

Phase II Study of Ramucirumab Plus Irinotecan Combination Therapy as Second-Line Treatment in Patients with Advanced Gastric Cancer: HGCSG1603

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Abstract

Background: Ramucirumab is a human IgG1 monoclonal vascular endothelial growth factor receptor-2 antibody that inhibits tumor cell growth and affects the tumor cell microenvironment. We assessed the efficacy and safety of ramucirumab plus irinotecan combination therapy as second-line treatment in patients with previously treated advanced gastric cancer.

Materials and Methods: Patients with advanced gastric cancer refractory or intolerant to primary chemotherapy were included. Ramucirumab 8 mg/kg plus irinotecan 150 mg/m² combination therapy was administered every 2 weeks. The primary endpoint was progression-free survival rate at 6 months and secondary endpoints were overall survival, progression-free survival, response rate, safety, and dose intensity for each drug.

Results: Thirty-five patients were enrolled between January 2018 and September 2019. The progression-free survival rate at 6 months was 26.5% [95%CI, 13.2%–41.8%, $P = .1353$]. Median progression-free and overall survivals were 4.2 months (95%CI, 2.5–5.4 months) and 9.6 months (95%CI, 6.4–16.6 months), respectively. The overall response rate was 25.9% (95%CI, 11.1–36.3%) and disease control rate was 85.2% (95%CI, 66.3–95.8%). Grade ≥ 3 adverse events that occurred in >10% of patients included neutropenia, leucopenia, anemia, anorexia, and febrile neutropenia. No death or new safety signals with a causal relation to the study treatment were observed.

Conclusion: Although the primary endpoint was not achieved statistically, combination therapy of ramucirumab plus irinotecan showed anticancer activity and a manageable safety profile for second-line treatment of patients with advanced gastric cancer.

Keywords: gastric cancer; ramucirumab; irinotecan; second-line treatment

Implications for Practice

There have been no studies into the efficacy of ramucirumab plus irinotecan combination therapy for advanced gastric cancer. This single arm, phase II multicenter trial evaluated the efficacy and safety of ramucirumab plus irinotecan combination therapy as second-line treatment in patients with previously treated advanced gastric cancer. Although the primary endpoint was not achieved statistically, this regimen showed anticancer activity and a manageable safety profile. Ramucirumab plus irinotecan might be considered as an option for second-line treatment of patients with advanced gastric cancer for whom taxane is difficult to use.

Introduction

Gastric cancer was the fifth leading cause of cancer death worldwide in 2020.¹ Approximately 60% of all patients diagnosed with gastric cancer are in East Asian countries, including Japan, Korea, and China.² Systemic chemotherapy is the standard treatment for advanced or recurrent cases and was shown to prolong survival and provide clinically significant benefits in several randomized controlled trials that compared best supportive care with chemotherapy in patients with advanced gastric cancer.³⁻⁵ Several clinical trials examining the use of primary chemotherapy for unresectable advanced or recurrent gastric and esophagogastric junction cancer have reported standard chemotherapy of platinum-based and fluoropyrimidine-based combinations for human epidermal growth factor receptor 2 (HER2)-negative gastric cancer and platinum-based and fluoropyrimidine-based in combination with trastuzumab for HER2-positive gastric cancer.⁶⁻⁸ Recently, the efficacy of nivolumab, immune checkpoint inhibitor, plus chemotherapy (oxaliplatin plus fluoropyrimidine) for HER2-negative gastric or gastro-esophageal cancer was reported in CheckMate-649 and ATTRACTION-4.^{9,10} Chemotherapy can be used as second-line treatment for gastric cancer, and several clinical trials have shown survival benefits with its administration.¹¹⁻¹⁶ Later lines of treatment have shown the efficacy of immune checkpoint inhibitors and trifluridine-tipiracil.^{17,18} In HER2-positive gastric cancer, the efficacy of trastuzumab deruxtecan has been reported in third-line DESTINY-Gastric01 and second-line DESTINY-Gastric02.^{19,20} However, treatment outcomes remain unsatisfactory and more effective treatment regimens are required.

