International Journal of Clinical Oncology (2018) 23:1084–1089
https://doi.org/10.1007/s10147-018-1308-1

ORIGINAL ARTICLE

Phase II study of S-1 plus oxaliplatin 130 mg/m^2 in Japanese patients with advanced gastric cancer

Yosuke Kito[1,2] · Nozomu Machida[1] · Sadayuki Kawai[3] · Satoshi Hamauchi[1] · Takahiro Tsushima[1] · Akiko Todaka[1] · Tomoya Yokota[1] · Kentaro Yamazaki[1] · Akira Fukutomi[1] · Yusuke Onozawa[2] · Kunihiro Tsuji[2] · Hisashi Doyama[4] · Yutaka Haraguchi[5] · Koji Nakashima[5] · Kenji Kunieda[6] · Keisei Taku[7] · Keita Mori[8] · Hirofumi Yasui[1]

Received: 24 April 2018 / Accepted: 17 June 2018 / Published online: 21 June 2018

Abstract

Purpose Although oxaliplatin 130 mg/m^2 every 3 weeks was approved for advanced gastric cancer in Japan, data regarding S-1 plus oxaliplatin 130 mg/m^2 (SOX130) are limited in Japanese patients with advanced gastric cancer. We investigated the feasibility and safety of SOX130 in Japanese patients with advanced gastric cancer.

Methods Patients with unresectable or recurrent gastric adenocarcinoma, no previous chemotherapy, and Eastern Cooperative Oncology Group Performance Status of 0–1 were treated with SOX130. The primary endpoint was the 3-cycle completion rate, defined as the proportion of patients who completed the first three cycles with ≥80% relative dose intensity of oxaliplatin.

Results Twenty-five patients were enrolled from April 2015 to 2016. The 3-cycle completion rate was 72.0% (90% confidence interval: 53.8–86.1), which was higher than the predetermined threshold rate of 50%. With the median number of cycles being 6 (range, 1–19+), grade 3 or 4 adverse events occurred in 10 patients (40%). Major grade 3 adverse events were anorexia (24%), thrombocytopenia (16%), and neutropenia (12%). No febrile neutropenia or treatment-related deaths occurred. Among 12 patients with measurable lesions, the overall response rate was 58.3%. Median progression-free and overall survival were 5.7 months (95% confidence interval 2.9–8.5) and 13.1 months (95% confidence interval 7.4–19.0), respectively.

Conclusion Results indicated that SOX130 was feasible in Japanese patients with advanced gastric cancer.

Keywords Advanced gastric cancer · SOX · Oxaliplatin · Japanese study

✉ Yosuke Kito
kitoyo9100@gmail.com

[1] Division of Gastrointestinal Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan

[2] Department of Medical Oncology, Ishikawa Prefectural Central Hospital, 2-1, Kuratsuki-higashi, Kanazawa, Ishikawa 920-8530, Japan

[3] Division of Clinical Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan

[4] Department of Gastroenterology, Ishikawa Prefectural Central Hospital, 2-1, Kuratsuki-higashi, Kanazawa, Ishikawa 920-8530, Japan

[5] First Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, 5200 Kihara, Kiyotake-cho, Miyazaki 889-1692, Japan

[6] Department of Medical Oncology, Saku Central Hospital Advanced Care Center, 3400-28 Nakagomi, Saku, Nagano 385-0051, Japan

[7] Division of Medical Oncology, Shizuoka General Hospital, 4-27-1 Kita-ando, Aoi-ku, Shizuoka 420-8527, Japan

[8] Clinical Research Promotion Unit, Clinical Research Center, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan

Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related death worldwide [1]. The combination of platinum-based and fluoropyrimidine-based chemotherapeutic agents has been established as first-line treatment for advanced gastric cancer (AGC), but currently there is no single, global standard regimen. In Japan, the combination of cisplatin and S-1 (CS) is a standard regimen based on two Japanese phase III trials, namely, the Japan Clinical Oncology Group 9912 trial that demonstrated the noninferiority of S-1 to 5-fluorouracil (5-FU) [2], and the SPIRITS trial that demonstrated the superiority of CS compared with S-1 [3].

