Advances in Systemic Therapy for Metastatic or Advanced Gastric Cancer

Kohei Shitara, MD, and Atsushi Ohtsu, MD, PhD

Abstract

In recent years, various new agents have been investigated for the treatment of advanced gastric cancer (AGC). The anti-HER2 antibody trastuzumab has been shown to prolong the overall survival of patients with HER2-positive AGC and has become a standard treatment. However, lapatinib, or ado-trastuzumab emtansine (T-DM1), did not show survival benefit in AGC, although it has shown remarkable efficacy for HER2-positive breast cancer. The efficacy of the anti-vascular endothelial growth factor receptor monoclonal antibody ramucirumab for pretreated gastric cancer is a milestone for antiangiogenic therapy for AGC. Early clinical trials of TAS-118, TAS-102, and STAT3 inhibitors; IMAB362 (anti-Claudin 18.2); and immune checkpoint inhibitors are all encouraging. These findings warrant further evaluation in larger clinical trials.

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Systemic chemotherapy is a standard treatment for metastatic or unresectable advanced or recurrent gastric cancer (AGC). Effective cytotoxic agents for AGC include 5-fluorouracil (5-FU), oral fluoropyrimidine, platinum agents, taxanes, irinotecan, and anthracyclines. Commonly used first-line therapy is the combination of fluoropyrimidine and platinum-based chemotherapy with or without docetaxel or anthracycline, which results in median progression-free survival (PFS) of 4 to 6 months and median overall survival (OS) of 10 to 15 months.^{1–4} The survival benefit of second-line therapy has recently been confirmed in several randomized trials.^{5–7} Regarding molecular targeting agents, trastuzumab, a monoclonal antibody against HER2, significantly improved the OS of HER2-positive AGC,⁸ making this agent standard (Table 1). Ramucirumab, an anti-vascular endothelial growth factor receptor (VEGFR-2) antibody, has proven effective for previously treated AGC. Its addition to best supportive care was associated with significantly improved OS in patients with disease progression on first-line chemotherapy.⁹ Moreover, ramu-

cirumab plus paclitaxel chemotherapy significantly increased OS compared with paclitaxel alone in patients after first-line treatment.¹⁰

Despite the introduction of these new agents, survival in AGC remains unsatisfactory; therefore, the introduction of more effective treatments is desired. Various phase III trials are underway to replace the current standard of care (Table 2). This article reviews the current status of chemotherapy development for AGC.

Molecular Profiles in Gastric Cancer

Growth factor receptors other than HER2 or receptor tyrosine kinases (RTKs), such as epidermal growth factor receptor (EGFR), mesenchymal-epithelial transition factor (MET; a receptor for hepatocyte growth factor receptor [HGFR]), and fibroblast growth factor receptor (FGFR), have been described.¹¹ Detailed molecular profiles of gastric cancer have also been recently reported in large-scale international cancer genome studies. The Cancer Genome Atlas (TCGA) research network used fresh frozen tissues of primary gastric ad-

From the Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan.
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Correspondence: Kohei Shitara, MD, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan.