Ramucirumab is a fully human IgG1 monoclonal vascular endothelial growth factor receptor-2 (VEGFR-2) antibody that prevents ligand binding of VEGF-A, VEGF-C, and VEGF-D as well as receptor-mediated pathway activation in endothelial cells, which subsequently inhibits neovascularization.²¹ Ramucirumab is an angiogenesis inhibitor that acts by inhibiting neogenesis and promoting the regression of tumor vessels, resulting in the normalization of residual blood vessels, which can then promote the delivery of anticancer drugs to the tumor.²²⁻²⁵ Therefore, ramucirumab inhibits tumor cell growth and affects the tumor cell microenvironment. The median overall survival in the ramucirumab monotherapy for previously treated advanced gastric or gastroesophageal junction adenocarcinoma (REGARD) study was 5.2 and 3.8 months in the ramucirumab and placebo groups, respectively [hazard ratio (HR), 0.776; 95% confidence interval (CI), 0.603-0.998; $P = .0473$].²⁶ Overall survival was longer in the ramucirumab plus paclitaxel group compared with placebo plus paclitaxel group in patients with previously treated advanced gastric or gastroesophageal junction adenocarcinoma (RAINBOW) trial in patients with disease progression at or within 4 months after first-line chemotherapy (platinum plus fluoropyrimidine) (median, 9.6 months; 95% CI, 8.5-10.8 versus 7.4 months; 95% CI, 6.3-8.4; HR, 0.807; 95% CI, 0.678-0.962; $P = .017$).¹⁶ In addition, there is a report that ramucirumab plus paclitaxel has better response after immune checkpoint inhibitor therapy in advanced gastric cancer.²⁷

In contrast, there have been no studies into the efficacy of ramucirumab plus irinotecan combination therapy as second-line treatment for gastric cancer. The WJOG 4007 study demonstrated that the efficacy of irinotecan was equivalent

to that of paclitaxel.¹⁴ Combination therapy of ramucirumab plus irinotecan has shown a favorable outcome in patients with colorectal cancer.²⁸

These results indicate that ramucirumab plus irinotecan combination therapy should show an improved efficacy. In addition, it is also considered that the patient who could not receive paclitaxel in the second-line treatment would increase by introduction of taxane to perioperative chemotherapy or first-line treatment and residual peripheral neuropathy by oxaliplatin of the first-line treatment. Therefore, the present trial, HGCSG1603, examined the efficacy and safety of ramucirumab plus irinotecan combination therapy as second-line treatment in patients with previously treated advanced gastric cancer.

Materials and Methods

Study Design and Participants

This non-randomized, single arm, prospective, multicenter, phase 2 trial was conducted at 22 centers in Japan. The study included adults aged ≥ 20 years with confirmed unresectable advanced or recurrent gastric adenocarcinoma that was refractory or intolerant to initial chemotherapy. Further inclusion criteria were: Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; no history of irinotecan treatment; laboratory findings of adequate bone marrow, hepatic, and renal function 14 days prior to enrollment; and confirmation of progression or recurrence following initial treatment and the potential presence of an evaluable lesion < 28 days prior to registration according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The presence or absence of a measurable lesion was not an inclusion criterion. Patients negative for HER-2/neu and those with unknown HER-2/neu status were eligible. HER-2/neu-positive patients were eligible if they had received treatment, including trastuzumab, and if disease progression was confirmed. Patients were excluded if they had undergone major surgery within 28 days prior to registration. Further exclusion criteria were: history of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism during the 3 months prior to the first dose of trial therapy; administration of anticoagulant therapy such as warfarin and low-molecular weight heparin; any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack within the previous 6 months; any grades 3-4 gastrointestinal bleeding within the previous 3 months; and pericardial or pleural effusion, or ascites requiring treatment. The Supplementary appendix provides the full inclusion and exclusion criteria.