Oxaliplatin has some advantages in terms of toxicity and administration compared with cisplatin. Oxaliplatin causes lower-frequency nausea, vomiting, and sensorineural hearing loss and fewer thromboembolic events [4]. Patients who receive cisplatin treatment require overnight admission or prolonged outpatient visits because intravenous hydration is necessary to prevent renal toxicity. In contrast, oxaliplatin can be given as an intravenous infusion within a 2-h period.

Several clinical studies comparing cisplatin and oxaliplatin for gastric cancer treatment have been conducted. The randomized two-by-two phase III study (REAL-2) of triplet therapy consisting of epirubicin, 5-FU or capecitabine, and cisplatin or oxaliplatin showed that oxaliplatin 130 mg/m^2 every 3 weeks was noninferior to cisplatin 60 mg/m^2 every 3 weeks [5]. The Arbeitsgemeinschaft Internistische Onkologie trial in Germany showed that oxaliplatin 85 mg/m^2 every 2 weeks was at least as effective as cisplatin 50 mg/m^2 every 2 weeks [6]. Recently, the SOPP study demonstrated that S-1 plus oxaliplatin 130 mg/m^2 (SOX130) was noninferior to CS in terms of progression-free survival (PFS) and well tolerated in Korean AGC patients [7].

In Japan, the combination of S-1 and oxaliplatin has been developed for colorectal and gastric cancers. The phase I/II study of SOX130 for colorectal cancer showed that the incidence of grade 3 or higher thrombocytopenia was 28% [8]. On revision of the criteria for oxaliplatin dose reduction, the initial oxaliplatin dose was determined to be 130 mg/m^2 for colorectal cancer. The phase III SOFT trial showed that SOX130 plus bevacizumab was noninferior to modified FOLFOX6 plus bevacizumab in terms of PFS, and was safe for chemotherapy-naïve Japanese patients with metastatic colorectal cancer as indicated by only 4% of grade 3 or higher thrombocytopenia [9]. Thus, SOX130 plus bevacizumab has been regarded as a standard first-line treatment for metastatic colorectal cancer in Japan. In contrast, the initial oxaliplatin dose for gastric cancer was determined to be 100 mg/m^2 because of possible bleeding from the primary lesion site and to maintain the S-1 dose intensity, which is a key drug against AGC. S-1 plus oxaliplatin 100 mg/m^2 (SOX100) statistically failed to show noninferiority to CS in the phase III G-SOX study [10]. Despite the lack of data about SOX130 in Japanese AGC patients, oxaliplatin 130 mg/m^2 every 3 weeks was approved for AGC in Japan in September 2014 based on the results of the REAL-2 study. Therefore, we conducted a phase II study to evaluate the feasibility and safety of SOX130 as the first-line treatment in Japanese AGC patients.

Patients and methods

Patients

This was a single-arm, open-label, multicenter, phase II study at 5 centers in Japan. Major inclusion criteria were histologically confirmed unresectable or recurrent gastric adenocarcinoma, negative or unknown HER2 status, age ≥ 20 years, Eastern Cooperative Oncology Group Performance Status of 0 or 1, no previous chemotherapy or radiation for advanced disease, adequate oral intake, and adequate organ function (e.g., creatinine clearance ≥ 60 mL/min). Major exclusion criteria were massive ascites, active infection, peripheral neuropathy, and active concomitant malignancy. All patients provided written informed consent. This study was approved by the institutional review board of each participating institution.