Trial/Author	Phase	Line	Target	Regimens	N	Median OS (mo)	Median PFS (mo)	ORR (%)			
ToGA ⁸	III	First	HER2 (with enrichment)	FP/XP + trastuzumab	294	13.8	6.7	47			
				FP/XP	290	11	5.5	35			
				HR, 0.74; P=.0046			HR, 0.71; P=.0002				
Logic ²¹	III	First	HER2 (with enrichment)	CapeOX + lapatinib	272	12.2	6	53			
				CapeOX	273	10.5	5.4	39			
				HR, 0.91; P=.35			HR, 0.82; P=.038				
TyTAN ²²	III	Second	HER2 (with enrichment)	Paclitaxel + lapatinib	132	11	5.4	27			
					129	8	4.4	9			
				HR, 0.84; P=.21			HR, 0.85; P=.24				
GATSBY ²³	III	Second	HER2 (with enrichment)	T-DMI	228	7.9	2.7	20.6			
				Paclitaxel, docetaxel	117	8.6	2.9	19.6			
				HR, 1.15; P=.86			HR, 1.13; P=.31				
REAL-3 ²⁴	III	First	EGFR	EOC + panitumumab	276	8.8	6	46			
				EOC	266	11.3	7.4	42			
				HR, 1.37; P=.013			HR, 1.22; P=.068				
EXPAND ²⁵	III	First	EGFR	XP + cetuximab	455	9.4	4.4	30			
				XP	449	10.7	5.6	29			
				HR, 1.0; P=.95			HR, 1.09; P=.32				
GRANITE-1 ²⁶	III	Second/Third	mTOR	Everolimus	439	5.39	1.68	4.5			
				Placebo	217	4.34	1.41	2.1			
				HR, 0.90; P=.1244			HR, 0.66; P<.0001				
RILOMETI ²⁷	III	First	HGF (with enrichment)	ECX + rilotumumab	304	9.6	5.7	30			
				ECX + placebo	305	11.5	5.7	39.2			
				HR, 1.36; P=.021			HR, 1.27; P=.025				
METGastric ²⁸	III	First	MET (with enrichment)	FOLFOX + onartuzumab	121	11	6.7	46			
				FOLFOX		11.3	6.8	41			
				HR, 0.82; P=.244			HR, 0.90; P=.43				
AVAGAST ²⁹	III	First	VEGF	XP + bevacizumab	387	12.1	6.7	46			
				XP + placebo	387	10.1	5.3	37			
				HR, 0.87; P=.1002			HR, 0.80; P=.0037				
REGARD ⁹	III	Second	VEGFR2	Ramucirumab	238	5.2	2.1	3			
				Placebo	117	3.8	1.3	3			
				HR, 0.776; P=.047			HR, 0.483; P<.0001				
RAINBOW ¹⁰	III	Second	VEGFR2	Paclitaxel + ramucirumab	330	9.63	4.4	28			
				Paclitaxel + placebo	335	7.36	2.86	16			
				HR, 0.807; P=.0169			HR, 0.635; P<.0001				
Li et al ³⁶	III		VEGFR2	Apatinib	176	6.5	2.6	1.7			
				Placebo	91	4.7	1.8	0			
				HR, 0.71; P<.015			HR, 0.44; P<.0001				
PHOENIX-GC ¹⁹	III	First	Cytotoxic	S-1 + paclitaxel IV IP	122	17.7	NR	53			
				S-1 + cisplatin	61	15.2	NR	60			
				HR, 0.72; P=.081							
DREAM ²⁰	III	Second	Cytotoxic	DHP107	118	9.7	3.3	17.8			
				Paclitaxel	118	8.9	2.7	25.4			
				HR, 1.04; P=.824			HR, 0.86; P=.294				
Hironaka et al ¹⁶	II	First	Cytotoxic	S-1 + LV + oxaliplatin (SOL)	47	18.4	8.3	66			
				S-1 + LV	47	15.6	4.2	43			
				S-1 + cisplatin (SP)	48	12.6	5.6	46			
				HR, 0.59; P=.023 (SOL vs SP)			HR, 0.60; P=.054 (SOL vs SP)				
Sato et al ³⁰	II	Second	EGFR	Irinotecan + nimotuzumab	40	293 d	85 d	18.4			
				Irinotecan	43	227 d	73 d	10.3			
				HR, 0.717; P=.22			HR, 0.86; P=.5668				
INTEGRATE ³⁷	II	Second	VEGFR, RET, RAF	Regorafenib	97	25 wk	11 wk	3			
				Placebo	50	19 wk	4 wk	2			
						HR, 0.68; P=.065			HR, 0.41; P<.0001		
Bang et al ⁴¹	II	Second	PARP	Paclitaxel + olaparib	62	13.1	3.91	26.4			
				Paclitaxel + placebo	62	8.3	3.55	19.1			
				HR, 0.56; P=.01			HR, 0.80; P=.131				
FAST ⁴⁵	II	First	CLDN18.2 (with enrichment)	EOX + IMAB362	84	13.2	7.9	25			
				EOX	77	8.4	4.8	39			
				HR, 0.51; P=.0001			HR, 0.47; P=.001				
Moehler et al ⁴⁹	II	First Maintenance	CTLA-4	Ipilimumab	57	12.7	2.92	1.8			
				BSC	57	12.1	4.9	7			
				NR			HR, 1.44; P=.097				

Abbreviations: BSC, best supportive care; CapeOX, capecitabine and oxaliplatin; CTLA-4, cytotoxic T-lymphocyte antigen 4; ECX, epirubicin, cisplatin, and capecitabine; EGFR, epidermal growth factor receptor; EOX, epirubicin, oxaliplatin, and capecitabine; HGFR, hepatocyte growth factor receptor; EOC, epirubicin plus oxaliplatin plus capecitabine; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; FP, 5-FU plus cisplatin; HR, hazard ratio; IP, intraperitoneal; IV, intravenous; LV, leucovorin; MET, mesenchymal-epithelial transition factor; NR, not reported; OS, overall survival; ORR, overall response rate; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; T-DMI, trastuzumab emtansine; VEGFR, vascular endothelial growth factor receptor; XP, capecitabine plus cisplatin.

