 months, HR, 0.85, P=0.05; median PFS, 6.9 vs. 6.4 months, HR, 0.84, P=0.04), although the ORR with pembrolizumab plus chemotherapy was higher than that with cytotoxic chemotherapy alone (48.6% vs. 37.2%) [29].

https://doi.org/10.5230/jgc.2023.23.e10

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The global phase III CheckMate-649 trial was a randomized, open-label study that investigated nivolumab plus chemotherapy as a first-line therapy for HER2-negative AGC. The original study design had a 3-arm setting comprising the nivolumab plus chemotherapy, nivolumab plus ipilimumab, and chemotherapy arms, and patients were randomly assigned to each arm in a 1:1:1 ratio. After the enrolment in the nivolumab plus ipilimumab arm was closed, 1,581 patients were enrolled regardless of PD-L1 status and randomly assigned to receive nivolumab plus chemotherapy (789 patients) or placebo plus chemotherapy (792 patients) [15]. The dual primary endpoints were OS and PFS, which were evaluated using a blinded independent central review, in patients with a PD-L1 CPS of ≥5. The hierarchically tested secondary endpoints were OS in patients with a PD-L1 CPS of ≥1 and OS in all randomized patients. In this study, chemotherapy consisted of oxaliplatin plus 5-fluorouracil or oxaliplatin plus capecitabine. The number of patients with a PD-L1 CPS of ≥5 was 955 (60.4%), whereas the numbers of patients with a PD-L1 CPS of 1 to 4 and those negative for PD-L1 were 341 (21.5%) and 285 (18.0%), respectively [15]. The nivolumab plus chemotherapy arm met both primary endpoints (OS, 14.4 vs. 11.1 months, HR, 0.71, P<0.001; PFS, 7.7 vs. 6.05 months, HR, 0.68, P<0.001) in patients with a PD-L1 CPS of ≥5 [15,16]. In patients with a PD-L1 CPS of ≥1, the median OS and PFS of the nivolumab plus chemotherapy and chemotherapy alone arms were 14.0 and 11.3 months (HR, 0.77, P<0.001) and 7.5 and 6.9 months (HR, 0.74), respectively. Moreover, the nivolumab plus chemotherapy combination also provided better OS and PFS than chemotherapy alone in all randomized patients regardless of PD-L1 status (median OS, 13.8 vs. 11.6 months, HR, 0.80, P< 0.001; median PFS, 7.7 vs. 6.9 months, HR, 0.77) [16]. In patients with a PD-L1 CPS of ≥5, the ORR with nivolumab plus chemotherapy was 60% (95% CI, 55–65) and that with chemotherapy alone was 45% (95% CI, 54–62). In addition, the median duration of response with nivolumab plus chemotherapy and chemotherapy alone was 9.7 and 7.0 months, respectively, in patients with a PD-L1 CPS of ≥5.

The ATTRACTION-4 trial was a randomized, double-blind, placebo-controlled, phase II/III study that targeted patients with HER2-negative AGC and was conducted in South Korea, Japan, and Taiwan. A total of 724 patients were enrolled regardless of PD-L1 expression and randomly assigned to the nivolumab plus chemotherapy and placebo plus chemotherapy arms in a 1:1 ratio. The chemotherapy regimen used in this study was oxaliplatin plus capecitabine or S-1. The combination of nivolumab and chemotherapy yielded better outcomes in terms of PFS (median, 10.45 vs. 8.34 months, HR, 0.68, P<0.001) and ORR (57.0% vs. 48.0%) compared with chemotherapy plus placebo; however, no differences were observed in OS (median, 17.45 vs. 17.15 months, HR, 0.90, P=0.260) [30]. Although a caveat exists in making direct comparisons between trials, the OS in the control arm of the ATTRACTION-4 trial (17.15 months) was longer than that in the experimental arm (nivolumab plus chemotherapy) of the CheckMate-649 trial (14.4 months). The reason for the lack of a difference in OS in the ATTRACTION-4 trial was that ATTRACTION-4 had a higher proportion of patients in the placebo arm who received subsequent systemic chemotherapies, including ICIs, than the CheckMate-649 study (66% of patients in ATTRACTION-4 vs. 39% of patients in CheckMate-649) [16,30]. In the ATTRACTION-4 study, 131 patients (18.1%) received nivolumab as a subsequent treatment (39 [11%] patients in the nivolumab arm vs. 92 [25%] patients in the placebo arm) [36]. In the CheckMate-649 study, 90 patients (5.7%) received immunotherapy as a subsequent treatment (17 [2%] patients in the nivolumab arm vs. 73 [9%] patients in the placebo arm) [16]. Thus, subsequent treatments might be a confounding factor in the ATTRACTION-4 study, which did not show any difference in OS between the 2 arms. On the basis of these results, the combination of nivolumab and chemotherapy has been globally approved by multiple regulatory authorities as a first-line