Treatment

S-1 was given orally twice daily for the first 2 weeks of a 3-week cycle. The dose was 80 mg/day for body surface area (BSA) < 1.25 m^2, 100 mg/day for BSA from 1.25 to < 1.5 m^2, and 120 mg/day for BSA ≥ 1.5 m^2. Oxaliplatin 130 mg/m^2 was infused intravenously for 2 h on day 1 of each 3-week cycle. Before oxaliplatin infusion, antiemetics (e.g., a 5-hydroxytryptamine 3 receptor antagonist and dexamethasone) were administered prophylactically to prevent nausea and vomiting. Treatment was continued until disease progression, unacceptable toxicity, patient's refusal, or physician's decision.

The criteria for dose reduction of S-1 and oxaliplatin were similar to those used in the SOFT trial [8]. The S-1 doses at level 1 and 2 were as follows: 60 and 50 mg/day for BSA < 1.25 m^2, 80 and 60 mg/day for BSA from 1.25 to < 1.5 m^2, and 100 and 80 mg/day for BSA ≥ 1.5 m^2, respectively. The oxaliplatin doses at level 1 and 2 were 100 and 75 mg/m^2, respectively. The dose of each drug was reduced by one level if the neutrophil count was less than 500/mm^3

at any time during a cycle; the neutrophil count was less than 1500/mm^3 on the first day of a cycle; grade 3 or higher febrile neutropenia developed; or the platelet count was less than 50,000/mm^3. In the event of grade 3 or higher diarrhea, the S-1 dose was reduced by one level. If the platelet count was between 75,000 and 100,000/mm^3 on the first day of a cycle, then the oxaliplatin dose was reduced by one level. Oxaliplatin could be skipped when patients had received a total oxaliplatin dose of at least 600 mg/m^2 and had grade 2 or higher peripheral sensory neuropathy.

Assessment

Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (version 1.1). Response rate was defined as the proportion of patients whose best response was complete or partial response and disease control rate as the proportion of patients whose best response was complete response, partial response, or stable disease. Computed tomography scans were performed before the start of treatment and repeated every 8 weeks. PFS was calculated from the date of enrollment to the date of progressive disease (PD) or death from any cause, whichever came first. Patients who were alive and progression-free were regarded as censored cases at the date of the last assessment. Overall survival (OS) was calculated from the date of enrollment to the date of death from any cause. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (version 4.03). Treatment duration was defined as the period from the date the first cycle was started to the date the third cycle was started plus 21 days. Dose intensity was calculated as the ratio of the cumulative dose of each drug to the treatment duration. Relative dose intensity (RDI) was defined as the ratio of the delivered dose intensity to the planned dose intensity.

Statistical analysis

The feasibility of SOX130 and the rate of completion were evaluated in all treated patients. The primary endpoint was the 3-cycle completion rate, which was defined as the proportion of patients who completed the first 3 cycles of treatment with 80% or higher RDI of oxaliplatin. This definition was based on the assumption that an 80% dose of oxaliplatin 130 mg/m^2 in 3 cycles ($0.80 \times 130 \times 3 = 312$ mg/m^2) was higher than a 100% dose of oxaliplatin 100 mg/m^2 in 3 cycles ($1.00 \times 100 \times 3 = 300$ mg/m^2). In this study, we would regard SOX130 as feasible in Japanese patients with AGC if the 3-cycle completion rate was statistically more than 50%. Assuming a 3-cycle completion rate of 75% from unpublished data of the SOFT trial, we calculated that we would need 23 patients with a one-sided α value of 0.05 and a power of 80%. The target sample size was set at 25 patients to allow for some dropouts. The secondary endpoints were safety, RDI, objective response rate (ORR), PFS, and OS. This study was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000016973).

Results

Patient characteristics

From April 2015 to June 2016, 25 patients were enrolled. All patients received the study treatment. The cut-off date for data collection was February 8, 2017, and the median length of follow-up for censored cases was 11.0 months (range, 7.8–15.0). Patient characteristics are shown in Table 1. Median age was 64.5 years (range, 32–76). All patients had metastatic disease. Histologically, tumors were of undifferentiated type in 18 patients (72%), and peritoneal dissemination was also present in 18 patients (72%).