The trial was conducted in accordance with the Declaration of Helsinki (October 2013 revision) and Ethics Guidelines 2014 of the Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labor, and Welfare notification tertiary for biomedical research on humans and was approved by the Institutional Review Boards of each participating institute. The trial received approval from the Hokkaido University Hospital Research Ethics Committee. All patients provided written informed consent prior to enrolling into the study. This trial was registered with the public database of the University Hospital Medical Information Network Clinical Trials Registry (UMIN000030372) and Japan Registry of Clinical Trials (jRCTs011180029).

Procedures

Patients received ramucirumab 8 mg/kg and irinotecan 150 mg/m² intravenously on day one of 14-day cycle. Patients with *UGT1A1* genetic polymorphisms who were homozygous or double heterozygous for *UGT1A1**6 or *UGT1A1**28 received 120 mg/m² irinotecan. Doses could be modified to manage treatment-related toxic effects. Criteria for dose reduction, dose delay or skip are presented in the Supplementary appendix.

The overall response rate was calculated based on the RECIST version 1.1 criteria. The progression-free survival and overall survival were determined using the Kaplan-Meier method. Safety was evaluated in the safety analysis group using the Common Terminology Criteria for Advanced Events version 4.0.

Outcomes and Statistical Analysis

The primary endpoint was the progression-free survival rate at 6 months. The secondary endpoints were overall survival, progression-free survival, overall response rate, safety, and dose intensity for each drug.

The median progression-free survival with irinotecan monotherapy as second-line treatment for gastric cancer was 2.3-4.2 months.¹¹⁻¹⁵ Furthermore, the median progression-free survival with ramucirumab in combination with paclitaxel in the RAINBOW study was 4.4 months.¹⁶ Based on these results, the target progression-free survival at 6 months was set with a threshold of 16% (median progression-free survival, 2.3 months) and an expected value of 39% (median progression-free survival, 4.4 months). A 2-sided significance level was set to 5%, a registration period was 24 months, and a follow-up period was 12 months. The minimum sample size required to achieve a detection power of 80% was found to be 31.²⁹ A total of 35 patients were planned for registration to allow for potential dropout (eg, due to ineligibility).

The progression-free survival and overall survival were estimated using Kaplan-Meier method and their 95% CIs were calculated with a complementary log-log transformation. Univariate and multivariate analyses using Cox proportional hazards models were performed to evaluate the association between clinical features (ie, age, sex, ECOG performance status, HER2, liver metastasis, peritoneum metastasis, and measurable lesion) and progression-free survival or overall survival. All statistical analyses were performed using IBM SPSS Statistic version 24.0 (IBM, Armonk, NY).

Results

Thirty-five patients were enrolled between January 2018 and September 2019. All patients received at least one cycle study

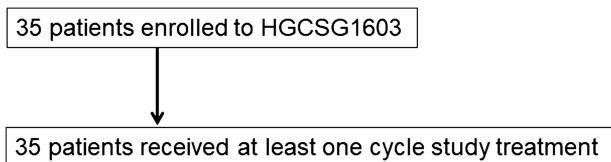


Figure 1. Flow chart of HGCSG1603. Thirty-five patients were enrolled during the planned registration period. All patients received at least one cycle study treatment and were included in the full analysis set and safety population.

Table 1. Baseline characteristics.