https://doi.org/10.5230/jgc.2023.23.e10

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treatment for patients with HER2-negative AGC. In the United States, Korea, and Japan, nivolumab plus chemotherapy was approved for all patients with HER2-negative AGC regardless of PD-L1 expression; however, in Europe, it was approved only for patients with a PD-L1 CPS of ≥5. In the first-line treatment of AGC, the appropriate PD-L1 criteria for selecting patients for whom nivolumab offers a true clinical benefit remain controversial.

With the same rationale, the ongoing phase III RATIONALE-305 trial (NCT03777657) is a global, double-blind, placebo-controlled, randomized, phase III study evaluating tislelizumab plus platinum-based doublet chemotherapy vs. placebo plus chemotherapy as a first-line treatment for patients with HER2-negative AGC [31]. A total of 997 patients from 13 countries were enrolled regardless of PD-L1 status. According to the interim analysis, tislelizumab in combination with chemotherapy showed a survival benefit in patients with PD-L1 expression [48]. The final efficacy analysis for all randomized patients is awaited. Moreover, the ongoing KEYNOTE-859 trial (NCT03675737), which enrolled patients regardless of PD-L1 status, is an international, randomized, double-blind, placebo-controlled, phase III study that aims to prove the effect of a pembrolizumab combination strategy compared with chemotherapy in the first-line treatment of HER2-negative AGC [32]. The results of these ongoing studies will provide evidence for the optimal selection of patients who are likely to gain a clinical benefit from ICIs.

Immunotherapy for HER2-positive GC

Trastuzumab in combination with chemotherapy is the standard first-line therapy for HER2-positive AGC, according to the ToGA trial [4]. Trastuzumab, an anti-HER2 monoclonal antibody, binds to the extracellular domain of HER2 and facilitates antibody-dependent cellular cytotoxicity, leading to immunogenic cell death [49]. In addition, trastuzumab upregulates PD-1 and PD-L1 and regulates major histocompatibility complex class II expression [49]. Thus, according to the mode of action of trastuzumab, the addition of ICIs to HER2-targeted therapy may result in an enhanced anti-tumor effect [33].

The global phase III KEYNOTE-811 trial was a randomized, double-blind, placebo-controlled study that aimed to assess the efficacy and safety of adding pembrolizumab to the chemotherapy plus trastuzumab combination as a first-line treatment for HER2-positive AGC [18]. The chemotherapy regimens used in this study were cisplatin plus 5-fluorouracil and oxaliplatin plus capecitabine. Participants were randomly assigned to receive either pembrolizumab or placebo in a 1:1 ratio. The preplanned first interim analysis of the KEYNOTE-811 study recently demonstrated that adding pembrolizumab to trastuzumab plus chemotherapy significantly improved ORR compared with the standard first-line treatment for HER2-positive AGC (ORR, 74.4% in the pembrolizumab arm vs. 51.9% in the placebo arm, P<0.001) [18]. On the basis of these results, the US Food and Drug Administration granted accelerated approval for pembrolizumab in combination with trastuzumab and chemotherapy as the first-line systemic treatment for HER2-positive AGC. The results for other efficacy outcomes, including OS and PFS, are further awaited.

