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Salvage-line of Capecitabine Plus Oxaliplatin Therapy (XELOX) for Patients With Inoperable/Advanced Gastric Cancer Resistant/Intolerant to Cisplatin (OGSG1403)

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Abstract. *Background/Aim: No prospective study has evaluated salvage chemotherapy with capecitabine plus oxaliplatin (XELOX) in patients with gastric cancer who are resistant to or intolerant of cisplatin. Patients and Methods: This multicenter, open-label, single-arm, phase II study was conducted at six centers in Japan, enrolling patients with metastatic or advanced gastric cancer resistant to or intolerant of fluoropyrimidine, cisplatin, taxane, and irinotecan. Capecitabine 1,000 mg/m^2 was administered orally twice daily for 14 days, followed by a 7-day rest period. Oxaliplatin 130 mg/m^2 was administered intravenously on day one. The primary endpoint was disease control rate (DCR). Secondary endpoints included response rate (RR), progression-free survival (PFS), overall survival (OS), time to treatment failure (TTF), and safety. Results: The study was terminated prematurely due to poor accrual, with 12 patients enrolled. Eight patients demonstrated resistance to prior cisplatin, while four experienced unacceptable toxicity. The median age was 64 years, and eight were male. Four, six, and two patients had Eastern Cooperative Oncology Group performance status 0, 1, and 2, respectively. Among 10 evaluable patients, DCR was 90%, with an RR of 30%. Median PFS, TTF, and OS were 4.2 months [95% confidence interval (CI)=1.4-5.3], 4.1 months (95%CI=1.4-4.4), and 7.1 months (95%CI=2.3-10.1), respectively. The most frequently reported grade 3-4 adverse events were fatigue (20%) and hypokalemia (20%). No treatment-related deaths occurred. Conclusion: Salvage chemotherapy with XELOX may offer clinical benefits for patients with metastatic or advanced gastric cancer resistant to or intolerant of cisplatin.*

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Key Words: Cancer chemotherapy agents, gastric cancer, platinum cross-resistant, progression-free survival, salvage therapy.

Gastric cancer is the fifth most common cancer worldwide and the fifth leading cause of cancer-related deaths annually (1). In most patients with inoperable advanced gastric cancer, the only option is palliative systemic therapy (2). Platinum compounds combined with fluoropyrimidines are the most common first-line treatment for patients with advanced or metastatic human epidermal growth factor receptor (HER)2-negative gastric cancer, with trastuzumab added for HER2-positive cases, as recommended by the European Society for Medical Oncology,

the Japanese Gastric Cancer Association (JGCA), the National Comprehensive Cancer Network, and the Asian resource-stratified treatment guidelines (3-6). Recently, immune checkpoint inhibitors combined with chemotherapy, as well as zolbetuximab combined with chemotherapy, have become first-line treatments for HER2-negative gastric cancer (7-12). However, the chemotherapy used in these regimens still includes platinum compounds and fluoropyrimidines.

For second-line treatment, ramucirumab, a vascular endothelial growth factor receptor (VEGFR)-2 inhibitor, combined with paclitaxel, has shown superior efficacy compared to paclitaxel alone in the RAINBOW trial (13). As a result, ramucirumab plus paclitaxel is recommended in the Japanese gastric cancer treatment guidelines (12).

The ATTRACTION-2 (14) and TAGS (15) trials demonstrated the efficacy of nivolumab and trifluridine/tipiracil (FTD/TPI) as salvage therapies. Consequently, both drugs have been approved by the Pharmaceuticals and Medical Devices Agency in Japan and are currently used in daily clinical practice for salvage treatment.

In the 4th edition of the Japanese Gastric Cancer Association (JGCA) guidelines (16), only first-line and second-line treatments were discussed, with no mention of salvage therapy. Thus, no established salvage treatments existed when we planned the current study in 2015, representing an unmet medical need for gastric cancer patients. We hypothesized that oxaliplatin-based chemotherapy could be a potential candidate, given that several reports have suggested the efficacy of FOLFOX, a regimen consisting of oxaliplatin, 5-FU, and leucovorin, as salvage chemotherapy in gastric cancer patients refractory to cisplatin (17-20). Since no prospective study had evaluated the efficacy of oral fluoropyrimidines plus oxaliplatin in this setting, we conducted a prospective phase II study to evaluate the efficacy and toxicity of capecitabine plus oxaliplatin combination therapy (XELOX) as a salvage treatment.