	N = 35 (%)
Age, years	
Median (range)	70 (47-80)
<70	16 (46%)
≥70	19 (54%)
Sex	
Female	10 (29%)
Male	25 (71%)
ECOG performance status	
0	22 (63%)
1	13 (37%)
Primary tumor site	
Gastroesophageal junction	4 (11%)
Stomach	31 (89%)
Histological subtype	
Intestinal	17 (49%)
Diffuse	13 (37%)
Mixed	5 (14%)
HER2 status	
Negative	24 (69%)
Positive	9 (26%)
Not tested	2 (6%)
<i>UGT1A1</i> status (*6/*28)	
Wild type	14 (40%)
Single heterozygous	13 (37%)
Double variant	1 (3%)
Not tested	7 (20%)
Metastatic site	
Lymph node	23 (66%)
Peritoneum	18 (51%)
Liver	12 (34%)
Lung	2 (6%)
Measurable lesion	
Present	27 (77%)
Absent	8 (23%)
First-line treatment	
S-1 + oxaliplatin	17 (49%)
Capecitabine + oxaliplatin	7 (20%)
FOLFOX	6 (17%)
Nab-paclitaxel + S-1 + oxaliplatin	1 (3%)
Docetaxel + S-1 + CDDP	1 (3%)
S-1 + CDDP	1 (3%)
Capecitabine + CDDP	1 (3%)
S-1 + docetaxel	1 (3%)
Prior trastuzumab	
Yes	9 (26%)
No	26 (74%)
Prior ramucirumab	
Yes	0 (0%)
No	35 (100%)
Previous gastrectomy	
Yes	8 (23%)
No	27 (77%)

Data are presented as N (%) or median (range). Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; S-1, tegafur, oteracil, and gimeracil; CDDP, cisplatin; FOLFOX, leucovorin, fluorouracil, and oxaliplatin.

Table 3. Univariate and multivariate analyses of overall survival.

	N	Univariate	P	Multivariate	P
Age, years					
<70	16	1 (ref)		1 (ref)	
≥70	19	0.430 [0.186-0.996]	0.049	0.253 [0.091-0.702]	0.008
Sex					
Female	10	1 (ref)		1 (ref)	
Male	25	1.401 [0.555-3.537]	0.476	1.289 [0.494-3.360]	0.604
ECOG performance status					
0	22	1 (ref)		1 (ref)	
1	13	1.701 [0.756-3.829]	0.199	2.122 [0.886-5.084]	0.091
HER2					
Negative + not tested	26	1 (ref)		1 (ref)	
Positive	9	1.891 [0.749-4.773]	0.178	1.320 [0.484-3.597]	0.587
Liver metastasis					
Absent	23	1 (ref)		1 (ref)	
Present	12	1.860 [0.800-4.323]	0.150	2.610 [0.938-7.258]	0.066
Peritoneum metastasis					
Absent	17	1 (ref)			
Present	18	1.031 [0.459-2.314]	0.941		
Measurable lesion					
Absent	8	1 (Ref)			
Present	27	1.121 [0.416-3.021]	0.821		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.