Zanidatamab, another HER2-targeted agent, is a humanized bispecific antibody directed against extracellular domains 2 and 4 of HER2. Zanidatamab is also being investigated in combination with tislelizumab, a PD-1 inhibitor, and chemotherapy in HER2-positive AGC [34]. The HERIZON-GEA-01 trial (NCT05152147), an ongoing global, randomized, open-label, phase III study, aims to evaluate and compare the efficacy and safety of zanidatamab plus chemotherapy with or without tislelizumab as the standard first-line therapy in patients with HER2-positive AGC.

https://doi.org/10.5230/jgc.2023.23.e10

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The MAHOGANY trial (NCT04082364) was a randomized, open-label, phase II/III study that aimed to assess the efficacy and safety of margetuximab (a second-generation anti-HER2 monoclonal antibody) plus retifanlimab (an anti-PD-1 monoclonal antibody) with or without chemotherapy and margetuximab plus MGD013 (a bispecific anti-PD-1 and anti-LAG-3 IgG molecule). Interestingly, in selected patients with HER2 immunohistochemistry 3+ tumors and a PD-L1 CPS of ≥1 (cohort A of the MAHOGANY trial), margetuximab in combination with retifanlimab, a chemotherapy-free regimen, resulted in a remarkable ORR of 53.0% with a median duration of response of 10.3 months (95% CI, 4.6–not evaluable) [35]. The disease control rate was 73% (29/40; 95% CI, 56.1–85.4).

Induction and maintenance strategies

With a focus on long-term durable responses to ICIs, some strategies have been investigated to test the role of ICIs as a maintenance treatment after induction chemotherapy in the first-line setting of AGC. A randomized, open-label, phase II trial was conducted to assess the efficacy of ipilimumab monotherapy as a maintenance therapy compared with the best supportive care (BSC) [36]. Patients who achieved complete or partial response to induction chemotherapy (oxaliplatin plus capecitabine, cisplatin plus capecitabine, cisplatin plus 5-fluorouracil, and cisplatin plus S-1) were enrolled in this study and randomly assigned to receive either ipilimumab or BSC in a 1:1 ratio. The primary endpoint was immune-related PFS, and patients in the BSC arm were allowed to receive maintenance chemotherapy [36]. Ipilimumab maintenance failed to improve immune-related PFS compared with BSC (median immune-related PFS, 2.92 months in the ipilimumab arm vs. 4.90 months in the BSC arm, HR, 1.44, P=0.097) [36].

The JAVELIN Gastric 100 trial was an open-label, phase III trial that evaluated the efficacy of avelumab maintenance therapy after induction chemotherapy compared with continued chemotherapy or BSC as a first-line therapy for patients with HER2-negative AGC [37]. All patients received induction platinum-based doublet chemotherapy for up to 12 weeks, and patients without disease progression after induction chemotherapy were randomly allocated in a 1:1 ratio to either switch maintenance therapy with avelumab or continued chemotherapy or BSC [37]. In all randomized patients, avelumab maintenance therapy did not improve OS compared with the continuation of chemotherapy (median OS, 10.4 vs. 10.9 months, HR, 0.91, P=0.178) [37]. However, similar to KEYNOTE-061 and KEYNOTE-062, crossing of OS curves was observed in this study, and the survival curve of the avelumab maintenance arm plateaued at 20 months after randomization. In the exploratory analysis, patients with a PD-L1 CPS of ≥1 had a more durable response to avelumab maintenance therapy than to chemotherapy (median OS, 14.9 vs. 11.6 months) [37]. With regard to safety, the avelumab maintenance arm had a lower incidence of all grades of treatment-related adverse events and grade ≥3 treatment-related adverse events than the chemotherapy arm [37]. These results suggest the potential activity of avelumab maintenance in selected patients and its favorable safety profile, which may serve as a basis for developing an induction strategy in patients with AGC.