Table 1 Patient characteristics ($n = 25$)

	n	%
Median age, years (range)	64.5 (32–76)	
Gender		
Female	4	16
Male	21	84
ECOG PS		
0	15	60
1	10	40
Unresectable	21	84
Recurrent		
Adjuvant chemotherapy (+)	3	12
Adjuvant chemotherapy (−)	1	4
Tumor histology		
Differentiated	7	28
Undifferentiated	18	72
Number of metastatic site		
1	12	48
2	9	36
≥ 3	4	16
Metastatic organ		
Liver	6	24
Lung	2	8
Lymph node	14	56
Peritoneal	18	72

ECOG PS Eastern Cooperative Oncology Group performance status

Treatment delivery

The 3-cycle completion rate was 72.0% [90% confidence interval (CI) 53.8–86.1]. In the first 3 cycles, 13 patients received oxaliplatin 130 mg/m^2 without any cessation or dose reduction, 9 patients underwent a cessation and/or dose reduction of oxaliplatin, and the study treatment was discontinued for 3 patients because of disease progression or grade 1 nausea. The RDI of oxaliplatin was 96.9% [interquartile range (IQR) 82.9–100] for the first 3 cycles and 75.8% (IQR 57.7–92.7) for all cycles. The RDI of S-1 was 90.0% (IQR 78.0–100) for the first 3 cycles and 83.3% (IQR 73.3–94.4) for all cycles.

The median number of treatment cycles was 6 (range, 1–19+). Disease progression was the most common reason for treatment discontinuation ($n=17$). The other reasons were investigators' decisions based on thrombocytopenia ($n=2$), grade 2 fatigue ($n=1$), prolonged grade 2 thrombocytopenia ($n=1$), and grade 1 nausea ($n=1$). Sixteen patients received subsequent chemotherapy as follows: taxane-containing regimens ($n=11$), irinotecan ($n=3$), and S-1 continuation after the study treatment ($n=2$).

Table 2 Relative dose intensity

	First 3 cycles	All cycles
S-1		
Median RDI	90.0%	83.3%
IQR	78.0–100	73.3–94.4
Oxaliplatin		
Median RDI	96.9%	75.8%
IQR	82.9–100	57.7–92.7

RDI relative dose intensity, *IQR* interquartile range

Safety

Adverse events are summarized in Table 2. Grade 3 or higher adverse events occurred in 10 patients, namely, anorexia ($n=6$), anemia ($n=5$), thrombocytopenia ($n=4$), and neutropenia ($n=3$). Eight patients received neurokinin-1 receptor antagonists for prevention of nausea and vomiting from the first cycle. Grade 3 thrombocytopenia was observed in 3 patients in the first 4 cycles and in 1 patient in the ninth cycle. One patient who experienced grade 4 gastric hemorrhage with grade 1 thrombocytopenia was treated with transcatheter arterial embolization. Another patient who experienced grade 3 gastric hemorrhage without thrombocytopenia received blood transfusion. Although peripheral sensory neuropathy developed in 19 patients, all events were grade 2 or lower. No febrile neutropenia or treatment-related deaths occurred (Table 3).

Efficacy

Among the 12 patients with measurable lesions, ORR and disease control rate were 58.3% and 83.3% (7 partial response and 3 stable disease), respectively. PFS was noted in 21 cases, and 15 deaths had occurred as of the cut-off date. Median PFS and OS were 5.7 months (95% CI 2.9–8.5) and 13.1 months (95% CI 7.4–19.0), respectively (Fig. 1).