Systemic Therapy for Gastric Cancer

Table 2. Ongoing Phase III Trials for Advanced Gastric Cancer

Trial (ClinicalTrials.gov Identifier)	Line	Control Arm	Agents (Experimental)	Target
JACOB (NCT01774786)	First	XP or FP/trastuzumab	+ Pertuzumab	HER2
SOLAR (NCT02322593)	First	S-1 + cisplatin	TAS-118 + oxaliplatin	Cytotoxic
JCOG1013 (UMIN000007652)	First	S-1 + cisplatin	+ Docetaxel	Cytotoxic
RAINFALL (NCT02314117)	First	XP	+ Ramucirumab	VEGFR2
KEYNOTE-062 (NCT02494583)	First	XP/FP	+ Pembrolizumab	PD-1
JAVELIN Gastric 100 (NCT02625610)	First (maintenance)	Continuation of first line	Avelumab	PD-L1
ENRICH (NCT01813253)	Second	Irinotecan	+ Nimotuzumab	EGFR
GOLD (NCT01924533)	Second	Paclitaxel	+ Olaparib	PARP
BRIGHTER (NCT02178956)	Second	Paclitaxel	+ BBI608	STAT3
ABSOLUTE (JapicCTI-132059)	Second	Paclitaxel	Nab-paclitaxel	Cytotoxic
KETNOTE-061 (NCT02370498)	Second	Paclitaxel	Pembrolizumab	PD-1
JAVELIN Gastric 300 (NCT02625623)	Third	Paclitaxel/Irinotecan/BSC	Avelumab	PD-L1
INTEGRATE-2 (planned) (NCT02773524)	Third or fourth	Placebo	Regorafenib	VEGFR, RET, RAF
ONO-4538-12 (NCT02267343)	Last	Placebo	Nivolumab	PD-1
Tags (NCT02500043)	Last	Placebo	TAS-102	Cytotoxic

Abbreviations: BSC, best supportive care; EGFR, epidermal growth factor receptor; FP, 5-FU plus cisplatin; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; STAT3, signal transducer and activator of transcription-3; VEGFR, vascular endothelial growth factor receptor; XP, capecitabine plus cisplatin.

*Not registered in ClinicalTrials.gov.

enocarcinoma from 295 patients to conduct analyses based on 6 platforms, comprising (1) somatic copy-number alterations, (2) whole-exome sequencing, (3) DNA methylation analysis, (4) mRNA analysis, (5) microRNA analysis, and (6) reverse phase protein array.¹² Additionally, whole genome analysis and analysis of microsatellite instability (MSI) has been performed.¹² Four subtypes of gastric cancers have been described: (1) tumors positive for Epstein-Barr virus (EBV), (2) MSI-high (MSI-H) tumors, (3) genomically stable tumors, and (4) tumors with chromosomal instability. The subtype of EBV-positive cancers is characterized by predilection for the gastric corpus, recurrent *PIK3CA* and *ARID1A* mutations, high amplification of 9p chromosomes

with increased expression of programmed cell death ligand 1 and 2 (PD-L1/L2), and extreme DNA hypermethylation, whereas the MSI-H subtype shows frequent mutations in multiple genes, such as *HER3*. The genomically stable subtype has a few somatic copy number alterations involving *ARID1A* and *RHOA* mutations or *CLDN18-ARHGAP* fusions. The subtype with chromosomal instability is rich in *TP53* mutations, and has relatively numerous amplifications of RTK genes. Although the TCGA study did not include samples from the Japanese population, a study of 121 Japanese patients with gastric cancer did not demonstrate much difference regarding gene mutations with relatively high frequencies, such as *TP53*, *PIK3CA*, *ARID1A*, *CDH1*, and gene

amplifications of RTKs and of those involved in the cell cycle.¹³ From the immunologic viewpoint, Asian gastric cancers showed significantly lower expression of T-cell markers (eg, CD3, CD45RO, CD8), and higher expression of the immunosuppressive transcription factor FOXP3 was reported in Japanese gastric cancers.¹⁴ In a comprehensive analysis of mostly South Korean patients, a classification of (1) MSI-H, (2) microsatellite stable (MSS)/epithelial mesenchymal transition (EMT), (3) MSS/TP53-positive, and (4) MSS/TP53-negative was also proposed. Particularly in the MSS/EMT subtype, approximately 70% of recurrences were peritoneal, with a significantly poorer prognosis compared with other subtypes, which highlights the need for therapy development for peritoneal dissemination.¹⁵