Patients and Methods

Study design and setting. This study, conducted by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG 1403), was a multicenter, open-label, single-arm, phase II trial conducted at six centers in Japan from July 2015 to December 2017. The study adhered to the Good Clinical Practice Guidelines and the ethical principles outlined in the Declaration of Helsinki (1964) and its subsequent amendments. The study protocol was approved by the institutional review boards of each center. The trial was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000016256).

Patients. Patients with metastatic or advanced gastric cancer who were resistant to or intolerant of fluoropyrimidines, cisplatin, taxanes, and irinotecan were eligible for this study. The eligibility criteria were as follows: patients aged 20 years or older with histologically confirmed unresectable advanced or recurrent gastric adenocarcinoma; prior chemotherapy including fluoropyrimidines, with cancer refractory or intolerant to fluoropyrimidines, cisplatin, taxanes, and irinotecan (intolerance included avoidance of administration due to concerns about adverse events); measurable lesions as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines (version 1.1); an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2; and adequate bone marrow function (hemoglobin level ≥8.0 g/dl, neutrophil count ≥1,500/mm^3, platelet count ≥100,000/mm^3), hepatic function [serum total bilirubin concentration ≤1.5 mg/dl, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤100 U/l], and renal function (serum creatinine concentration ≤1.2 mg/dl).

The exclusion criteria were as follows: prior treatment with oxaliplatin, insufficient oral intake, brain metastasis, interstitial pneumonia, pulmonary fibrosis, active bleeding, massive pleural effusions or ascites, and grade 2 or higher severe peripheral sensory neuropathy.

All patients provided written informed consent before enrollment in the study.

Treatment. Within one treatment cycle, capecitabine 1,000 mg/m^2 was administered orally twice daily for 14 days, followed by a 7-day rest period. Oxaliplatin 130 mg/m^2 was administered by intravenous infusion on day one. This treatment cycle was repeated until disease progression, unacceptable toxicity, or patient withdrawal of consent. The primary endpoint was the disease control rate (DCR), and the secondary endpoints were objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety.

Measurable lesions were assessed according to RECIST version 1.1. No independent radiologic review was performed. DCR and ORR were evaluated based on these response criteria. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. PFS was defined as the interval from the start of treatment to death from any cause or radiologic progression, as judged by the investigators. OS was defined as the interval from the start of treatment to death from any cause. Patients without progressive disease who were alive at the data cutoff date and those lost to follow-up were censored at the date of their last evaluation.

Statistical methods. Continuous data were presented as the median (range). Categorical variables were presented as the number (%). The DCR threshold for accepting the null hypothesis was defined as 25%, and the expected DCR under the alternative hypothesis was 45%, based on the GRANITE-1 and REGARD trials (21, 22). A significance level of 5% and a power of 80% were used, considering patients excluded from the full analysis set. Given the possibility of patient withdrawal and ineligibility, we planned to enroll 30 patients in the study. As this study was the first to investigate this combination regimen, the Data and Safety Monitoring Committee initially assessed feasibility in six patients. ORR, DCR, PFS, OS, and safety analyses were performed in the full analysis set, which included all enrolled patients who received the study treatment. Survival data were analyzed using the Kaplan–Meier method. All statistical analyses were performed using R software, version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients. Although we initially planned to enroll 30 patients in the study, it was terminated prematurely due to poor accrual. As a result, 12 patients were enrolled from six institutions between

Table I. *Patients' demographical and clinical characteristics in this study on capecitabine plus oxaliplatin salvage treatment for advanced gastric cancer.*

