Second-Line Treatment of Advanced Gastric Cancer: Where Do We Stand?

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Abstract

Gastric cancer is a leading cause of cancer death and is associated with poor prognosis. The treatment of advanced gastric cancer is changing with the development of novel agents. Until recently, no standard treatment was available for patients with advanced gastric cancer in the second-line setting. Single-agent chemotherapy with docetaxel or irinotecan has been shown to improve survival and quality of life in patients whose disease has progressed while on prior chemotherapy. Combination chemotherapy is associated with a modest benefit at the expense of increased toxicity. Recently, ramucirumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF) receptor-2, has been approved for the treatment of refractory advanced gastric cancer as a single agent or in combination with paclitaxel. Apatinib, a small molecule tyrosine kinase inhibitor targeting VEGF, has demonstrated activity in Asian populations whose disease has progressed on 2 lines of therapy. However, much work is still needed, including the development of biomarkers that could predict response to therapy. (J Natl Compr Canc Netw 2015;13:1281–1292)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the current standard of care and the rationale for the development of novel therapies for the second-line treatment of advanced gastric cancer
- Discuss the clinical data supporting the use of currently approved and emerging targeted therapies in the second-line setting

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Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer death.¹ Approximately 70% of the diagnoses and deaths have occurred in developing countries, with China accounting for the highest incidence. There is marked geographic variation, with high incidence rates in Eastern Asia, Eastern Europe, and South America, and the lowest rates in North America and Africa. Gastric cancer is a global health burden, with almost a million new patients diagnosed annually, representing 8% of all new cancer diagnoses. In 2014, an estimated 22,220 new cases were diagnosed and 10,990 patients died of gastric cancer in the United States.²

Most patients present with locally advanced or metastatic gastric cancer, for which the curative potential is low. Even among patients who undergo surgical resection for localized disease, 40% to 60% experience recurrence.³ Thus, most patients with gastric cancer will develop systemic disease during their disease course. Chemotherapy remains the mainstay of treatment for metastatic and locally advanced gastric cancer (AGC) and has been associated with improved quality of life and survival in patients with advanced disease.⁴ Recently, the FDA approved 2 targeted agents, trastuzumab and ramucirumab, for the treatment of AGC.

The first-line chemotherapy regimen is decided by reviewing a patient's performance status, medical comorbidities, toxicity profile, and HER2/neu status. However, based on several large phase III studies, anthracyclines and platinum- and fluoropyrimidine-based regimens are frequently used for the first-line treatment of gastric cancer. In the past, there was no established second-line therapy or data to support chemotherapy over best supportive care (BSC) in the second-line setting in AGC. However, recent results of at least 3 randomized large trials have provided support for single cytotoxic chemotherapy over BSC along with targeted agents, showing overall survival (OS) benefit in the second-line setting.^{5–8} This article assesses the armamentarium of approved and emerging agents in the second-line treatment of AGC.

Overview of First-Line Treatment

For the first-line treatment of AGC, initially 2 small randomized controlled trials demonstrated that chemotherapy improved survival compared with BSC.^{9,10} Meta-analysis of these trials demonstrated a survival

benefit, with a hazard ratio (HR) of 0.37 (95% CI, 0.24–0.55) favoring chemotherapy.¹¹ Chemotherapy was associated with significant improvement in quality of life in another trial and in meta-analyses.¹² These trials established that chemotherapy improves not only survival but also quality of life in patients with metastatic gastric cancer.

The current standard of care for the front-line treatment of AGC has regional differences, but usually includes a fluoropyrimidine and a platinum agent.¹³ In principle, combination chemotherapeutic regimens have been shown to improve survival compared with single-agent chemotherapy. A meta-analysis of 13 randomized trials demonstrated a 1.6-month improvement in OS with combination chemotherapy, from a median OS of 6.7 months with single-agent chemotherapy to 8.3 months.¹¹ Three-drug chemotherapy regimens provide marginal benefit over 2-drug regimens but are associated with increased toxicities. Table 1 lists selected phase III trials for the first-line treatment of AGC. Commonly used regimens include docetaxel/cisplatin/5-fluorouracil (DCF); epirubicin/cisplatin/5-fluorouracil (ECF); epirubicin/oxaliplatin/5-fluorouracil (EOX); and cisplatin/5-fluorouracil. However, potential toxicity complications along with impairment of quality of life and a small relative benefit must be taken into consideration when using triplet combinations.¹⁴ S-1 is an oral dihydropyrimidine dehydrogenase inhibitor and fluoropyrimidine that has been shown to improve survival in combination with cisplatin in Japanese populations, but it is not approved in the United States.¹⁵ Patients with HER2-overexpressing tumors should receive trastuzumab in addition to chemotherapy based on data from the ToGA (Trastuzumab for Gastric Cancer) trial.¹⁶

Second-Line Treatment

Even with recent advances, the median OS for patients with gastric cancer remains approximately 1 year. Patients with good performance status whose disease progresses after first-line chemotherapy may receive second-line therapy. Until recently, there was no standard treatment option available. However, as a result of recent studies, more options are now available, including targeted agents.