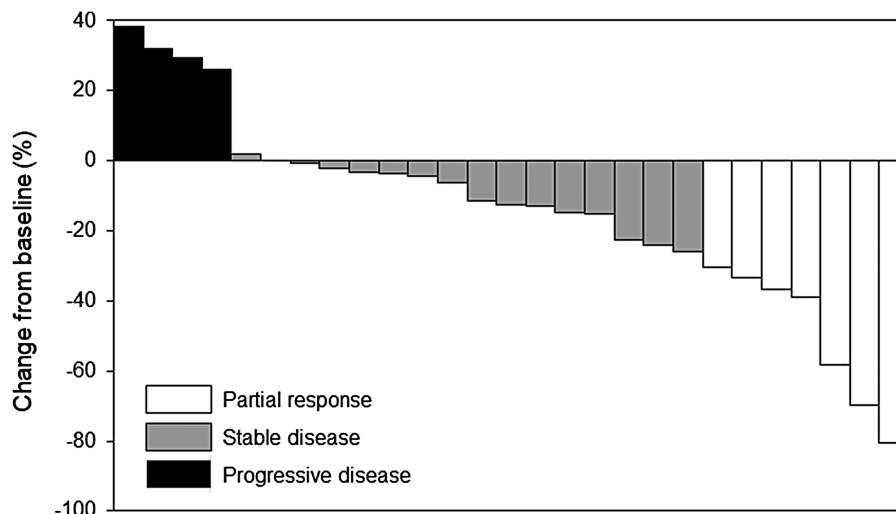


Figure 3. Waterfall plot of maximum percentage in tumor size from baseline. Change in tumor size was assessed by Response Evaluation Criteria in Solid Tumors version 1.1. The overall response rate was 25.9% (95%CI, 11.1%-36.3%) and the disease control rate was 85.2% (95%CI, 66.3%-95.8%) in 27 patients with at least one measurable lesion.

One patient received curative resection and one continued the study treatment at the data cutoff for analysis. The other 3 patients discontinued study treatment at the discretion of the attending physician.

Progression-free survival rate at 6 months was 26.5% (95%CI, 13.2%–41.8%, $P = .1353$). Median progression-free survival and overall survival were 4.2 months (95%CI, 2.5–5.4 months) and 9.6 months (95%CI, 6.4–16.6 months),

respectively (Fig. 2). Univariate and multivariate analyses of progression-free survival and overall survival according to Cox proportional hazards models are presented in Tables 2 and 3. Analysis of patients aged <70 years and ≥70 years revealed progression-free survival of 2.8 and 4.2 months, and overall survival of 5.1 and 15.6 months, respectively. The efficacy of this therapy was even shown in the elderly. The overall response rate was 25.9% (95%CI, 11.1%–36.3%) and the

Table 4. Adverse events occurring in $\geq 10\%$ of the patients, irrespective of causality.

	All grade		\geq Grade 3	
	n	%	n	%
<i>Non-hematological adverse events</i>				
Hypertension	32	91	3	9
Fatigue	24	69	1	3
Anorexia	22	63	5	14
Proteinuria	18	51	3	9
Diarrhea	17	49	3	9
Alopecia	15	43	—	—
Nausea	12	34	0	0
Vomiting	9	26	0	0
Epistaxis	4	11	0	0
<i>Hematological adverse events</i>				
Neutrophil count decreased	29	83	18	51
Anemia	29	83	7	20
White blood cell count decreased	27	77	15	43
Platelet count decreased	22	63	2	6
Febrile neutropenia	4	11	4	11

disease control rate was 85.2% (95%CI, 66.3%–95.8%) in patients with at least one measurable lesion (Fig. 3).

Adverse events are shown in Table 4. Adverse events of grade ≥ 3 that occurred in $>5\%$ of patients included neutropenia (51%), leucopenia (43%), anemia (20%), anorexia (14%), febrile neutropenia (11%), diarrhea (9%), hypertension (9%), proteinuria (9%), and thrombocytopenia (6%). No death or new safety signals with a causal relation to the study treatment were observed.

Discussion

This single arm, phase II multicenter trial evaluated the efficacy and safety of ramucirumab plus irinotecan combination therapy as second-line treatment in patients with advanced gastric cancer. The progression-free survival rate at 6 months was 26.5% and the trial did not meet its primary endpoint. However, the secondary endpoints of median overall survival and progression-free survival were comparable to those reported in the RAINBOW trial,¹⁶ and the antitumor activity was effective. These results are clinically encouraging, particularly since more elderly patients were enrolled in the present trial. The response rate was 25.9%, which was also comparable to that reported in the RAINBOW trial.¹⁶ Despite a median progression-free survival comparable to that of RAINBOW trial, the reasons why the progression-free survival rate at 6 months for the primary endpoint was not statistically hypothesized were high expectation setting and smaller sample size. Expected value was estimated from Kaplan-Meier curve of progression-free survival from RAINBOW trial, but an exploratory phase II trial may have required a slightly lower expectation and a larger sample size.