Characteristics	(N=12)
Median age, y (range)	64 (57-75)
Sex, male/female	8/4
ECOG PS, 0/1/2	4/6/2
Histology, diff/undiff/unknown	4/7/1
HER2, +/–	1/11
Prior surgery, yes/no	8/4
Neoadjuvant chemotherapy, yes/no	2/10
Adjuvant chemotherapy, yes/no	7/5
Cisplatin, resistant/intolerable	8/4
Cisplatin, neoadjuvant or adjuvant setting/unresectable advanced or recurrent setting	4/10*
Prior fluoropyrimidine, S-1/capecitabine	10/3*
Prior fluoropyrimidine, neoadjuvant or adjuvant setting/unresectable advanced or recurrent setting	7/9*
Taxane, neoadjuvant or adjuvant setting/unresectable advanced or recurrent setting	2/12*
Irinotecan, neoadjuvant or adjuvant setting/unresectable advanced or recurrent setting/no	0/9/3
Number of drugs for unresectable advanced or recurrent setting (among fluoropyrimidines, cisplatin, taxanes, and irinotecan), 1/2/3/4	1/1/3/7
Number of prior regimens for unresectable advanced or recurrent setting, 1/2/3/4/5/6	1/2/5/3/0/1

ECOG PS: Eastern Cooperative Oncology Group performance score; diff: differentiated; undiff: undifferentiated; HER2: human epidermal growth factor receptor 2; *Duplicates included.

Table II. *Adverse events in this study on capecitabine plus oxaliplatin salvage treatment for advanced gastric cancer (n=10).*

	All Grades n (%)	>G3 n (%)
Leucopenia	4 (40)	0
Neutropenia	2 (20)	0
Anemia	3 (30)	1 (10)
Thrombocytopenia	4 (40)	1 (10)
Nausea	3 (30)	0
Vomiting	2 (20)	0
Fatigue	3 (30)	2 (20)
Anorexia	2 (20)	1 (10)
Infection	1 (10)	1 (10)
Diarrhea	6 (60)	1 (10)
Fever	3 (30)	1 (10)
Sensory neuropathy	5 (50)	0
Hypoalbuminemia	5 (50)	1 (10)
Hypokalemia	4 (40)	2 (20)

July 2015 and December 2017. Patient characteristics are summarized in Table I. The median age of the patients was 64 years (range=57-75 years). Two patients (17%) had an ECOG performance status of 2. The number of prior treatment regimens was two or three in eight patients (67%) and four or more in four patients (33%). Cisplatin was administered to all patients: eight patients discontinued cisplatin therapy due to disease progression, two due to unacceptable toxicities, and two did not receive postoperative cisplatin due to frailty, despite having received neoadjuvant cisplatin. All patients had previously received fluorouracil and taxanes; ten patients (83%) had received ramucirumab, and nine (75%) had received irinotecan.

Table III. *Best overall response.*

	CR	PR	SD	PD	NE
(n=10)	0	3	6	1	0

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluated.

At the time of analysis, protocol treatment had been discontinued in all patients. The reasons for discontinuation included two patients who discontinued prior to treatment initiation (one due to elevated liver enzymes and one due to vomiting caused by obstruction), seven patients due to disease progression, and three patients due to unacceptable toxicities. Four patients had received subsequent chemotherapy, including taxane-containing regimens (three patients) and nivolumab (one patient).

Safety. Safety was evaluated in ten patients, excluding two who discontinued protocol treatment before its initiation. The median number of treatment cycles was 4.5 (range=2-11). Treatment-related adverse events of any grade that occurred in at least 10% of patients are shown in Table II. Grade 3-4 hematological toxicities observed were anemia (10%) and thrombocytopenia (10%). No neutropenia was reported. The most frequently reported grade 3-4 adverse events were fatigue (20%) and hypokalemia (20%). No treatment-related deaths were observed. The relative dose intensity was 81.1% for capecitabine and 85.7% for oxaliplatin.