Single-Agent Chemotherapy

Multiple trials have used single agents in the second-line setting, including 3 randomized con-

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Table 1 Selected First-Line Clinical Trials for Advanced Gastric Cancer

Author (y)	Phase	N	Regimen	RR (%)	PFS/TTP (mo)	OS (mo)	P Value ^a
Webb et al ⁴⁹ (1997)	III	121	ECF	46	7.4 ^b	8.9	<.01
		116	FAMTX	21	3.4	5.7	
Ross et al ⁵⁰ (2002)	III	289	ECF	42	7	9.4	NS
		285	MCF	44	7	8.7	
Van Cutsem et al ⁵¹ (2006)	III	221	DCF	37	5.6 ^b	9.2	.02
		224	CF	25	3.7	8.6	
Cunningham ⁵² (2008)	III	249	ECF	41	6.2	9.9	.02 (ECF vs EOX)
		241	ECX	46	6.7	9.9	
		235	EOF	42	6.5	9.3	
		239	EOX	48	7.0	11.2	
Koizumi et al ¹⁵ (2008)	III	148	Cisplatin/S-1	54	6.0 ^b	13.0	.04
		150	S-1	31	4.0	11.0	
Kang et al ⁵³ (2009)	III	160	CX	41	5.6	10.5	NS
		156	CF	29	5.0	9.3	
Ajani ⁵⁴ (2010)	III	521	Cisplatin/S-1	29	4.8	8.6	NS
		508	Cisplatin/5-FU	32	5.5	7.9	
Bang et al ¹⁶ (2010)	III	298	Trastuzumab/Chemotherapy	47	6.7 ^b	13.8	.005
		296	Chemotherapy	34	5.5	11.1	
Ohtsu et al ⁴² (2011)	III	387	Bevacizumab/CX	46	6.7 ^b	12.1	.10
		387	CX	37	5.3	10.1	

Abbreviations: 5-FU, 5-fluorouracil; CF, cisplatin, 5-FU; CX, cisplatin, capecitabine; DCF, docetaxel, cisplatin, 5-FU; ECF, epirubicin, cisplatin, 5-FU; ECX, epirubicin, cisplatin, capecitabine; EOF, epirubicin, oxaliplatin, 5-FU; EOX, epirubicin, oxaliplatin, capecitabine; FAMTX, 5-FU, doxorubicin, methotrexate; MCF, mitomycin, cisplatin, 5-FU; NS, not significant.

^bThe P values are for difference in median survival.

^aDenotes significant difference.

trolled trials demonstrating improvement in OS (Table 2).^{8,17,18} COUGAR-02, a phase III trial, compared docetaxel with BSC in patients with adenocarcinoma of the esophagus and stomach.⁸ Median OS was significantly longer in the docetaxel group (5.2 vs 3.6 months), and dysphagia and abdominal pain were also improved. Furthermore, another randomized trial comparing salvage chemotherapy (docetaxel or irinotecan) with BSC showed that patients receiving chemotherapy had a higher median OS (5.3 vs 3.8 months).¹⁷ No significant difference in survival was seen among patients receiving docetaxel versus irinotecan.

Yet another phase III trial compared irinotecan (every-3-week schedule) with BSC as second-line therapy in patients with AGC.¹⁸ Unfortunately, the trial was closed due to poor accrual. In the 40 patients studied, survival was significantly longer in the irinotecan arm (median OS, 4.0 vs 2.4 months). Tumor-related symptoms were significantly improved in the experimental arm.

Other single agents, such as paclitaxel and S-1, have also shown activity. In a phase II trial, patients whose disease had progressed on the combination regimen of

5-fluorouracil, cisplatin, and epirubicin (PELF) received paclitaxel at 225 mg/m² every 3 weeks.¹⁹ An objective response rate (ORR) of 22.2% and a median OS of 8 months were reported. The regimen was reasonably well tolerated, with leukopenia and thrombocytopenia being the only grade 3 toxicities. Kodaera et al²⁰ reported an ORR of 16% and a median OS of 7.8 months using weekly paclitaxel at a dose of 80 mg/m². Weekly paclitaxel was compared with irinotecan at 150 mg/m² every 2 weeks in a randomized phase III trial.²¹ No significant difference was seen in ORR (20.99% vs 13.60%), progression-free survival (PFS; 3.6 vs 2.3 months), or OS (9.5 vs 8.4 months).

S-1 as a single agent was tested in patients with poor performance status who were not candidates for combination chemotherapy.²² S-1 was administered twice daily for 2 weeks in a 3-week cycle. Of 51 patients, 30 had previously received chemotherapy. An ORR of 12% was obtained in this difficult-to-treat population.

