Phase II Prospective Study of Trastuzumab in Combination with S-1 and Oxaliplatin (SOX100) Therapy for HER2-Positive Advanced Gastric Cancer

Yoshinori Mori1 · Hiromi Kataoka2 · Masahide Ebi3 · Kazunori Adachi3 · Yoshiharu Yamaguchi3 · Noriyuki Hayashi4 · Yoshikazu Hirata4 · Satoshi Sobue4 · Ryosuke Inoue5 · Izumi Hasegawa6 · Satoshi Ono1,3 · Atsuyuki Hirano1 · Yoshihide Kimura1 · Keiji Ozeki2 · Takaya Shimura2 · Eiji Kubota2

Accepted: 8 September 2021 / Published online: 22 September 2021 © Springer Science+Business Media, LLC, part of Springer Nature 2021

Abstract

Purpose The standard first-line treatment for human epidermal growth factor receptor type 2 (HER2)-positive advanced gastric cancer (AGC) is trastuzumab in combination with cisplatin and fluoropyrimidines. We evaluated the efficacy and safety of S-1 and oxaliplatin (100 mg/m²) (SOX100) combined with trastuzumab, a monoclonal antibody against HER2 for HER2-positive AGC.

Methods In this single-arm, multicenter phase II study, patients with HER2-positive AGC received S-1 (80–120 mg per day) orally on days 1–14, oxaliplatin (100 mg/m²) intravenously on day 1, and trastuzumab (8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks) intravenously. The primary end point was 1-year survival rate. The secondary end points included overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and safety.

Results A total of 25 patients from six centers were enrolled from December 2015 to March 2020. In the 25 patients evaluable for analysis, the 1-year survival rate was 70.8% [90% confidence interval (CI) = 55.5–86.1%], whereas the median OS, PFS, and ORR were 17.8 (95% CI 10.5–22.9) months, 7.6 (95% CI 5.0–10.9) months, and 75.0% (95% CI 53.3–90.2), respectively. Major grade 3/4 adverse events included anorexia (20%), anemia (16%), peripheral sensory neuropathy (16%), and diarrhea (15%).

Conclusion SOX100 combined with trastuzumab was effective with a favorable safety profile in patients with HER2-positive AGC.

Keywords Human epidermal growth factor receptor type 2 (HER2) · Trastuzumab · S-1 · Oxaliplatin · Advanced gastric cancer (AGC)

Introduction

Gastric cancer is the fourth leading cause of cancer-related deaths worldwide [1]. Although systemic chemotherapy is used for the treatment of advanced gastric cancer (AGC), the prognosis still remains poor. The standard therapy for metastatic gastric cancer is a combination regimen that includes fluoropyrimidines and cisplatin as first-line chemotherapy. A phase III trial demonstrated that an oral fluoropyrimidine, S-1, was superior to 5-FU [2, 3] and that S-1 plus cisplatin (SP) was superior to S-1 (SPIRITS trial). As a result, SP is regarded as the standard first-line treatment for AGC in Japan [4–6]. However, the continuity and toxicity of cisplatin-based regimens are associated with severe toxicity. Oxaliplatin-based regimens are less toxic and more tolerable. Subsequently, the G-SOX study showed that S-1 plus oxaliplatin (SOX) for gastric cancer was equal to SP [7]. The dose of oxaliplatin in the study was 100 mg/m². Therefore, 100 mg/m² of oxaliplatin is an alternative option for patients with gastric cancer in Japan.

Approximately 15% of metastatic gastric cancers overexpress human epidermal growth factor 2 (HER2) [8]. Trastuzumab, a humanized monoclonal anti-HER2
antibody, binds to the HER2 ectodomain. Trastuzumab prevents dimerization and inhibits downstream signaling, which induces apoptosis and cell cycle arrest [9]. These effects result in improved outcomes for HER2-positive cancer.

In the Trastuzumab for Gastric Cancer (ToGA) trial, trastuzumab plus fluoropyrimidines and cisplatin showed improved overall survival (OS) in first-line treatment for HER2-positive AGC [10]. Previously, we reported that S-1 and cisplatin combined with trastuzumab are effective and tolerable for the treatment of HER2-positive AGC [11].