The ongoing LEAP-015 trial (NCT04662710) is a randomized, open-label, phase III trial assessing the efficacy and safety of pembrolizumab plus lenvatinib and chemotherapy as a first-line therapy for HER2-negative AGC [38]. Patients were randomly assigned to the pembrolizumab + lenvatinib + chemotherapy arm and the standard-of-care chemotherapy arm in a 1:1 ratio. In the experimental arm, patients received induction therapy with pembrolizumab plus lenvatinib and chemotherapy for 12 weeks and subsequently continued the pembrolizumab plus lenvatinib combination to determine the role of maintenance therapy.

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Combination therapy with anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) antibodies

CTLA-4 is a well-known therapeutic target, and the combination of anti-CTLA-4 antibodies with PD-1 or PD-L1 inhibitors has been investigated as a dual immunotherapy strategy for various cancer types [11,50]. In the CheckMate-032 trial, patients who received the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg regimen showed a higher ORR than those who received nivolumab 3 mg/kg monotherapy as a later-line treatment for AGC [51]. However, in the CheckMate-649 study, nivolumab plus ipilimumab failed to improve survival, and rather resulted in lower PFS and ORR, compared with chemotherapy as the first-line treatment for patients with HER2-negative AGC [16]. In contrast, responders to nivolumab plus ipilimumab dual immunotherapy had more durable responses than responders to chemotherapy (median duration of response, 13.2 vs. 6.9 months) [16]. An ongoing phase III trial, ATTRACTION-6 (NCT05144854), which aims to evaluate dual immunotherapy with a modified dose of nivolumab (360 mg every 3 weeks) plus ipilimumab (1 mg/kg every 6 weeks) in combination with chemotherapy compared with chemotherapy alone, is currently underway.

Combination therapy with anti-angiogenic agents

Abnormal angiogenesis is one of the most notable features of solid tumors, and many angiogenesis inhibitors that target vascular endothelial growth factor signaling have been developed [52]. Anti-angiogenic drugs can augment immunotherapy as a result of the immunomodulatory activities of the vascular endothelial growth factor, altering the tumor microenvironment from an immunosuppressive to an immune-supportive state by intensifying the recruitment and induction of immune cell activities [19,44]. In the phase Ib REGONIVO trial, nivolumab plus regorafenib resulted in an ORR of 44% (95% CI, 24.4%–65.1%), a PFS of 5.6 months (95% CI, 2.7–10.4), and an OS of 12.3 months (95% CI, 5.3–not reached) in patients with heavily treated AGC [53]. Interestingly, among 7 responders, 3 ICI-exposed patients achieved an objective response with nivolumab plus regorafenib, suggesting that combination treatment with anti-angiogenic agents can be a therapeutic strategy to overcome ICI resistance [53]. In addition, the phase II LEAP-005 trial, which investigated the combination of pembrolizumab and lenvatinib, reported an ORR of only 10% (95% CI, 2–26), a PFS of 2.5 months (95% CI, 1.8–4.2), and an OS of 5.9 months (95% CI, 2.6–8.7) in the AGC cohort [20]. However, these results are preliminary, as the above-mentioned studies were nonrandomized trials. The phase III INTEGRATE-IIb trial is ongoing and aims to investigate the combination of nivolumab and regorafenib compared with the investigator's choice of chemotherapy, such as docetaxel, irinotecan, or TAS-102, in the later-line setting [21]. In the first-line setting, the phase III LEAP-015 trial, which aims to evaluate pembrolizumab plus lenvatinib in combination with chemotherapy compared with chemotherapy alone, is in progress [38].

BIOMARKERS FOR GC IMMUNOTHERAPY

MSI

MSI is defined as a hypermutable phenotype that occurs at genomic microsatellites in the presence of deficient DNA mismatch repair [26]. Tumors with MSI are potentially sensitive to immunotherapy owing to their intrinsic mutational burden and immune checkpoint expression [26]. Thus, MSI is considered a tumor-agnostic marker for predicting the response to immunotherapy, and various basket trials investigating ICI treatment strategies in patients with MSI-high solid tumors have been initiated [54]. The KEYNOTE-158 trial, the most representative basket trial that enrolled patients with MSI-high tumors, approved