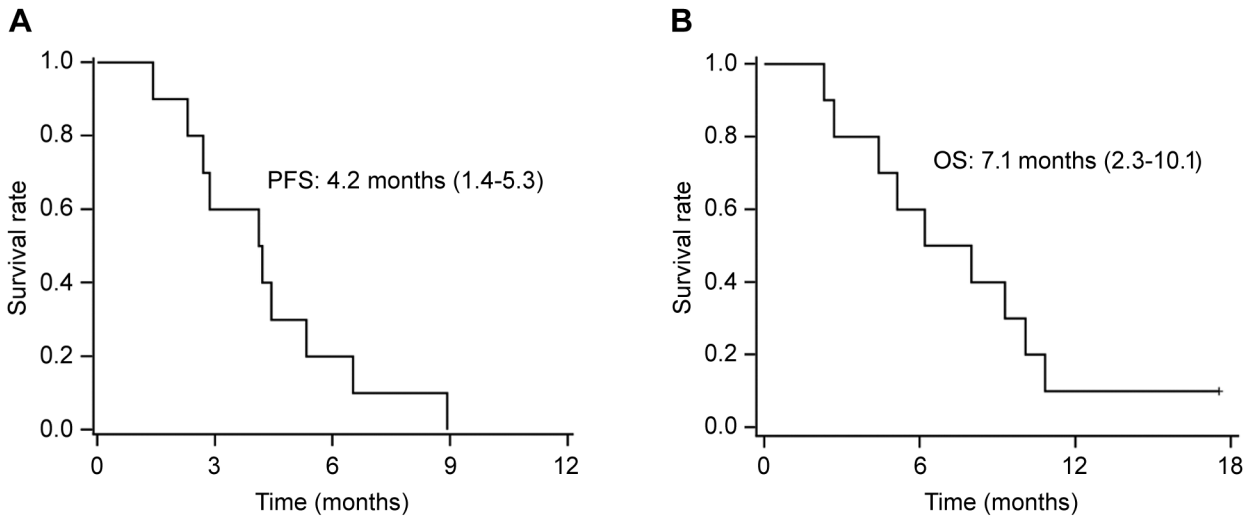

Figure 1. *Progression-free survival (A) and overall survival (B) in this study of capecitabine plus oxaliplatin salvage treatment for advanced gastric cancer (n=10). The median progression-free survival was 4.2 months [95% confidence interval (CI)=1.4-5.3 months]. The median overall survival was 7.1 months (95%CI=2.3-10.1 months).*

Efficacy. Efficacy was evaluated in ten patients, excluding two who discontinued protocol treatment before its initiation (Table III). The ORR assessed by the investigators was 30% (95%CI=6.7-65.2), and the DCR was 90% (95%CI=55.5-99.7, p=0.011), suggesting a benefit with respect to the primary endpoint. During a median follow-up time of 7.1 months (range=0.9-17.5 months), the median PFS was 4.2 months (95%CI=1.4-5.3; Figure 1A), and the median OS was 7.1 months (95%CI=2.3-10.1; Figure 1B).

We further analyzed post hoc the treatment efficacy based on the reason for the discontinuation of cisplatin treatment. Tumor shrinkage was observed exclusively in the cisplatin-resistant group compared to the cisplatin-intolerant group (50% *vs*. 0%). No significant difference was found in the DCR between the cisplatin-resistant and cisplatin-intolerant groups (83.3% *vs*. 100%). No significant differences were observed between the groups in terms of PFS (4.3 months *vs*. 3.5 months, Figure 2A) and OS (8.6 months *vs*. 5.3 months, Figure 2B).

Discussion

This was the first prospective study exploring the efficacy and safety of XELOX as salvage-line chemotherapy in gastric cancer. Although the study did not enroll a sufficient number of patients to allow for robust statistical analysis, XELOX demonstrated a DCR of 90% with an ORR of 30%, and median PFS and OS of 4.2 and 7.1 months, respectively.

When we planned this study in 2015, no salvage treatment was established. Recently, newly developed drugs, including apatinib, nivolumab, and FTD/TPI, demonstrated a survival benefit over best supportive care in heavily pretreated gastric cancer patients with good performance scores (0-1) in phase III studies (14, 15, 23). The reported ORR, median PFS, and OS were 2.8%, 2.6 months, and 6.5 months for apatinib; 11.2%, 1.6 months, and 5.3 months for nivolumab; and 4.0%, 2.0 months, and 5.7 months for FTD/TPI, respectively. While caution is warranted when comparing findings, our study suggests potentially better efficacy for XELOX than apatinib, nivolumab, and FTD/TPI, despite including patients with poor performance scores.

Oxaliplatin has shown preclinical activity against various cancers resistant to cisplatin and has synergistic effects with 5-FU (24). Furthermore, Bruno *et al*. (25) reported that oxaliplatin differs from cisplatin and carboplatin in its mechanism of action: oxaliplatin induces ribosome biogenesis stress to kill cells, rather than relying on a DNA-damage response.