Discussion

This study met its primary endpoint because the 3-cycle completion rate exceeded the pre-specified threshold. The safety profile of SOX130 in Japanese patients in this study was comparable with that in the REAL-2 study and the

Table 3 Adverse events

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4, %
Leucopenia	4	0	1	0	4
Neutropenia	7	7	3	0	12
Anemia	12	7	4	1	20
Thrombocytopenia	12	7	4	0	16
Fatigue	9	10	1	–	4
Anorexia	9	8	6	0	24
Nausea	5	8	1	0	4
Vomiting	6	0	0	0	0
Diarrhea	6	0	0	0	0
Stomatitis	4	0	1	0	4
Allergic reaction	0	0	0	0	0
Peripheral sensory neuropathy	11	8	0	0	0
Gastric hemorrhage	0	0	1	1	8
Febrile neutropenia	–	–	0	0	0

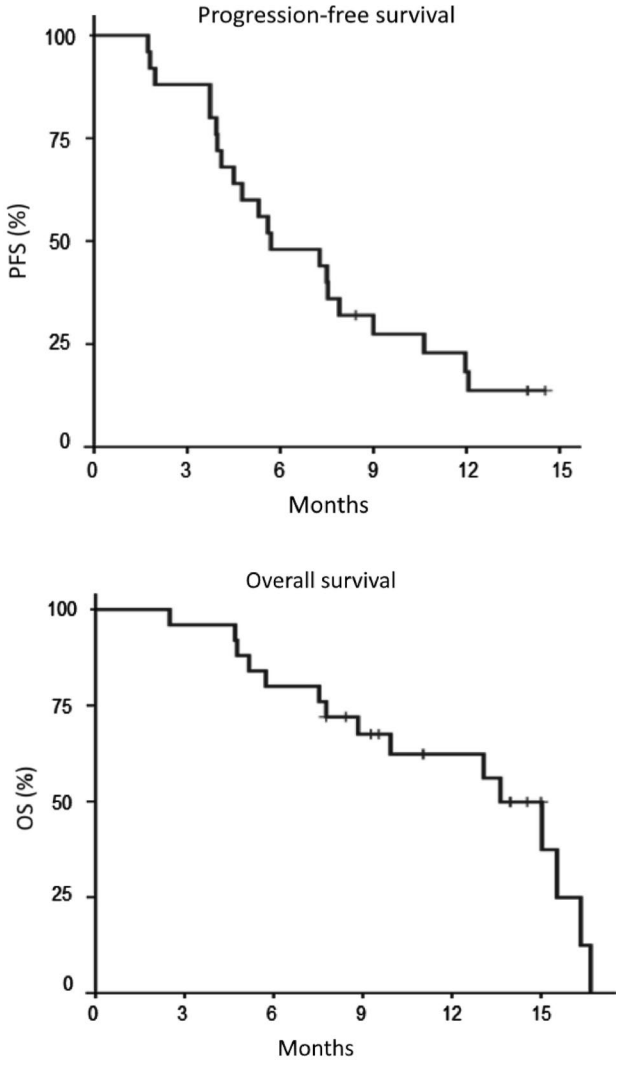

Fig. 1 Progression-free survival (PFS) and overall survival (OS)

SOPP study [5, 7]. Therefore, we can regard SOX130 to be feasible in Japanese patients with AGC.

Oxaliplatin 130 mg/m^2 is the global standard dose for the combination regimen of capecitabine and oxaliplatin [11–13]. For metastatic and resected colorectal cancer, capecitabine plus oxaliplatin 130 mg/m^2 is one of the standard regimens in the world, including Japan. Recently, the capecitabine plus oxaliplatin 130 mg/m^2 demonstrated the safety and feasibility in Japanese patients with resected gastric cancer [14]. S-1-based chemotherapy was reported to be associated with a better safety profile in Asian patients compared with capecitabine-based therapy [15]. No ethnic difference in absorption, distribution, and metabolism of oxaliplatin was noted because it undergoes a series of spontaneous, nonenzymatic conversions in biological fluids [16]. SOX130 has shown the efficacy and safety in Japanese patients with metastatic colorectal cancer [9] and in Korean patients with AGC [7]. In addition, oxaliplatin 85 mg/m^2 is regarded as the standard dose for FOLFOX regimen in Japanese patients with AGC as well as in patients with metastatic colorectal cancer. There are few rationales for reducing oxaliplatin dose of SOX regimen from the first cycle. Therefore, SOX130 is expected to be safe and feasible even in Japanese patients with AGC.