The success of neoadjuvant and adjuvant chemotherapy containing docetaxel was recently reported in the FLOT and JACCRO GC-07 studies.³⁰⁻³² Furthermore, the effectiveness of taxane combination therapy as a first-line therapy has been previously reported in advanced gastric cancer.³³⁻³⁵ The phase

II RAMIRIS study showed that second-line paclitaxel plus ramucirumab was less effective in patients pretreated with docetaxel.³⁶ In addition, the use of oxaliplatin has become the mainstay of first-line treatment for gastric cancer. Oxaliplatin is increasingly used in the control arms of recent first-line clinical trials, and has been administered in most of the first-line therapies even in general practice. In the present trial, 89% of patients also received oxaliplatin in their pretreatment. It is anticipated that patients who are taxane refractory to prior therapy or transition to second-line therapy in an inappropriate condition due to residual peripheral neuropathy by oxaliplatin would remain constant and may be an important second-line treatment option for these patients.

It is unclear why better results have been obtained in people aged 70 years or older in univariate and multivariate analyses. This trial had a small sample size and may include some potential bias. Rather than better results at age 70 years or older, it is also considered that patients younger than 70 years may have had a poor prognosis that was refractory to treatment.

Although 26% of HER2-positive patients were included in this trial, according to the findings of DESTINY-Gastric 02 study, HER2-positive patients may become the mainstay of treatment with trastuzumab-deruxtecan in the second-line setting in the future.²⁰

Combined treatment using ramucirumab plus irinotecan showed an acceptable safety profile and no new or unexpected toxicities were observed in this trial. The most common grade ≥ 3 adverse events included neutropenia, leucopenia, anemia, anorexia, and febrile neutropenia. Myelosuppression was slightly more frequent than in RAINBOW trial. The large number of elderly patients in this trial may be influential. However, all of them were manageable with appropriate supportive care.

The present trial has some limitations. First, this was a single arm phase II trial with a small sample size. A phase III trial comparing ramucirumab plus irinotecan with ramucirumab plus paclitaxel, the standard second-line therapy, may be considered. Second, immune checkpoint inhibitors are transitioning to first-line treatment of gastric cancer and the consequences in patients receiving immune checkpoint inhibitors as first-line therapy remain unknown. No patients used immune checkpoint inhibitors as first-line treatment in this trial. Third, no biomarker studies were conducted in this trial and the populations that are likely to benefit from using this regimen were not identified.

Conclusion

Although the primary endpoint was not achieved statistically, combination therapy of ramucirumab plus irinotecan showed anticancer activity and a manageable safety profile. Although larger further explore studies are warranted, this therapy might be considered as an option for second-line treatment of patients with advanced gastric cancer for whom taxane administration is inappropriate due to prior treatment or residual peripheral neuropathy.

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Conflict of Interest

Yasuyuki Kawamoto: Eli Lilly Japan, Merck Biopharma, Daiichi Sankyo, Taiho Pharma, Takeda Pharma and Yakult Honsha (H), Takeda Pharma (RF); **Satoshi Yuki:** Eli Lilly Japan, and Yakult Honsha (H); **Kentaro Sawada:** Chugai Pharma, Ono Pharma, Taiho Pharma, Merck Biopharma, and Takeda Pharma (H); **Michio Nakamura:** Eli Lilly Japan, Takeda Pharma, Sanofi, Daiichi Sankyo, Taiho Pharma, Chugai Pharma, Bayer Holding, and Bristol-Myers Squibb (H); **Yasushi Tsuji:** Eli Lilly Japan (H); **Yuh Sakata:** Eli Lilly Japan, Yakult Honsha, Taiho Pharma, and Bristol-Myers Squibb (H), Delta-Fly Pharma (OI—family); **Yoshito Komatsu:** Chugai, Eli Lilly Japan, Taiho Pharma, Takeda Pharma, Daiichi-Sankyo, and Ono Pharma (H), Taiho Pharma, and Chugai Pharma (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Author Contributions

Conception/Design: Y.K., S.Y., Y.S., N.S., and Y.K. Provision of study material/patients: Y.K., S.Y., K.S., M.N., Y.T., Y.S., and Y.K. Collection and/or assembly of data: Y.K., S.Y., M.S., Y.S., N.S., and Y.K. Data analysis and interpretation: Y.K., S.Y., K.O., Y.M.I., Y.S., N.S., and Y.K. Manuscript writing: Y.K., S.Y., Y.S., N.S., and Y.K. Final approval of manuscript: All authors.