https://doi.org/10.5230/jgc.2023.23.e10

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pembrolizumab as a tissue-agnostic salvage treatment for MSI-high solid tumors. In this study, the GC cohort treated with pembrolizumab showed a durable response with an ORR of 31.0% (95% CI, 17.6–47.1), a PFS of 3.2 months (95% CI, 2.1–12.9), and an OS of 11.0 months (95% CI, 5.8–31.5) [55]. Most important, the median duration of response was not reached (95% CI, 6.3–51.1+) and the 3-year OS rate was 34.5%, demonstrating a long-lasting response in patients with a good response to pembrolizumab [55]. In addition, in a post hoc analysis combined with the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 trials, pembrolizumab monotherapy or the combination of pembrolizumab and chemotherapy showed a durable anti-tumor effect in patients with MSI-high AGC [24]. A subgroup analysis of the phase III CheckMate-649 trial in patients with MSI-high tumors demonstrated that the combination of nivolumab and chemotherapy improved OS (unstratified HR, 0.38) and ORR (55% vs. 39%) compared with chemotherapy alone [16]. Moreover, in the CheckMate-649 study, the nivolumab and ipilimumab combination provided OS benefits (unstratified HR, 0.28) and improved ORR (70% vs. 57%) compared with chemotherapy in patients with MSI-high AGC [16]. In a meta-analysis based on these results, ICIs in combination with chemotherapy had an OS benefit in MSI-high AGC compared with the microsatellite-stable type (HR, 0.34 for MSI-high AGC, HR, 0.85 for microsatellite-stable AGC) [25]. MSI-high GC showed a good response to ICIs, as did other cancers, in a tissue-agnostic manner. In addition, MSI-high GC showed a good response to ICIs combined with chemotherapy or other ICIs as well as to ICI monotherapy.

EBV

The molecular classification of GC divides tumors into 4 subtypes: EBV-positive tumors, tumors with MSI, genomically stable tumors, and tumors with chromosomal instability. EBV-associated GC accounts for approximately 9% of all GCs [9]. In the EBV-positive subgroup, 9p amplifications are enriched, resulting in PD-L1 overexpression in cancer cells. In addition, enhancement of interleukin-12-mediated signaling signatures is observed, suggesting that patients with EBV-positive GC might respond well to immunotherapy. According to a meta-analysis, the pooled positivity rate for PD-L1 in EBV-associated GC was 54.6%, which indicates a potential benefit of immunotherapy in this GC subtype [56]. A prospective observational study showed that 3 of 9 patients with EBV-positive GC treated with ICIs achieved partial response after immunotherapy, with a longest duration of response of 18 months [57]. Furthermore, through next-generation sequencing-based detection of EBV infection, patients with EBV-positive GC showed a better response to immunotherapy than those with EBV-negative GC [58]. Thus, EBV positivity is a potential predictive biomarker for immunotherapy response in GC.

PD-L1

PD-L1 is the most well-known biomarker for predicting response to immunotherapy; however, no clear consensus has been established in GC owing to the use of different antibodies and different definitions of PD-L1 positivity for each ICI [59]. In the KEYNOTE-059 trial, PD-L1 positivity was defined as a PD-L1 CPS of ≥1, and patients with PD-L1-positive GC showed a higher ORR than those with PD-L1-negative GC [14]. A similar trend was observed in the post hoc subgroup analysis of the KEYNOTE-061 trial, which investigated pembrolizumab compared with chemotherapy as a second-line treatment. Patients with a PD-L1 CPS of ≥10 had a higher response rate than those with a PD-L1 CPS of ≥1 [27]. In the ATTRACTION-2 and JAVELIN Gastric 300 trials, PD-L1 positivity was defined as PD-L1 staining in ≥1% of tumor cells (similar to the tumor positivity score) [13,28]. In the ATTRACTION-2 study, nivolumab monotherapy showed a survival benefit regardless of PD-

https://doi.org/10.5230/jgc.2023.23.e10

L1 status [13]. However, in the JAVELIN Gastric 300 trial, avelumab did not show a survival benefit in all patients and in the PD-L1-positive population [28].