Several clinical studies regarding SOX130 for AGC are on-going. The ONO-4538-37 (NCT02746796) is a phase II/III study to compare nivolumab plus chemotherapy (SOX130 or capecitabine plus oxaliplatin 130 mg/m^2) and placebo plus chemotherapy as first-line treatment in Japan, Korea, and Taiwan. The MK-3475-659/KEYNOTE-659 (NCT03382600), a phase II study performed in Japan, has also adopted SOX130 in combination with pembrolizumab. The KSCC/HGCSG/CCOG/PerSeUS1501B (UMIN000017552) and HIGHSOX study (UMIN000017602) are being conducted to examine the efficacy and safety of trastuzumab plus SOX130 for HER2-positive AGC previously untreated with chemotherapy. These studies regard SOX130 as a standard regimen for HER2-negative AGC. The results of this study can support the notion that SOX130 is one of the standard first-line treatments for Japanese AGC.

The adverse events of SOX130 in this study were generally tolerable. The frequency of grade 3 or higher thrombocytopenia (16%) was similar to that of the G-SOX study (15.1%) [10]. It did not lead to gastric hemorrhage. No grade 3 or higher peripheral sensory neuropathy was noted. However, grade 3 or higher anorexia was observed more frequently (24%) than that of the G-SOX study (15.4%). This result might suggest that gastrointestinal toxicities developed with higher frequency compared with SOX100. Seventy-two percent of patients had peritoneal metastasis at the registration, although 19.2% of patients had it in SOX100 arm of the G-SOX study. The higher proportion of patients with peritoneal metastasis possibly contributed to the higher incidence of severe anorexia.

The efficacy of SOX130 in this study was similar to that of SOX130 in the SOPP study [7] or that of SOX100 in the G-SOX study [10]. Because there is no head-to-head study comparing SOX130 and SOX100, it is difficult to describe the difference in the efficacy. It seems to be unrealistic to conduct head-to-head study to verify the superiority of SOX130 due to requiring a very large sample size. The efficacy of SOX130 have been already shown in the pivotal studies [7, 9]. Therefore, the target sample size in this study was designed to evaluate the feasibility, not the efficacy, of SOX130. A small sample size and a single-arm study were major limitations of this study.

No standard endpoint has been established to evaluate the feasibility of chemotherapy in AGC. We adopted the 3-cycle completion rate for some reasons. First, it can

provide information for feasibility earlier than other endpoints, such as safety and PFS. We needed to know early whether SOX130 would be feasible in Japanese patients with AGC because oxaliplatin 130 mg/m^2 every 3 weeks had been approved at the start of this study. Second, we used the feasibility study of FOLFOX4 for Japanese patients with unresectable metastatic colorectal cancer as reference [17]. The study allowed us to accept that oxaliplatin 85 mg/m^2 every 2 weeks was feasible in Japanese patients. The primary endpoint of the study was the completion rate, defined as completion of the first 4 cycles with 80% or higher RDI of oxaliplatin. Lastly, we considered that a higher dose intensity for at least 3 cycles might be needed to obtain higher antitumor activity compared with SOX100. When the RDI is higher than 80% in SOX130 treatment, the dose intensity of oxaliplatin is higher than that in SOX100 treatment.

In conclusion, the results of this study indicated that SOX130 was feasible in Japanese patients with AGC with the criterion for dose reduction in the SOFT trial. The higher incidence of severe anorexia was thought to result from the increased oxaliplatin dose and the higher proportion of patients with peripheral metastasis compared with SOX100 in the G-SOX study.

Acknowledgements This study was supported by the Clinical Research Center of Shizuoka Cancer Center. We thank the patients and their families for their participation in this study. We also thank Misako Kama from the Data Center of Shizuoka Cancer Center for data management.

Funding No funding was received.