Combination Chemotherapy

Multiple combination chemotherapy regimens have been evaluated in the second-line setting for the

Table 2 Selected Single-Agent Chemotherapy Trials for Patients With Advanced Gastric Cancer in the Second-Line Setting

Author (y)	Phase	N	Regimen	RR (%)	SD (%)	PFS/TTP (mo)	OS (mo)	Selected Grade ≥3 AEs
Ford et al ⁸ (2014)	III	84	Docetaxel, 75 mg/m ² q3wk	7	46	2.8	5.2 ^a	Neutropenia (15%), infection (19%), febrile neutropenia (7%)
		84	BSC			NR	3.6	Infection (3%), pain (20%)
Kang et al ¹⁷ (2012)	III	66	Docetaxel, 60 mg/m ² q3wk	11	27	NR	5.2	Neutropenia (15%), anemia (30%), fatigue (26%)
		60	Irinotecan, 150 mg/m ² q2wk	8	35	NR	6.5	Neutropenia (18%), anemia (32%), fatigue (10%), diarrhea (8%)
		62	BSC				3.8 ^a	Fatigue (27%), anemia (23%)
Giuliani et al ⁵⁵ (2003)	II	30	Docetaxel, 100 mg/m ² q3wk	17	30		6	Neutropenia (18%), leukopenia (7%), anemia (7%)
Lee et al ⁵⁶ (2008)	II	49	Docetaxel, 75 mg/m ² q3wk	16	41	2.5	8.3	Neutropenia (18%), febrile neutropenia (5%), fatigue (33%), diarrhea (10%), neuropathy (8%)
Cascinu et al ¹⁹ (1998)	II	36	Paclitaxel, 225 mg/m ² q3wk	22			8	Neutropenia (17%), grade 2 neuropathy (19%)
Kodera et al ²⁰ (2007)	II	45	Paclitaxel, 80 mg/m ² weekly	16	48	2.6	7.8	Neutropenia (16%)
Thuss-Patience et al ¹⁸ (2011)	III	21	Irinotecan, 250 mg/m ² q3wk BSC	0	53	2.5	4	Diarrhea (26%), leukocytopenia (21%), neutropenic fever (16%), anemia (11%), nausea (5%), vomiting (5%)
		19		0	NR	NR	2.4	
Kanat et al ⁵⁷ (2003)	II	16	Irinotecan, 350 mg/m ² q3wk	6	19	NR	5	Neutropenia (19%), diarrhea (19%), thrombocytopenia (6%)
Hironaka et al ²¹ (2013)	III	108	Paclitaxel, 80 mg/m ² days 1, 8, and 15	21	NR	3.6	9.5	Neutropenia (29%), anemia (21%), anorexia (7%), neuropathy (7%)
		111	Irinotecan, 150 mg/m ² on days 1 and 15	14	NR	2.3	8.4	Neutropenia (39%), anemia (30%), anorexia (17%), death (2%)
Chun et al ⁵⁸ (2004)	II	37	Irinotecan, 125 mg/m ² qwk 4 weeks on/ 2 weeks off	20	23	2.6	5.2	Neutropenia (67%), neutropenia fever (8%), diarrhea (19%), nausea/vomiting (19%)

Abbreviations: AE, adverse event; BSC, best supportive care; NR, not reported; OS, overall survival; PFS, progression-free survival; RR, relative risk; SD, stable disease; TTP, time to progression.

^aDenotes significant difference.

treatment of AGC (Table 3). The combination of irinotecan and cisplatin was evaluated in a few phase II trials with modest results.^{23–25} A randomized phase III Japanese trial comparing biweekly irinotecan and cisplatin with irinotecan alone²⁴ showed that PFS was significantly longer in the combination group (3.8 vs 2.8 months), but there was no survival benefit.

The combination of irinotecan and mitomycin was evaluated in 2 phase II trials. Giuliani et al²⁶ reported an ORR of 32%, including 1 patient with a complete response, and a median OS of 8 months. In the second trial, a much lower ORR of 12.5% was

reported, but the median OS was similar. Grade 3/4 toxicities were observed in only 7.5% of the patients.²⁷

Docetaxel has been combined with irinotecan, epirubicin, or cisplatin (Table 3). However, because most of the trials were single-arm phase II studies, the benefit against the monotherapy cannot be established. With the increased use of 5-fluorouracil in the first-line setting, an interest has been shown in assessing fluoropyrimidine-based combination regimen in the second-line setting. FOLFIRI (5-fluorouracil, leucovorin, and irinotecan) and FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) regimens have been