Data Availability

The data underlying this article cannot be shared publicly because informed consent has not been obtained from the study subjects for secondary use of the data in the study. The data will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

References

1. The Global Cancer Observatory. Available at <https://gco.iarc.fr/>. (November 22, 2021, date accessed).
2. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer*. 2010;46:765-781. <https://doi.org/10.1016/j.ejca.2009.12.014>.
3. Glimelius B, Hoffman K, Haglund U, Nyren O, Sjoden PO. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. *Ann Oncol*. 1994;5:189-190. <https://doi.org/10.1093/oxfordjournals.annonc.a058778>.
4. Murad AM, Santiago FF, Petroianu A, et al. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer*. 1993;72:37-41.
5. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer*. 1995;71:587-591. <https://doi.org/10.1038/bjc.1995.114>.
6. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27:v38-v49. <https://doi.org/10.1093/annonc/mdw350>.
7. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer*. 2021;24:1-21. <https://doi.org/10.1007/s10120-020-01042-y>.
8. Bang YJ, Van Cutsem E, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687-697. [https://doi.org/10.1016/S0140-6736\(10\)61121-X](https://doi.org/10.1016/S0140-6736(10)61121-X).
9. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021;398:27-40. [https://doi.org/10.1016/S0140-6736\(21\)00797-2](https://doi.org/10.1016/S0140-6736(21)00797-2).
10. Kang YK, Chen LT, Ryu MH, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2022;23:234-247. [https://doi.org/10.1016/S1470-2045\(21\)00692-6](https://doi.org/10.1016/S1470-2045(21)00692-6).
11. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer*. 2011;47:2306-2314. <https://doi.org/10.1016/j.ejca.2011.06.002>.
12. Kang JH, Lee SI, Lim do H, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol*. 2012;30:1513-1518.
13. Mochizuki Y, Ohashi N, Kojima H, et al. CPT-11 as a second-line treatment for patients with advanced/metastatic gastric cancer who failed S-1 (CCOG0702). *Cancer Chemother Pharmacol*. 2013;72:629-635. <https://doi.org/10.1007/s00280-013-2235-5>.
14. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol*. 2013;31:4438-4444. <https://doi.org/10.1200/JCO.2012.48.5805>.
15. Satoh T, Lee KH, Rha SY, et al. Randomized phase II trial of nimotuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer. *Gastric Cancer* 2015;18:824-832. <https://doi.org/10.1007/s10120-014-0420-9>.
16. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol*. 2014;15:1224-1235. [https://doi.org/10.1016/S1470-2045\(14\)70420-6](https://doi.org/10.1016/S1470-2045(14)70420-6).
17. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;390:2461-2471. [https://doi.org/10.1016/S0140-6736\(17\)31827-5](https://doi.org/10.1016/S0140-6736(17)31827-5).
18. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3