Advances and Ongoing Development in the Treatment for AGC

Cytotoxic Chemotherapy

Cytotoxic agents remain important in AGC. A randomized phase II trial of S-1 plus leucovorin (LV) versus S-1 plus LV and oxaliplatin (SOL) versus S-1 plus cisplatin in patients with AGC showed a higher response rate to SOL with a longer OS (Table 1).¹⁶ Currently, a phase III SOLAR study comparing TAS-118 (S-1 and LV) plus oxaliplatin with S-1 plus cisplatin is ongoing in Asian countries (ClinicalTrials.gov identifier: NCT02322593). TAS-102 is a novel oral nucleoside antitumor agent containing trifluridine and tipiracil hydrochloride, which prevents the degradation of trifluridine. In a pivotal phase III trial for colorectal cancer, TAS-102 showed an OS benefit compared with placebo in patients with metastatic colorectal cancer that failed to respond to standard chemotherapies.¹⁷ A phase II trial of TAS-102 for pretreated AGC showed a disease control rate of 65.5%.¹⁸ The median PFS and OS were 2.9 and 8.7 months, respectively. Currently, the ongoing global phase III trial is investigating the efficacy and safety of TAS-102 in patients with AGC refractory to standard treatments (ClinicalTrials.gov identifier: NCT02500043).

The control of peritoneal dissemination is extremely important in gastric cancers, but no breakthrough has yet been obtained. Intraperitoneal paclitaxel (PTX) provides sustained high local concentrations. Based on previous promising results in

a phase II trial of intraperitoneal PTX in combination with S-1 plus intravenous PTX, a phase III trial was conducted (PHOENIX-GC).¹⁹ A total of 183 patients were enrolled, and 164 were included in the efficacy analysis. However, OS was not significantly affected (Table 1). Further study might be necessary to identify suitable candidates for intraperitoneal therapy.

DHP107 is a novel oral lipid formulation of paclitaxel. DREAM is a multicenter, open-label, prospective, randomized phase III study comparing DHP107 and intravenous paclitaxel in AGC after failure of first-line therapy.²⁰ Noninferiority of PFS was confirmed. Currently, albumin-bound paclitaxel (nab-paclitaxel) is also being evaluated in a Japanese phase III trial, and results will be presented in the near future.

Molecular Targeting Agents

Since the emergence of HER2 as a treatment target for AGC, a variety of molecular targeting drugs for EGFR, HGF, MET, and mTOR have been examined.^{21–30} However, most did not demonstrate significant benefit in phase III trials (Table 1). T-DM1, one of the antibody-drug conjugates for HER2 that demonstrates remarkable effectiveness in breast cancer, did not demonstrate an effect on prolonged OS in HER2-positive AGC.²³ A phase III trial of pertuzumab, a monoclonal antibody against the dimerization domain of HER2, in combination with cytotoxic chemotherapy and trastuzumab (JACOB), is ongoing (ClinicalTrials.gov identifier: NCT01774786). Although promising results have been obtained in MET inhibitors or FGFR inhibitors for patients with these oncogenic amplifications,^{31–33} these cases are rare. The SCRUM project,³⁴ a joint genome screening project in Japan performed in cooperation with major cancer centers and pharmaceutical companies, is underway, and enrollment in clinical studies that deal with patients with rare genomic alterations is anticipated.

Ramucirumab, a fully human immunoglobulin G1 monoclonal antibody against the extracellular VEGF-binding domain of VEGFR-2, has become a standard chemotherapeutic agent for pretreated AGC based on 2 pivotal phase III trials (Table 1),^{9,10} although it has not shown success as a first-line agent.³⁵ When its efficacy was also evaluated in a randomized phase II study of first-line treatment, it

did not show an improvement in PFS.³⁵ Further, a higher rate of discontinuation from study treatment for reasons other than progressive disease was seen in the ramucirumab arm compared with the placebo arm (50% vs 19%), which led to lower study drug exposure in the experimental arm. Currently, the ongoing phase III RAINFALL trial is comparing PFS in patients treated with intensive doses of ramucirumab with cisplatin/capecitabine (or 5-FU) versus placebo with cisplatin/capecitabine (or 5-FU) as first-line treatment (ClinicalTrials.gov identifier: NCT02314117). Apatinib is a multikinase inhibitor that mainly targets VEGFR-2, and which significantly improves OS in patients with pretreated AGC.³⁶ Similarly, regorafenib, a multikinase inhibitor, significantly prolonged PFS compared with placebo as second-line or later therapy for AGC.³⁷ A phase III trial is planned.