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Author (y)	Phase	N	Regimen	RR (%)	SD (%)	PFS/TTP (mo)	OS (mo)	Selected Grade ≥3 AEs
Higuchi et al ²⁴ (2014)	III	64	Irinotecan, 60 mg/m ² ; cisplatin, 30 mg/m ² q2wk	22	53	3.8	10.7	Neutropenia (39%), anemia (16%), diarrhea (2%)
		63	Irinotecan, 150 mg/m ² q2wk	16	38	2.8	10.1	Neutropenia (36%), anemia (18%), diarrhea (6%)
Park et al ²⁵ (2005)	II	28	Irinotecan, 70 mg/m ² days 1 and 15; cisplatin, 70 mg/m ² day 1 q4wk	25	14	3.5	5.6	Nausea/vomiting (46%), neuropathy (43%), diarrhea (25%), neutropenia (11%)
Ajani et al ²³ (2002)	II	32	Irinotecan, 50 mg/m ² ; cisplatin, 30 mg/m ² q4wk	31	NR	1.7	5	Diarrhea (12%), neutropenia (28%), fatigue (28%), vomiting (16%), thrombocytopenia (9%)
Bamias et al ²⁷ (2003)	II	40	Irinotecan, 125 mg/m ² ; mitomycin, 5 mg/m ² q2wk	12	55	5	8	Neutropenia (7%), diarrhea
Giuliani et al ²⁶ (2005)	II	38	Irinotecan, 150 mg/m ² days 1 and 15; mitomycin, 8 mg/m ² day 1 q4wk	32	21	4	8	Neutropenia (21%), leukopenia (8%), anemia (5%)
Sym et al ⁵⁹ (2008)	II	49	Irinotecan, 160 (or 120) mg/m ² ; docetaxel, 65 (or 50) mg/m ² q3wk	20	35	2.7	8.9	Neutropenia (90%), febrile neutropenia (50%), asthenia (40%), diarrhea (10%)
Barone et al ⁶⁰ (2007)	II	38	Docetaxel, 75 mg/m ² ; oxaliplatin, 80 mg/m ² q3wk	10	47	4	8.1	Neutropenia (26%), fatigue (16%), nausea (16%)
Zhong et al ⁶¹ (2008)	II	48	Docetaxel, 60 mg/m ² ; oxaliplatin, 130 mg/m ² q3wk	23	33	4.4	7.2	Neutropenia (26%), febrile neutropenia (6%), nausea/vomiting (32%), diarrhea (15%)
Park et al ⁶² (2004)	II	43	Docetaxel, 60 mg/m ² ; cisplatin, 60 mg/m ²	17	5	2.2	5.8	Neutropenia (28%), nausea/vomiting (12%), neuropathy (5%)
Nguyen et al ⁶³ (2006)	II	50	Docetaxel, 75 mg/m ² ; epirubicin, 60 mg/m ² q3wk	16	NR	2.4	5.0	Neutropenia (68%), febrile neutropenia (40%)
Seo et al ⁶⁴ (2007)	II	37	Paclitaxel, 175 mg/m ² ; cisplatin, 60 mg/m ² q3wk	13	40	4	12.6	Neutropenia (14%), anemia (3%), grade ≥2 neuropathy (17%)
Takiuchi et al ⁶⁵ (2008)	II	35	Paclitaxel, 80 mg/m ² days 1 and 8; doxifluridine, 600 mg/m ² days 1–14 q3wk	18	45	3.9	10.5	Neutropenia (23%), anemia (17%), febrile neutropenia (3%)
Hamaguchi et al ⁶⁶ (2008)	II	56	Methotrexate, 100 mg/m ² ; 5-FU, 600 mg/m ²	9	NR	NR	7.8	Neutropenia (17%), hyperbilirubinemia (10%), anemia (9%)
Hartmann et al ³¹ (2007)	II	34	Mitomycin, 10 mg/m ² days 1 and 22; 5-FU, 500 mg/m ² weekly q6wk	26	29	3.3	7.2	Mucositis (9%), diarrhea (9%)
Kim et al ³⁰ (2003)	II	26	Oxaliplatin, 85 mg/m ² ; 5-FU, 500 mg/m ² bolus followed by 2.4–3.0 g/m ² over 48-h infusion q2wk	26	9	4.3	7.3	Leukopenia (2%), grade 1–2 neuropathy (27%)
Kim et al ²⁸ (2007)	II	36	Irinotecan, 150 mg/m ² ; 5-FU, 400 mg/m ² bolus followed by 600 mg/m ² on days 1 and 2 q2wk	10	37	3.3	10.9	Neutropenia (18%), febrile neutropenia (2%), nausea/vomiting (3%)
Park et al ⁶⁷ (2008)	II	42	Mitomycin, 7 mg/m ² day 1; S-1, 40 mg/m ² bid q4wk	21	21	3.4	8	Fatigue (12%), diarrhea (10%), hemolytic-uremic syndrome (2%), grade ≥2 hand-foot syndrome (7%)
Shin et al ⁶⁸ (2008)	II	45	Capecitabine, 2500 mg/m ² days 1–14; doxorubicin, 30 mg/m ² day 1 q3wk	7	40	2.6	6.7	Nausea/vomiting (11%), neutropenia (4%), hand-foot syndrome (2%)

Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; NR, not reported; OS, overall survival; PFS, progression-free survival; RR, relative risk; SD, stable disease; TTP, time to progression.

studied in this setting. With the FOLFIRI regimen, ORR rates seem to range from 10% to 29%, with a median OS of up to 10.9 months.^{28,29} The FOLFOX regimen was tested in patients whose disease had previously progressed on 5-fluorouracil and cisplatin, showing an ORR of 26% and a median OS of 7.3 months.³⁰ Oxaliplatin-induced peripheral neuropathy was reported in 27% of the patients. Infusional 5-fluorouracil and mitomycin in combination yielded an ORR of 26.5%.³¹

Generally with combination therapy, ORRs seem to be higher, but toxicity of the regimens also seems to be increased. Furthermore, most of these published studies are limited by small sample size, selection bias, and lack of a control arm, and contain heterogeneous populations of patients receiving different types of first-line chemotherapy.

Targeted Agents

Ramucirumab: Ramucirumab is a fully human IgG1 monoclonal antibody against vascular endothelial growth factor receptor-2 (VEGFR-2) that prevents ligand binding and pathway activation in endothelial cells. Ramucirumab has now demonstrated an OS benefit in 2 well-designed randomized phase III studies^{5,6} and is now approved by the FDA for the treatment of refractory gastric cancer. In the first trial, REGARD (Ramucirumab for AGC), patients with advanced gastroesophageal adenocarcinoma whose disease progressed on fluoropyrimidine- or platinum-based therapy were randomized to either ramucirumab or placebo.⁵ The median OS was significantly better in the ramucirumab group (5.2 vs 3.8 months; $P=.047$) despite the low ORR. The survival benefit was similar in the Asian and Western population, but only 7.3% of the patients in this trial were from Asia. Overall, it was very well tolerated as a single agent, except for reports of grade 3 or higher hypertension (16% vs 8% in the placebo group). Quality of life at 6 weeks was improved or stable in a higher proportion of patients in the ramucirumab group, but the difference was not statistically significant, probably because of treatment discontinuation in the placebo arm before the 6-week assessment.

In the RAINBOW trial, patients were randomized to receive combination treatment with either ramucirumab and paclitaxel or placebo and paclitaxel.⁶ This is the largest trial of this kind reported to date, involving 665 patients with advanced gastroesophageal cancer treated in the second-line setting.

OS was significantly longer in the theramucirumab/paclitaxel arm (median, 9.6 vs 7.4 months), with an HR of 0.807 (95% CI, 0.678–0.962). The 12-month survival of 40% was longer than in past trials. In the subgroup analysis, the benefit of adding ramucirumab was more pronounced in the Western population (HR, 0.726; 95% CI, 0.580–0.909) compared with the Asian population (HR, 0.986; 95% CI, 0.727–1.337), perhaps suggesting differences in pharmacogenetics between populations. In the experimental arm, higher incidences of grade 3/4 neutropenia (41%), leucopenia (17%), hypertension (14%), abdominal pain (6%), and fatigue (12%) were reported.

Other Targeted Agents: Apatinib is an oral tyrosine kinase inhibitor (TKI) of VEGFR-2 that has demonstrated activity in gastric cancer. Results were recently reported of the placebo-controlled phase III trial conducted in China involving 270 patients.⁷ Patients must have experienced disease progression on 2 lines of chemotherapy to be eligible for this trial. Treatment with apatinib significantly improved PFS (median, 2.6 vs 1.8 months) and OS (median, 6.5 vs 4.7 months), with very few responses observed (2.8%). Severe toxicities included hypertension, hand-foot syndrome, proteinuria, fatigue, anorexia, and elevated aminotransferase. Apatinib is the first small molecular inhibitor that has demonstrated survival benefit in AGC.

Based on activity of trastuzumab in HER2/neu-positive gastric cancer as part of first-line treatment, lapatinib, an oral TKI that blocks HER2, was evaluated as second-line treatment in patients with AGC in Asia (TyTAN trial).³² Patients with HER2-positive tumors by fluorescence in situ hybridization were randomized to receive either lapatinib and paclitaxel or paclitaxel alone. ORR was higher in the combination group (27% vs 9%) but survival was not significantly different between the groups (median, 11.0 vs 8.9 months). HER2 expression was also evaluated by immunohistochemistry (IHC). In the subgroup analysis, patients with IHC3+ tumors had improved survival with the combination regimen (HR, 0.59; 95% CI, 0.37–0.93).