In locally advanced or metastatic biliary tract cancers, modified FOLFOX has proven effective in patients previously treated with cisplatin plus gemcitabine combination chemotherapy (26). Similarly, several retrospective (20, 27) and prospective studies (17-20, 28) have indicated that salvage chemotherapy with FOLFOX is effective in gastric cancer patients refractory to cisplatin. The reported ORR, PFS, and OS in these studies ranged from 21-27%, 2.2-4.3 months, and 4.2-8.0 months, respectively. In comparison, salvage therapy with XELOX in our study demonstrated promising efficacy in gastric cancer patients.

Importantly, XELOX does not require an infuser pump, extended infusion times, or a central venous port. However, to date, no studies have evaluated XELOX as a salvage-line treatment, either retrospectively or prospectively, in gastric cancer.

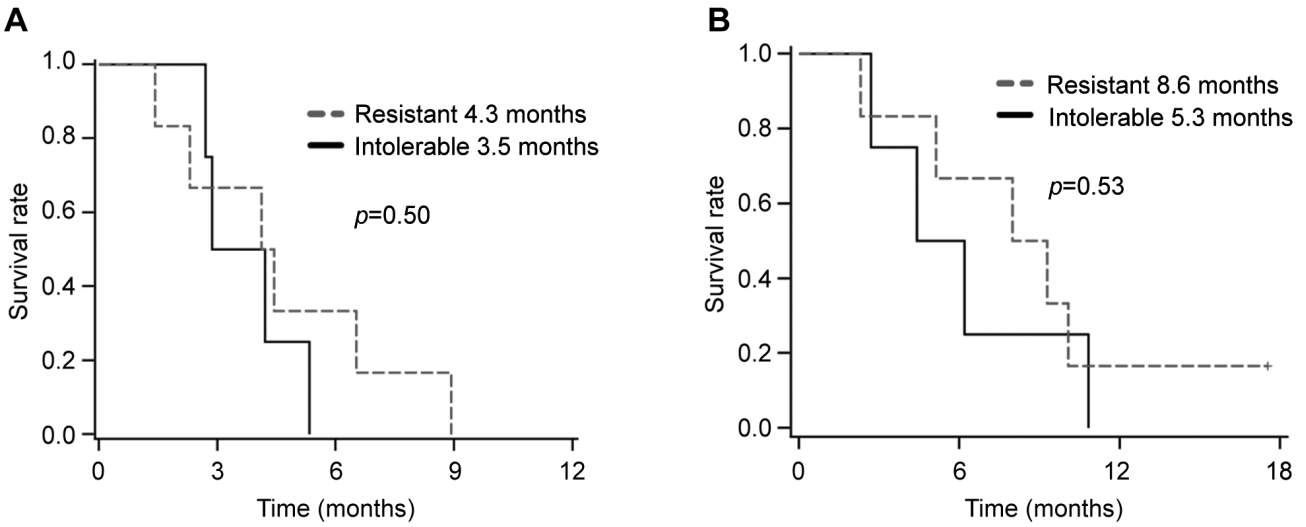

Figure 2. *Progression-free survival (A) and overall survival (B) in this study of capecitabine plus oxaliplatin salvage treatment for advanced gastric cancer (n=10). The median progression-free survival in patients with resistant tumors (dashed line) was 4.3 months, while in those who were intolerant of cisplatin (solid line), it was 3.5 months (p=0.50). The median overall survival in patients with resistant tumors (dashed line) was 8.6 months, while in those who were intolerant of cisplatin (solid line), it was 5.3 months (p=0.53).*

In our analysis, we compared treatment efficacy based on the reasons for discontinuation of cisplatin. No significant differences were observed in the DCR, PFS, or OS between cisplatin-resistant and cisplatin-intolerant cases. Although preliminary, our data suggest the potential for a platinum rechallenge using oxaliplatin in gastric cancer patients who were previously resistant to cisplatin.

When chemotherapy is administered to gastric cancer patients who have undergone multiple lines of treatment, safety becomes a critical concern. Although our study found that hematological toxicity was not more frequent than in previous reports, fatigue was commonly observed (20%). Compared to FOLFOX (85 mg/m^2), a higher dose of oxaliplatin is administered in XELOX on day one (130 mg/m^2), which might explain the higher incidence of fatigue. Particularly for patients with poor performance scores or diminished appetite, dose reductions of oxaliplatin may be a practical consideration in daily clinical practice.