A recently published meta-analysis that aimed to determine the appropriate cutoff value and definition of PD-L1 for predicting response to immunotherapy suggested that PD-L1 CPS can be used as a reliable biomarker, and patients with a PD-L1 CPS of ≥1 showed good response to ICI monotherapy [60]. In addition, in the subgroup analysis of the CheckMate-649 trial, the unstratified HR for OS with nivolumab plus chemotherapy in patients with a PD-L1 CPS of ≥10, ≥5, and ≥1 were 0.66 (95% CI, 0.56–0.77), 0.69 (95% CI, 0.60–0.79), and 0.74 (95% CI, 0.66–0.84), respectively [16], demonstrating that a higher PD-L1 CPS indicates a greater effect of immunotherapy. Furthermore, a meta-analysis of the CheckMate-649, KEYNOTE-062, and KEYNOTE-590 trials found insufficient evidence of a clinical benefit of ICIs in combination with chemotherapy in low PD-L1 populations [61]. These findings provide a basis for initiating a more detailed assessment of the selection of treatment options for patients with AGC.

Tumor mutational burden (TMB)

In a previous study of all malignant tumors, TMB was correlated with survival in patients with various cancer types treated with ICIs [62]. Accordingly, other studies have aimed to evaluate the relationship between TMB and the response to ICIs in GC. In a post hoc analysis of the KEYNOTE-061 trial, TMB was suggested to predict the OS benefit of ICIs [27]. Moreover, in an explorative analysis of the KEYNOTE-062 trial, an association was observed between TMB and the clinical efficacy of first-line pembrolizumab plus chemotherapy in patients with AGC, and the cutoff value of TMB to distinguish patients who are likely to gain a clinical benefit from ICIs was suggested to be 10 mutations/Mb [63]. However, the TMB-high and MSI-high AGC populations are not mutually exclusive. Thus, the clinical utility of TMB alone for predicting response to ICIs is attenuated when the MSI-high group is completely excluded [63,64].

ROLE OF IMMUNOTHERAPY IN EARLY RESECTABLE GC

With the success of the combination strategy of immunotherapy and chemotherapy in various malignant tumors, clinical trials have investigated this combination in the neoadjuvant or adjuvant setting [30]. The ATTRACTION-05 trial (NCT03006705) was conducted to compare the addition of nivolumab to adjuvant chemotherapy (S-1 monotherapy or capecitabine plus oxaliplatin combination) with adjuvant chemotherapy alone in patients with pathologic stage III GC who underwent curative surgery with D2 dissection, and the results are awaited [31]. In addition, to reveal the role of immunotherapy combinations as a perioperative treatment, including in the neoadjuvant and adjuvant settings, the KEYNOTE-585 (NCT03221426) and MATTERHORN (NCT04592913) trials are in progress [15,48]. In the KEYNOTE-585 study, patients with initial clinical stage II, III, or IVa GC were enrolled and randomly assigned to the pembrolizumab plus chemotherapy (cisplatin plus capecitabine or 5-fluorouracil) and placebo plus chemotherapy arms in a 1:1 ratio. After 3 cycles, the patients underwent curative-intent surgery and continued 3 cycles of chemotherapy and pembrolizumab or placebo maintenance for 1 year. The primary endpoints were OS, event-free survival, and complete pathologic response. The phase III MATTERHORN trial has a similar design to the KEYNOTE-585 trial; however, backbone chemotherapy uses the FLOT regimen (docetaxel, 5-fluorouracil, and oxaliplatin combination) and the additional ICI is the anti-PD-L1 inhibitor durvalumab.

https://doi.org/10.5230/jgc.2023.23.e10

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CONCLUSION

Immunotherapy has gained enormous momentum in the treatment of AGC, as the ICI combination strategy has been proven to improve OS as a first-line systemic therapy for AGC. Accumulating evidence suggests that patients with GC respond to immunotherapy in various settings. Notable clinical trials investigating combination strategies with multiple kinase inhibitors or dual ICIs are ongoing, and further investigations are needed to optimize patient selection based on biomarkers.

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