Unfortunately, disappointing results have been seen with other targeted therapies for refractory gastric cancer (Table 4). Treatment with sunitinib, an oral multitargeted TKI of VEGFR and other receptor tyrosine kinases, was associated with low ORR (2.6%) and a median PFS of 2.3 months as second-line treatment.³³ Similar results were reported in another phase

II trial with sunitinib in patients with pretreated gastric cancer.³⁴ In another phase II trial, sorafenib and oxaliplatin in combination yielded an ORR of 2.5%, and stable disease in 47.2% of patients, with a median OS of 6.5 months.³⁵ Everolimus, an oral mTOR inhibitor, was evaluated for the treatment of AGC in the second-line setting in a Japanese population.³⁶ Disease control rate (DCR), the primary end point of the trial, was 56%, with a PFS of 2.7 months. Based on this promising activity, a large randomized placebo-controlled phase III trial was conducted in previously treated patients with gastric cancer.³⁷ Treatment with everolimus did not result in significant improvement in survival compared with the placebo group (median OS, 5.4 vs 4.3 months; $P=.124$).

MET, the receptor for hepatocyte growth factor, is amplified in 5% to 23% of gastric tumors.³⁸ Fortenib, an oral multikinase inhibitor that targets MET and VEGFR-2, was evaluated in previously treated patients with gastric cancer.³⁹ No responses were seen, with only 23% of the patients achieving stable disease. Tivantinib, selective c-MET inhibitor, resulted in a DCR of 36.7%, with no objective responses.⁴⁰ None of these trials used predictive biomarkers as prescreening criteria. Kwak et al⁴¹ reported the clinical activity of AMG337, oral MET inhibitor, in patients MET-amplified gastroesophageal, gastric, or esophageal cancers. Among the 10 MET-amplified gastroesophageal cancers, there was 1 complete response with a duration of objective response (DOR) of 100.4 weeks, and 4 partial responses with a DOR of up to 52 weeks.

Discussion

Despite recent advances, the prognosis of metastatic gastric cancer remains poor. However, a new era has emerged with recent second-line trials in AGC. Data support the use of single cytotoxic agents, and targeted agents as either single agents or in combination with chemotherapy in the second-line setting. Targeting antiangiogenesis seems to be an important oncogenic pathway for AGC.

VEGF inhibition is complex, resulting in the interruption of cell signaling resulting in angiogenesis and lymphangiogenesis. Bevacizumab was tested in first-line AGC in combination with cisplatin and capecitabine in the AVAGAST (Avastin in Gastric Cancer) study, which failed to demonstrate an improvement in OS.⁴² However, VEGF-A inhibition

resulted in improvement in ORR and PFS, hinting at the biological effect of antiangiogenesis in AGC. Ramucirumab was also tested in the first-line setting in combination with FOLFOX chemotherapy in a randomized phase II study in 164 patients.⁴³ No difference in median PFS (6.4 vs 6.7 months) nor OS (11.7 vs 11.5 months) was noted between treatment arms. The difference in clinical efficacy between first- and second-line therapy could be explained by change in biology of chemotherapy-naïve AGC, geographical difference in proportions of patients, and heterogeneity of AGC. In the RAINBOW trial, the benefit of adding ramucirumab was more pronounced in the Western population (HR, 0.726; 95% CI, 0.580–0.909) compared with the Asian population (HR, 0.986; 95% CI, 0.727–1.337). A subgroup analysis of the AVAGAST trial also demonstrated a modest survival benefit in the Western population but no benefit in the Asian population.⁴²

These trials highlight how the biology and treatment pattern of gastric cancer vary in different parts of the world. For example, a greater proportion of patients in Asia receives second- and third-line therapy for AGC. Perhaps the chemotherapy backbone that is combined with targeted agents may also impact clinical efficacy in AGC. Chemotherapeutic agents such as taxanes and irinotecan have been shown to decrease hypoxia-inducible factor (HIF- α), and VEGF inhibition has been shown to reverse paclitaxel sensitivity in gastric cells.⁴⁴ Biomarker analysis from the AVAGAST trial revealed OS to be greatest in patients with high plasma VEGF-A levels receiving bevacizumab (HR, 0.72; $P=.07$).⁴⁵ Tissue neuropilin (NRP) expression was both prognostic and predictive. Biomarker analyses from the REGARD and RAINBOW trials may help improve clinical outcomes in patients with AGC and select patients who will benefit from ramucirumab.

Shah et al⁴⁶ evaluated the benefit of bevacizumab in AGC, and showed a difference in outcomes according to disease subtype and region. Gene expression profiling on gastric cancer cell lines identified 2 major genomic gastric cancer subtypes that were associated with prognosis and response to chemotherapy.⁴⁷ This genomic differential profiling might explain the regional difference noted in the AVAGAST and RAINBOW trials. Apatinib, a TKI targeting VEGFR-2, seems to be effective in Chinese patients.⁷ In contrast to the subset analysis of the

Table 4 Selected Trials With Targeted Agents in Patients With Previously Treated Advanced Gastric Cancer