Study limitations. First, it was a single-arm, phase II exploratory study. Second, the total number of patients enrolled was very small due to poor accrual. One potential reason for the poor accrual is that oxaliplatin-based chemotherapy is often preferred over cisplatin-based regimens in first-line treatment due to its convenience in outpatient settings. Additionally, nivolumab and FTD/TPI were only approved in Japan in 2017 and 2019, respectively. Despite these limitations, our study represents the first prospective evaluation of XELOX's safety and efficacy in patients with inoperable or advanced gastric cancer who were either resistant to or intolerant of cisplatin.

Conclusion

Our findings suggest that salvage-line XELOX is a viable treatment option for patients with metastatic gastric cancer, providing potential clinical benefits.

Conflicts of Interest

NS received lecture fee from Chugai Pharm, Daiichi Sankyo, Ono and Eli Lilly, and received a research grant from Chugai Pharm, Daiichi Sankyo, MSD and Pfizer; KN received lecture fee from BMS KK, Daiichi Sankyo, EA Farma, Eli Lilly, MSD, Ono, Otsuka, Taiho, and Yakult Honsha; YK received lecture fees from Taiho Pharmaceutical, Ono Pharmaceutical, Eli Lilly, Yakult Honsha, Nippon Kayaku, MSD, Astellas Pharma, and Daiichi Sankyo, and research grants from Taiho Pharmaceutical, Ono Pharmaceutical, Yakult Honsha, and AstraZeneca outside of the submitted work. HK received lecture fee from BMS KK, Ono, Taiho and Daiichi Sankyo, and received a research grant from BMS KK, Chugai Pharm, Eisai, Kobayashi Pharmaceutical, Taiho and Daiichi Sankyo; DS received lecture fee from Chugai Pharm, Daiichi Sankyo, and received a research grant from Eli Lilly, Daiichi Sankyo, Chugai Pharm, Ono and Yakult Honsha; TSa received lecture fee from Ono, Daiichi Sankyo, Eli Lilly, Taiho and Chugai Pharm, received a research grant from Ono, Daiichi Sankyo, BMS, Eli Lilly, Taiho and Chugai Pharm, received scholarship donations from Daiichi Sankyo and Taiho, and endowed chairs from Yakult Honsha, Ono and Chugai Pharm. JK, YO, SU, KM, KF, SE, and TSh have no conflicts of interest. All Authors had full access to all of the data in the study and accepted final responsibility for the decision to submit the article for publication.

Authors' Contributions

NS, YK, KF, HK, SE, DS, and TSa contributed to the conception and design of the work, as well as the acquisition and interpretation of data. JK, YO, SU, KM, and KN contributed to the acquisition of data. TSh contributed to the statistical analysis. All Authors participated in drafting the manuscript, approved the final version to be published, and have agreed to be accountable for all aspects of the work, ensuring that any questions related to the accuracy and integrity of the work are appropriately investigated and resolved.

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References

1 Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74(3): 229-263, 2024. DOI: 10.3322/caac.21834

2 Salati M, Di Emidio K, Tarantino V, Cascinu S: Second-line treatments: moving towards an opportunity to improve survival in advanced gastric cancer? ESMO Open 2(3): e000206, 2017. DOI: 10.1136/esmoopen-2017-000206

3 Ohtsu A, Yoshida S, Saijo N: Disparities in gastric cancer chemotherapy between the East and West. J Clin Oncol 24(14): 2188-2196, 2006. DOI: 10.1200/JCO.2006.05.9758

4 Sugano K: Screening of gastric cancer in Asia. Best Pract Res Clin Gastroenterol 29(6): 895-905, 2015. DOI: 10.1016/j.bpg.2015.09.013

5 Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Chao J, Das P, Denlinger CS, Fanta P, Farjah F, Fuchs CS, Gerdes H, Gibson M, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Korn WM, Leong S, Linn C, Lockhart AC, Ly QP, Mulcahy MF, Orringer MB, Perry KA, Poultsides GA, Scott WJ, Strong VE, Washington MK, Weksler B, Willett CG, Wright CD, Zelman D, McMillian N, Sundar H: Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 14(10): 1286-1312, 2016. DOI: 10.6004/jnccn.2016.0137

6 Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, ESMO Guidelines Committee: Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol (suppl 5): v38-v49, 2016. DOI: 10.1093/annonc/mdw350