Molecular-targeting drugs, such as inhibitors of poly(ADP-ribose) polymerases (PARPs) or of signal transducer and activator of transcription-3 (STAT3) protein, which are factors involved in the resistance mechanism to conventional chemotherapies, are under development for AGC. Clinically, high PARP-1 expression is associated with tumor invasion and poor prognosis in gastric cancer.³⁸ A preclinical study using PARP inhibitors showed them to be effective for platinum-resistant cell lines,³⁹ and a certain degree of effect has been suggested in ovarian cancer with or without *BRCA* mutations in clinical studies,⁴⁰ leading to interest in developing agents of this type for patients with AGC. Improved PFS and OS were seen in patients with recurrent or metastatic gastric cancer (Table 1).⁴¹ Low expression of ataxia telangiectasia mutated (*ATM*) protein was suggested to be associated with remarkable efficacy of olaparib. However, the phase III GOLD trial (ClinicalTrials.gov identifier: NCT01924533) that evaluated olaparib in combination with paclitaxel chemotherapy for advanced gastric cancer did not meet its primary end point of improving OS in all cohorts and in an *ATM*-negative cohort. Detailed reports and biomarker analysis are awaited.

STAT3 is a transcription factor located downstream of a variety of cytokines and JAK, whose expression of STAT3 is associated with a poor prognosis in multiple cancers.⁴² It is reported that phosphorylated STAT3 activates the transcription of *Nanog* and *Myc*, genes involved in the “stemness.” BBI608

is a drug that specifically inhibits cancer stem-like cells that are highly positive for the glycoprotein CD44 and for STAT3, and that possess the capability to form spheres.⁴² Encouraging anticancer activity of BBI608 and paclitaxel in refractory AGC was observed in a phase Ib and subsequent phase II study including 46 patients with AGC with an overall response rate (ORR) of 31% and disease control rate of 75%.⁴³ Currently, the phase III BRIGHTER trial (ClinicalTrials.gov identifier: NCT02178956) is ongoing to compare BBI608 plus paclitaxel and placebo plus paclitaxel after first-line chemotherapy for patients with AGC.

Claudin 18.2 (*CLDN18.2*) is a tight junction protein expressed by several cancers, including gastric adenocarcinoma. IMAB362 is a chimeric monoclonal antibody that mediates specific killing of *CLDN18.2*-positive cancer cells by activation of immune effector mechanisms. It has shown antitumor activity as monotherapy for pretreated AGC with an ORR of 10% and response duration of 34 weeks.⁴⁴ A randomized phase II trial of IMAB362 in combination with first-line chemotherapy showed promising efficacy for *CLDN18.2*-positive AGC,⁴⁵ which may warrant evaluation in phase III trials. Efficacy was more prominent in patients with high expression of *CLDN18.2*.

Immune Checkpoint Inhibitors

Pembrolizumab is a humanized IgG4 monoclonal antibody without antibody-dependent cytotoxicity (ADCC) activity. It competitively inhibits the binding of PD-1 to PD-L1 and PD-L2. In a phase Ib gastric clinical study (KEYNOTE-012), 39 patients (19 Asians and 20 non-Asians) with PD-L1-positive AGC received pembrolizumab.⁴⁶ Immunohistochemistry with PD-L1 antibody (22C3 antibody) was performed as screening, and those with 1% or more staining in cancer cells or any staining of stromal cells were assessed as PD-L1-positive. In total, 65 of 162 patients (40%) were PD-L1-positive. The ORR by central assessment was 22.2% and that of investigator judgment was 33%, and a reduction in the size of the target lesions was observed in 53.1% of the patients. Although the median PFS was 1.9 months, the 6-month survival rate was 69% and the median response duration was as long as 40 weeks, with an excellent median OS of 11.4 months, despite the fact that 67% of the patients had received