Author (y)	Phase	N	Regimen	RR	SD	PFS/TTP (mo)	OS (mo)	Selected Grade ≥3 AEs
Fuchs et al ⁵ (2014)	III	238	Ramucirumab, 8 mg/kg q2wk	3	45	2.1	5.2 ^a	Hypertension (8%), fatigue (6%), bleeding (3%)
		117	Placebo	3	21	1.3	3.8	
Wilke et al ⁶ (2014)	III	330	Ramucirumab, 8 mg/kg days 1 and 15; paclitaxel, 80 mg/m ² days 1, 8, and 15 q4wk	27	52	4.4	9.6 ^a	Neutropenia (41%), leukopenia (17%), hypertension (14%), fatigue (12%)
		325	Paclitaxel, 80 mg/m ² days 1, 8, and 15 q4wk	16	47	2.9	7.4	Neutropenia (19%), leukopenia (7%), hypertension (2%), fatigue (5%)
Qin ⁷ (2014)	III (failed 2 lines)	180	Apatinib, 850 mg qd	3	39	2.6	6.5 ^a	Hypertension (9%), elevated transaminase (8%), hyperbilirubinemia (8%), neutropenia (6%)
		90	Placebo	0	9	1.8	4.7	
Satoh et al ³² (2014)	III	132	Lapatinib, 1,500 mg qd; paclitaxel, 80 mg/m ² qwk	27		5.4	11	Neutropenia (57%), leukopenia (29%), fatigue (5%), cardiac event (<1%)
		129	Paclitaxel, 80 mg/m ² qwk	9		4.4	8.9	Neutropenia (31%), leukopenia (9%)
Ohtsu et al ³⁷ (2013)	III	439	Everolimus 10 mg/d	4	39	1.7	5.4	Anemia (16%), anorexia (11%), fatigue (8%), thrombocytopenia (5%)
		217	BSC	2	20	1.4	4.3	
Bang et al ³³ (2011)	II	78	Sunitinib, 50 mg/d 4 weeks on/2 weeks off	3	32	2.3	6.8	Fatigue (10%), nausea/vomiting (7%), anorexia (6%), hand-foot syndrome (6%)
Doi et al ³⁶ (2010)	II	53	Everolimus, 10 mg/d	0	56	2.7	10.1	Anemia (9%), hyponatremia (9%), lymphopenia (7%), increased GGT (7%)
Kang et al ⁴⁰ (2014)	II	30	Tivantinib	0	37	1.4	11.3	Neutropenia (13%), anemia (13%)
Lee et al ⁶⁹ (2013)	II	47	Capecitabine, 650 mg/m ² bid days 1–14; everolimus, 5 mg bid days 1–21	11	38	2.6	4.8	Nausea (4%), diarrhea (6%), stomatitis (6%)
Martin-Richard ³⁵ (2013)	II	40	Sorafenib, 800 mg bid; oxaliplatin, 130 mg/m ² q3wk	2	47	3	9.7	Neutropenia (10%), thrombocytopenia (7%), neuropathy (5%), diarrhea (5%)
Moehler et al ³⁴ (2011)	II	52	Sunitinib, 50 mg/d 4 weeks on/2 weeks off	4	16	1.3	5.8	Neutropenia (8%), leukopenia (10%), anemia (4%), fatigue (6%), hand-foot syndrome (2%)
Shah et al ³⁹ (2013)	II	48	Fortenib, 240 mg/d days 1–5 q2wk	0	23	1.6	7.4	Increased AST (10%), fatigue (6%)
		26	Fortenib, 80 mg/d	0	20	1.8	4.3	Fatigue (15%), hypertension (4%)

Abbreviations: AE, adverse event; AST, aspartate aminotransferase; BSC, best supportive care; GGT, gamma glutamyltransferase; NR, not reported; OS, overall survival; PFS, progression-free survival; RR, relative risk; SD, stable disease; TTP, time to progression.

^aDenotes significant difference.

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AVAGAST and RAINBOW trials, targeting angiogenesis can be active in Asian patients. Apatinib must be evaluated in the United States or European countries to confirm its benefit in the Western population. Further, whether apatinib can be an option in second-line setting or in patients with ramucirumab-refractory disease remains unknown.

Table 5 lists selected ongoing clinical trials in patients with AGC undergoing treatment in the second-line setting. The agents evaluated in this setting include albumin-bound paclitaxel, raltitrexed (thymidylate synthase inhibitor), cabazitaxel (microtubule inhibitor), afuresertib (AKT inhibitor), afatinib (TKI with specificity for HER1, HER3, and HER4), dovitinib (fibroblast growth factor receptor 2), nimotuzumab (EGFR inhibitor), and regorafenib (TKI targeting VEGFR). Based on chemotherapy class effect of taxanes, it is likely that albumin-bound paclitaxel and cabazitaxel may be effective in refractory AGC. However, most of the trials are ongoing,

and results are eagerly awaited. Recent data suggest that blockade of program death 1 (PD-1), an inhibitory receptor expressed by T cells, may have activity in AGC. Pembrolizumab, an anti-PD-1 monoclonal antibody, was evaluated in 39 patients with AGC or gastroesophageal cancers expressing programmed death ligand 1 (PD-L1).⁴⁸ An ORR of 22% with a median DOR of 24 weeks was reported. A 6-month OS rate of 69% was favorable in this heavily pretreated population. PD-L1 positivity was observed in 40% of patients with AGC. Four patients (10%) experienced grade 3 or higher toxicities. Based on these results, further trials are being planned with drugs targeting the PD-1/PD-L1 pathway.