7 Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, Wyrwicz L, Yamaguchi K, Skoczylas T, Campos Bragagnoli A, Liu T, Schenker M, Yanez P, Tehfe M, Kowalyszyn R, Karamouzis MV, Bruges R, Zander T, Pazo-Cid R, Hitre E, Feeney K, Cleary JM, Poulart V, Cullen D, Lei M, Xiao H, Kondo K, Li M, Ajani JA: 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 398(10294): 27-40, 2021. DOI: 10.1016/S0140-6736(21)00797-2

8 Kang YK, Chen LT, Ryu MH, Oh DY, Oh SC, Chung HC, Lee KW, Omori T, Shitara K, Sakuramoto S, Chung IJ, Yamaguchi K, Kato K, Sym SJ, Kadowaki S, Tsuji K, Chen JS, Bai LY, Oh SY, Choda Y, Yasui H, Takeuchi K, Hirashima Y, Hagihara S, Boku N: 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 23(2): 234-247, 2022. DOI: 10.1016/S1470-2045(21)00692-6

9 Rha SY, Oh DY, Yañez P, Bai Y, Ryu MH, Lee J, Rivera F, Alves GV, Garrido M, Shiu KK, Fernández MG, Li J, Lowery MA, Çil T, Cruz FM, Qin S, Luo S, Pan H, Wainberg ZA, Yin L, Bordia S, Bhagia P, Wyrwicz LS, KEYNOTE-859 investigators: Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 24(11): 1181-1195, 2023. DOI: 10.1016/S1470-2045(23)00515-6

10 Shitara K, Lordick F, Bang YJ, Enzinger P, Ilson D, Shah MA, Van Cutsem E, Xu RH, Aprile G, Xu J, Chao J, Pazo-Cid R, Kang YK, Yang J, Moran D, Bhattacharya P, Arozullah A, Park JW, Oh M, Ajani JA: Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. Lancet 401(10389): 1655-1668, 2023. DOI: 10.1016/S0140-6736(23)00620-7

11 Shah MA, Shitara K, Ajani JA, Bang YJ, Enzinger P, Ilson D, Lordick F, Van Cutsem E, Gallego Plazas J, Huang J, Shen L, Oh SC, Sunpaweravong P, Soo Hoo HF, Turk HM, Oh M, Park JW, Moran D, Bhattacharya P, Arozullah A, Xu RH: Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med 29(8): 2133-2141, 2023. DOI: 10.1038/s41591-023-02465-7

12 Japanese Gastric Cancer Association: Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). Gastric Cancer 26(1): 1-25, 2023. DOI: 10.1007/s10120-022-01331-8

13 Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A, RAINBOW Study Group: 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 15(11): 1224-1235, 2014. DOI: 10.1016/S1470-2045(14)70420-6

14 Kang YK, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, Chung HC, Chen JS, Muro K, Kang WK, Yeh KH, Yoshikawa T, Oh SC, Bai LY, Tamura T, Lee KW, Hamamoto Y, Kim JG, Chin K, Oh DY, Minashi K, Cho JY, Tsuda M, Chen LT: 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 390(10111): 2461-2471, 2017. DOI: 10.1016/S0140-6736(17)31827-5

15 Shitara K, Doi T, Dvorkin M, Mansoor W, Arkenau HT, Prokharau A, Alsina M, Ghidini M, Faustino C, Gorbunova V, Zhavrid E, Nishikawa K, Hosokawa A, Yalçın Ş, Fujitani K, Beretta GD, Cutsem EV, Winkler RE, Makris L, Ilson DH, Tabernero J: Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 19(11): 1437-1448, 2018. DOI: 10.1016/S1470-2045(18)30739-3

16 Japanese Gastric Cancer Association: Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 20(1): 1-19, 2017. DOI: 10.1007/s10120-016-0622-4

17 Kim DY, Kim JH, Lee SH, Kim TY, Heo DS, Bang YJ, Kim NK: Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer. Ann Oncol 14(3): 383-387, 2003. DOI: 10.1093/annonc/mdg106

18 Kim YS, Hong J, Sym SJ, Park SH, Park J, Cho EK, Lee JH, Shin DB: Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX-4) combination chemotherapy as a salvage treatment in advanced gastric cancer. Cancer Res Treat 42(1): 24-29, 2010. DOI: 10.4143/crt.2010.42.1.24