- trial. *Lancet Oncol.* 2018;19:1437-1448. [https://doi.org/10.1016/S1470-2045\(18\)30739-3](https://doi.org/10.1016/S1470-2045(18)30739-3).
19. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med.* 2020;382:2419-2430. <https://doi.org/10.1056/NEJ-Moa2004413>.
 20. Van Cutsem E, Di Bartolomeo M, Smyth E, et al. Primary analysis of a phase II single-arm trial of trastuzumab deruxtecan (T-DXd) in western patients (Pts) with HER2-positive (HER2+) unresectable or metastatic gastric or gastroesophageal junction (GEJ) cancer who progressed on or after a trastuzumab-containing regimen. *Ann Oncology* 2021;32(suppl_5):S1283-S1346.
 21. Spratlin JL, Cohen RB, Eadens M, et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol.* 2010;28:780-787. <https://doi.org/10.1200/JCO.2009.23.7537>.
 22. Dickson PV, Hamner JB, Sims TL, et al. Bevacizumab-induced transient remodeling of the vasculature in neuroblastoma xenografts results in improved delivery and efficacy of systemically administered chemotherapy. *Clin Cancer Res.* 2007;13:3942-3950. <https://doi.org/10.1158/1078-0432.CCR-07-0278>.
 23. O'Connor JP, Carano RA, Clamp AR, et al. Quantifying antivascular effects of monoclonal antibodies to vascular endothelial growth factor: insights from imaging. *Clin Cancer Res.* 2009;15:6674-6682. <https://doi.org/10.1158/1078-0432.CCR-09-0731>.
 24. Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat Med.* 2004;10:145-147. <https://doi.org/10.1038/nm988>.
 25. Yanagisawa M, Yorozu K, Kurasawa M, et al. Bevacizumab improves the delivery and efficacy of paclitaxel. *Anti-cancer Drugs.* 2010;21:687-694. <https://doi.org/10.1097/CAD.0b013e32833b7598>.
 26. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014;383:31-39. [https://doi.org/10.1016/S0140-6736\(13\)61719-5](https://doi.org/10.1016/S0140-6736(13)61719-5).
 27. Sasaki A, Kawazoe A, Eto T, et al. Improved efficacy of taxanes and ramucirumab combination chemotherapy after exposure to anti-PD-1 therapy in advanced gastric cancer. *ESMO Open* 2020;5:e000775. <https://doi.org/10.1136/esmoopen-2020-000775>.
 28. Tabarnero J, Yoshino T, Cochrane AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol.* 2015;16:499-508.
 29. Fleming TR, Harrington DP. Counting processes and survival analysis. Wiley 1991:236-237.
 30. Al-Batran SE, Homann N, Pauligk C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: The AIO-FLOT3 trial. *JAMA Oncol* 2017;3:1237-1244. <https://doi.org/10.1001/jamaoncol.2017.0515>.
 31. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 2019;393:1948-1957. [https://doi.org/10.1016/S0140-6736\(18\)32557-1](https://doi.org/10.1016/S0140-6736(18)32557-1).
 32. Yoshida K, Kodera Y, Kochi M, et al. Addition of docetaxel to oral fluoropyrimidine improves efficacy in patients with stage III gastric cancer: interim analysis of JACCRO GC-07, a randomized controlled trial. *J Clin Oncol.* 2019;37:1296-1304. <https://doi.org/10.1200/JCO.18.01138>.
 33. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol.* 2006;24:4991-4997. <https://doi.org/10.1200/JCO.2006.06.8429>.
 34. Ajani JA, Moiseyenko VM, Tjulandin S, et al. Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 Study Group. *J Clin Oncol.* 2007;25:3205-3209. <https://doi.org/10.1200/JCO.2006.10.4968>.
 35. Shah MA, Janjigian YY, Stoller R, et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US gastric cancer consortium. *J Clin Oncol.* 2015;33:3874-3879. <https://doi.org/10.1200/JCO.2015.60.7465>.
 36. Thuss-Patience PC, Al-Batran S, Pauligk C, et al. FOLFIRI plus ramucirumab versus paclitaxel plus ramucirumab as second-line therapy for patients with advanced or metastatic gastroesophageal adenocarcinoma with or without prior docetaxel—final results from the phase II RAMIRIS study of the AIO. *Ann Oncol.* 2020;31:S841-S873.