2 or more of lines of prior therapy. No significant difference in clinical outcomes was observed between Asians and non-Asians in terms of response, PFS, or OS. Treatment-related adverse events were similar to those of a previous study for another solid tumor. Clinical trials of pembrolizumab are currently underway, including a large phase II trial (KEYNOTE-059; ClinicalTrials.gov identifier: NCT02335411), a phase III trial (KEYNOTE-061; ClinicalTrials.gov identifier: NCT02370498) comparing pembrolizumab with paclitaxel as second-line therapy, and a phase III trial (KEYNOTE-062; ClinicalTrials.gov identifier: NCT02494583) comparing single-agent pembrolizumab with a combination of 5-FU (or capecitabine), cisplatin, and pembrolizumab versus placebo as first-line therapy for patients with PD-L1-positive and HER2-negative AGC.

Nivolumab is a humanized IgG4 recombinant anti-PD-1 monoclonal antibody. In a phase I/II trial (CheckMate-032), 59 patients, 83% of whom had received 2 or more prior regimens, were treated with nivolumab monotherapy.⁴⁷ The ORR was 14%, median PFS was 1.4 months, and median OS was 5.0 months. The 6-month and 12-month survival rates were 49% and 36%, respectively. A phase III clinical study of nivolumab in patients with AGC refractory to 2 or more lines of treatment (ONO-4538-12; ClinicalTrials.gov identifier: NCT02267343) has finished its recruitment and the results will be reported in the near future.

In a phase I trial with an expansion cohort of Japanese patients with gastric cancer, the anti-PD-L1 antibody avelumab demonstrated an ORR of 15% with median PFS of 11.9 weeks.⁴⁸ Currently, 2 phase III studies of maintenance therapy after first-line (JAVELIN Gastric 100; ClinicalTrials.gov identifier: NCT02625610) and third-line (JAVELIN Gastric 300; ClinicalTrials.gov identifier: NCT02625623) treatment are ongoing.

Although there have been no established biomarkers of immune checkpoint inhibitors to date, an association has been suggested in several different types of cancers among therapeutic effects and PD-L1 expression, types of tumor-infiltrating lymphocytes, number of somatic mutations (mainly passenger mutations), and immune-related gene expression in tumor tissues. At this time, the definitive impact of PD-L1 expression or RNA signature as biomarkers in AGC is not clear^{46,47} and will be analyzed in a

larger cohort from ongoing phase III trials.

Because the results mentioned earlier indicate that single-agent response rates in AGC are approximately 10% to 20%, and that half of patients exhibit early disease progression, it may be more effective to develop combination treatments to improve outcomes. These strategies include combinations of systemic chemotherapy; molecular targeting agents; radiotherapy; immune checkpoint inhibitors, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin domain, mucin domain (Tim-3); inhibitors of suppressive factors, such as indoleamine 2,3-dioxygenase (IDO) or transforming growth factor β (TGF- β); and depletors of suppressive lymphocytes, such as chemokine receptor 4 (CCR4) antibody, as well as local injection of oncolytic viruses to enhance the local immune response. Although monotherapy with anti-CTLA-4 ipilimumab did not show superior efficacy as maintenance therapy after first-line chemotherapy compared with best supportive care in a randomized phase II trial (Table 1),⁴⁹ a combination of nivolumab and ipilimumab in the CheckMate-032 trial showed a relatively higher ORR than monotherapy (14% with nivolumab monotherapy and 26% with a lower dose of nivolumab in combination with ipilimumab).⁵⁰ Currently, a phase III trial of this combination is in planning.

Combinations of anti-CTLA-4 antibody tremelimumab with anti-PD-L1 antibody MED4736, and single-agent therapies of MED4736 and tremelimumab are also being evaluated for AGC. Regarding the combination of the existing molecular targeting drugs and immune checkpoint inhibitors, a phase I study of ramucirumab combined with pembrolizumab is ongoing.⁵¹ VEGF-A in tumor tissues has been reported to induce the expression of inhibitory molecules and to exhaust CD8-positive T cells in a mouse model, suggesting the possibility of the combined use of immune checkpoint inhibitors and VEGF inhibitors.⁵²

Future Perspectives

Treatment for AGC in the near future depends on the results of ongoing clinical trials. Personalized medicine is expected to become more important, wherein a series of therapies, such as cytotoxic drugs, molecular targeting agents, immunotherapy, and

Systemic Therapy for Gastric Cancer

intraperitoneal agents are tailored for individual patients according to their tumor profiling and genomic status or immunologic condition. Optimal timing/sequence should also be evaluated in future clinical trials.

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