19 Seo HY, Kim DS, Choi YS, Sung HJ, Park KH, Choi IK, Kim SJ, Oh SC, Seo JH, Choi CW, Kim BS, Shin SW, Kim YH, Kim JS: Treatment outcomes of oxaliplatin, 5-FU, and leucovorin as salvage therapy for patients with advanced or metastatic gastric cancer: a retrospective analysis. Cancer Chemother Pharmacol 63(3): 433-439, 2009. DOI: 10.1007/s00280-008-0753-3

20 Kondoh C, Kadowaki S, Komori A, Narita Y, Taniguchi H, Ura T, Ando M, Muro K: Salvage chemotherapy with the combination of oxaliplatin, leucovorin, and 5-fluorouracil in advanced gastric cancer refractory or intolerant to fluoropyrimidines, platinum, taxanes, and irinotecan. Gastric Cancer 21(6): 1050-1057, 2018. DOI: 10.1007/s10120-018-0825-y

21 Ohtsu A, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, Sahmoud T, Shen L, Yeh KH, Chin K, Muro K, Kim YH, Ferry D, Tebbutt NC, Al-Batran SE, Smith H, Costantini C, Rizvi S, Lebwohl D, Van Cutsem E: Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J Clin Oncol 31(31): 3935-3943, 2013. DOI: 10.1200/JCO.2012.48.3552

22 Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, Dos Santos LV, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Zalcberg JR, Chau I, Campbell W, Sivanandan C, Pikiel J, Koshiji M, Hsu Y, Liepa AM, Gao L, Schwartz JD, Tabernero J: Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 383(9911): 31-39, 2014. DOI: 10.1016/S0140-6736(13)61719-5

23 Li J, Qin S, Xu J, Xiong J, Wu C, Bai Y, Liu W, Tong J, Liu Y, Xu R, Wang Z, Wang Q, Ouyang X, Yang Y, Ba Y, Liang J, Lin X, Luo D, Zheng R, Wang X, Sun G, Wang L, Zheng L, Guo H, Wu J, Xu N, Yang J, Zhang H, Cheng Y, Wang N, Chen L, Fan Z, Sun P, Yu H: Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol 34(13): 1448-1454, 2016. DOI: 10.1200/JCO.2015.63.5995

24 Stordal B, Pavlakis N, Davey R: Oxaliplatin for the treatment of cisplatin-resistant cancer: A systematic review. Cancer Treat Rev 33(4): 347-357, 2007. DOI: 10.1016/j.ctrv.2007.01.009

25 Bruno PM, Liu Y, Park GY, Murai J, Koch CE, Eisen TJ, Pritchard JR, Pommier Y, Lippard SJ, Hemann MT: A subset of platinum-containing chemotherapeutic agents kills cells by inducing ribosome biogenesis stress. Nat Med 23(4): 461-471, 2017. DOI: 10.1038/nm.4291

26 Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, Falk S, Gillmore R, Wadsley J, Patel K, Anthoney A, Maraveyas A, Iveson T, Waters JS, Hobbs C, Barber S, Ryder WD, Ramage J, Davies LM, Bridgewater JA, Valle JW, Advanced Biliary Cancer Working Group: Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol 22(5): 690-701, 2021. DOI: 10.1016/S1470-2045(21)00027-9

27 Tsuji K, Yasui H, Onozawa Y, Boku N, Doyama H, Fukutomi A, Yamazaki K, Machida N, Todaka A, Taniguchi H, Tsushima T, Yokota T: Modified FOLFOX-6 therapy for heavily pretreated advanced gastric cancer refractory to fluorouracil, irinotecan, cisplatin and taxanes: a retrospective study. Jpn J Clin Oncol 42(8): 686-690, 2012. DOI: 10.1093/jjco/hys084

28 Mitani S, Kadowaki S, Komori A, Kondoh C, Oze I, Kato K, Masuishi T, Honda K, Narita Y, Taniguchi H, Ando M, Tanaka T, Tajika M, Muro K: A phase II study of modified FOLFOX6 for advanced gastric cancer refractory to standard therapies. Adv Ther 37(6): 2853-2864, 2020. DOI: 10.1007/s12325-020-01358-2

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