Compliance with ethical standards

Conflict of interest Yosuke Kito declares that he has no conflict of interest. Nozomu Machida declares that he has no conflict of interest. Sadayuki Kawai declares that he has no conflict of interest. Satoshi Hamauchi declares that he has no conflict of interest. Takahiro Tsushima received honoraria from Chugai Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical, and Ono Pharmaceutical. Akiko Todaka declares that she has no conflict of interest. Tomoya Yokota declares that he has no conflict of interest. Kentaro Yamazaki received honoraria from Yakult Honsha and Taiho Pharmaceutical. Akira Fukutomi declares that he has no conflict of interest. Yusuke Onozawa declares that he has no conflict of interest. Kunihiro Tsuji declares that he has no conflict of interest. Hisashi Doyama declares that he has no conflict of interest. Yutaka Haraguchi declares that he has no conflict of interest. Koji Nakashima declares that he has no conflict of interest. Kenji Kunieda declares that he has no conflict of interest. Keisei Taku declares that he has no conflict of interest. Keita Mori declares that he has no conflict of interest. Hirofumi Yasui declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki declaration and its later amendments, or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Ferlay J, Soerjomataram I, Dikshit R et al (2014) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359–E386
2. Boku N, Yamamoto S, Fukuda H et al (2009) Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomized phase 3 study. Lancet Oncol 10:1063–1069
3. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
4. Starling N, Rao S, Cunningham D et al (2009) Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. J Clin Oncol 27:3786–3793
5. Cunningham D, Starling N, Rao S et al (2008) Capecitabine and oxaliplatin for advanced gastric cancer. N Engl J Med 358:36–46
6. Al-Batran SE, Hartmann JT, Probst S et al (2008) Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 26:1435–1442
7. Ryu MH, Park YI, Chung IJ et al (2016) Phase III trial of S-1 plus oxaliplatin (SOX) vs S-1 plus cisplatin (SP) combination chemotherapy for first-line treatment of advanced gastric cancer (AGC): SOPP study. In: Abstracts of the 2016 ASCO Annual Meeting (abstr 4015). https://meetinglibrary.asco.org/record/122676/abstract. Accessed 24 April 2018
8. Yamada Y, Tahara M, Miya T et al (2008) Phase I/II study of oxaliplatin with oral S-1 as first-line therapy for patients with metastatic colorectal cancer. Br J Cancer 98:1034–1038
9. Yamada Y, Takahari D, Matsumoto H et al (2013) Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT): an open-label, non-inferiority, randomised phase 3 trial. Lancet Oncol 14:1278–1286
10. Yamada Y, Higuchi K, Nishikawa K et al (2015) Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer. Ann Oncol 26:141–148
11. Cassidy J, Clarke S, Díaz-Rubio E et al (2008) Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 26:2006–2012
12. Schmoll HJ, Tabernero J, Maroun J et al (2015) Capecitabine plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the NO16968 randomized controlled phase III trial. J Clin Oncol 33:3733–3740
13. Bang YJ, Kim YW, Yang HK et al (2012) Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 379:315–321
14. Fuse N, Bando H, Chin K et al (2017) Adjuvant capecitabine plus oxaliplatin after D2 gastrectomy in Japanese patients with gastric cancer: a phase II study. Gastric Cancer 20:332–340
15. He MM, Wu WJ, Wang F et al (2013) S-1-based chemotherapy versus capecitabine-based chemotherapy as first-line treatment for advanced gastric carcinoma: a meta-analysis. PLoS One 8:e82798
16. Graham MA, Lockwood GF, Greenslade D et al (2000) Clinical pharmacokinetics of oxaliplatin: a critical review. Clin Cancer Res 6:1205–1218
17. Fuse N, Doi T, Ohtsu A et al (2007) Feasibility of oxaliplatin and infusional fluorouracil/leucovorin (FOLFOX4) for Japanese patients with unresectable metastatic colorectal cancer. Jpn J Clin Oncol 37:434–439