Conclusions

With guarded optimism, progress is finally being made in the treatment of refractory gastric cancer.

Table 5 Selected Ongoing Clinic Trials for Previously Treated Advanced Gastric Cancer

ClinicalTrials.gov Identifier	Phase	Clinical Trial Name
NCT01921673	I/II	Dovitinib Plus Docetaxel in Gastric Cancer
NCT01719549	II	Dovitinib for Gastric Cancer With FGFR2 Amplification
NCT02072317	II	Paclitaxel Plus Raltitrexed Plug Compare With Paclitaxel Second-Line Treatment for Advanced Gastric Cancer
NCT02229045	II	Phase II Study of Albumin Bound Paclitaxel With 5-FU and CF as Second Line in Taxanes Naive Advanced Gastric Cancer
NCT01813253	III	Phase 3 Study of Nimotuzumab and Irinotecan as Second Line With Advanced or Recurrent Gastric and Gastroesophageal Junction Cancer
NCT02274012	III	Trial of Afatinib in Combination With Weekly Paclitaxel in the Second Line Treatment of HER2 Amplified Advanced Gastric, Gastroesophageal Junction and Esophageal Cancer
NCT01956149	II	Study With Cabazitaxel in Previously Treated Patients With Advanced or Metastatic Gastric Cancer
NCT02240212	I/II	Study of Afuresertib Combined With Paclitaxel in Gastric Cancer
NCT01839773	III	A Phase 3 Study to Compare Efficacy and Safety of DHP107 Versus Paclitaxel in Patients With Metastatic or Recurrent Gastric Cancer After Failure of First-line Chemotherapy (DREAM)
NCT01624025	II	A Comparative Study of Salvage Treatment With Combination of Docetaxel and Epirubicin
NCT02178956	III	A Study of BBI608 Plus Weekly Paclitaxel to Treat Gastric and Gastro-Esophageal Junction Cancer (BRIGHTER)
NCT02241720	II	Regorafenib Second Line Treatment of Metastatic or Advanced Upper GI Cancers
NCT01967875	II	A Phase 2 Trial of Optimizing Platinum-Based Chemotherapy Based on ERCC1 Expression as First-Line Treatment in Patients With Locally Advanced or Metastatic Gastric Cancer
NCT02340975	I/II	A Phase 1b/2 Study of MEDI4736 With Tremelimumab, MEDI4736 or Tremelimumab Monotherapy in Gastric or GEJ Adenocarcinoma
NCT02335411	II	A Study of Pembrolizumab (MK-3475) in Participants With Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (MK-3475-059/KEYNOTE-059)

Based on the evidence presented, the authors believe that patients with adequate performance status should be offered second-line therapy. Emerging evidence for OS improvement in the second-line setting in AGC should allow clinicians to reconsider when triplet chemotherapy is appropriate in the first-line setting in view of high toxicity and marginal benefit.

Paclitaxel and ramucirumab can be considered for patients with preserved performance status who have previously experienced disease progression on fluoropyrimidine- and platinum-based therapies. For patients who have previously received taxanes or have significant preexisting neuropathy, single-agent ramucirumab or other single-agent chemotherapy agents not used in the first-line should be considered. For patients with HER2-positive disease in whom first-line chemotherapy plus trastuzumab failed, the optimal second-line therapy is unclear. Therefore, enrollment in a clinical trial is strongly encouraged.

An urgent need exists to develop biomarkers that predict response to active agents. Correlatives should be a mandated part of clinical trial design in the era of targeted therapies. The survival benefit must be weighed against the cost and toxicity of AGC treatment in the palliative setting. Pharmacogenetic variation also must be addressed in clinical trials. This underscores the need to support translational research and encourage accrual on clinical trials. The next generation of clinical trials will continue to test novel targeted agents with biomarkers with the hope of offering new options to patients with refractory gastric cancer.

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Posttest Questions

1. True or False: Second-line chemotherapy improves survival and tumor-related symptoms compared with supportive care for patients with advanced gastric cancer.
2. Which of the following targeted therapy advanced gastric cancer progressing on fluoropyrimidine- and platinum-based therapies.
 - a. Trastuzumab
 - b. Ramucirumab

- c. Apatinib
 - d. Bevacizumab
3. What is the mechanism of action of pembrolizumab that is being evaluated in clinical trials as second-line therapy for advanced gastric cancer?
 - a. Thymidylate synthase inhibitor
 - b. VEGFR inhibitor
 - c. Anti-PD-1 monoclonal antibody
 - d. MET inhibitor