Recently, phase II studies of trastuzumab in combination with S-1 and oxaliplatin in HER2-positive GC (HIGHSOX study, KSCC/HGCSG/CCOG/PerSeUS1501B) demonstrated promising anti-tumor effects and manageable side effects [12, 13]. The dose of oxaliplatin in these studies was 130 mg/m²; however, the dose of oxaliplatin still remains controversial. S-1 and oxaliplatin (100 mg/m²) plus trastuzumab for gastric cancer have not been evaluated yet. On the basis of these findings, we conducted a phase II study to evaluate the efficacy and safety of SOX100 plus trastuzumab in HER2-positive AGC.

Methods

Patients

Eligible patients were adults (aged ≥20 to ≤80 years) with histologically proven unresectable or recurrent HER2-positive AGC. HER2 status was confirmed via immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). HER2 positivity was defined as 3+ on IHC or 2+ on IHC with positive FISH. Patients with unmeasurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, were permitted enrollment. Other inclusion criteria were as follows: patients having an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, adequate bone marrow reserve (with leucocyte count <12,000 cells/mm³, neutrocyte count ≥1,500 cells/mm³, hemoglobin ≥8.0 g/dL, and platelet count ≥100,000 cells/mm³), hepatic function (aspartate aminotransferase/alanine aminotransferase ≤100 IU/L and serum bilirubin ≤2.0 mg/dL), renal function (creatinine clearance ≥50 mL/min), and cardiac function (left ventricular ejection fraction >50%). Exclusion criteria included the presence of uncontrolled pleural effusion or pericardial effusion, sensory neuropathy, serious diarrhea, brain tumor with active malignancy, or serious allergy to medicinal drugs. All patients provided written informed consent before enrollment. This study was registered with UMIN-CTR (UMIN000017182).

Treatment

The patients received oral S-1 twice daily at a dose based on body surface area (<1.25 m², 80 mg/day; 1.25 ≤ to < 1.5 m², 100 mg/day; and ≥ 1.5 m², 120 mg/day) on days 1–14 of a 21-day cycle, oxaliplatin (100 mg/m²) intravenously on day 1, and trastuzumab (cycle 1, 8 mg/kg; cycle 2 onward, 6 mg/kg) intravenously on day 1 and every 3 weeks onward. This schedule was repeated until disease progression, development of unacceptable toxicity, or patient withdrawal from consent. If administration was delayed > 21 days, the protocol treatment was discontinued. Doses of S1 and oxaliplatin were reduced starting from the next cycle if patients exhibited neutropenia (< 500/mm³), febrile neutropenia, thrombocytopenia (< 25,000/mm³), grade 3 to 4 diarrhea, or stomatitis. Only oxaliplatin was reduced if patients had thrombocytopenia (< 75,000/mm³) until day 29. Only the oxaliplatin dose was reduced if patients had grade 2 sensory neuropathy, skipped if patients had grade 3 sensory neuropathy, and discontinued if patients had grade 4 sensory neuropathy.

Evaluation

The primary end point was 1-year survival rate. The secondary end points included OS, progression-free survival (PFS), overall response rate (ORR), and safety. Attending physicians evaluated response according to the RECIST guidelines (version 1.1). Patients were re-examined at 8-week intervals to evaluate target lesions. OS was defined as the time from registration to death resulting from any cause. PFS was defined as the time from registration to disease progression, symptomatic deterioration, or death from any cause. Physical and blood examinations were mandatory before every cycle, and the left ventricular ejection fraction was assessed every 12 weeks during treatment. Adverse events were evaluated according to the National Cancer Institution Common Terminology Criteria for Adverse Events, version 4.0.

Statistics

From the Kaplan–Meier curve of the ToGA and HERBIS-1 trials, 1-year survival rate was predicted to be 65% and 67.9%, respectively. Assuming the 1-year survival rate of this study was 65% with a 90% confidence interval (CI) of ±15%, at least 27 patients are required; thus, we concluded that the sample size for the study was 30 patients.

Statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation...
Results

Patient Characteristics

Twenty-five patients were enrolled from six centers in Japan from December 2015 to March 2020. A total of 25 patients were enrolled, and all patients were received protocol treatment. Twenty-five patients were analyzed for efficacy and safety, but 24 patients were analyzed for treatment responses because one patient was not evaluable because of no enhanced CT (Fig. 1).

The patient demographics and disease characteristics are summarized in Table 1. The median age was 68 years (range 46–78 years). The most common patient characteristics were male sex, ECOG PS of 0, and intestinal-type adenocarcinoma. Seventeen and eight cases were scored as IHC3+ and IHC2+/FISH-positive gastric cancers, respectively. The median follow-up time was 16.1 months (range 3.5–60.9).

Treatment Delivery and Efficacy

The median treatment cycle was 7 cycles (range: 1–41). The relative dose intensity of S-1, oxaliplatin, and trastuzumab was 84.8%, 80.5%, and 91%, respectively. Twenty-one patients discontinued protocol treatment. The reason for discontinuation was disease progression (n = 11), adverse events (n = 5), >21 days treatment delay (n = 3), or prohibited therapy (operation, radiation) (n = 2).

Of a total of 25 patients, 24 patients had measurable lesions and were evaluable. One (4.2%) patient had a complete response; 17 (70.8%) achieved a partial response with an ORR of 75.0% (95% CI, 53.3–90.2%). Four patients (16.7%) had stable disease with a disease control rate of 91.7% (95% CI, 73.0–99.0%). One patient could not undergo enhanced CT because of poor physical condition, and this case was classified as “not evaluable” (Fig. 2 and Table 2).

The median PFS was 7.6 (95% CI, 5.0–10.9) months, and the median OS was 17.8 (95% CI, 10.5–22.9) months (Fig. 3). The OS rate at 1 year was 70.8% (90% CI, 55.5–86.1).

Adverse Events

The hematological and non-hematological toxicities of all patients are summarized in Table 3. The major grade ≥3 hematological adverse events were leukopenia (8%), neutropenia (8%), anemia (16%), and thrombocytopenia (4%). The major grade ≥3 non-hematological adverse events were anorexia (20%), peripheral sensory neuropathy (16%), diarrhea (15%), nausea (8%), and fatigue (4%). One patient showed grade 4 pneumonitis at the time of interstitial lung disease (ILD) diagnosis and died of respiratory failure within 1 month of diagnosis. The planned sample size was initially 30 patients, but contrary to our expectations, it required more time to enroll a sufficient number of patients with HER2-positive AGC, so the study was closed at 25 patients.

Discussion

In this study, we investigated the efficacy and safety of combination therapy including S-1 and oxaliplatin (100 mg/m²) plus trastuzumab for HER2-positive AGC. The efficacy of
the combination therapy including S-1, oxaliplatin, and trastuzumab was comparable with that of previous cisplatin-containing regimens such as the ToGA study [10]. In this study, the 1-year survival rate, OS, and PFS were 70.8%, 17.8 months, and 7.6 months, respectively. In the ToGA trial, these metrics were 65%, 15.3 months, and 7.5 months, respectively.

Recently, Takahari et al. and Yuki et al. reported that the ORR, OS, and PFS were 70.7%, 18.1, and 8.8 months and 82.1%, 27.6, and 7.0 months, respectively, in AGC with SOX130 (130 mg/m² of oxaliplatin) plus trastuzumab [12, 13]. Other clinical trials with fluoropyrimidines, oxaliplatin, and trastuzumab are summarized in Table 4. The comparison of characteristics and adverse event with SOX130 (130 mg/m² of oxaliplatin) trials is shown in Table 5. These results should be compared cautiously because of different conditions. The following points may have negatively affected our trial. First, the ratio of IHC3 + was lower than that of other trials, because the efficacy of trastuzumab depends on the relative positivity of HER2 [10]. Second, most patients in our trial had metastatic tumor at the time of diagnosis, whereas only one patient had locally advanced gastric cancer. Moreover, only one patient had a previous gastrectomy in our trial. Previous gastrectomy is one of the clinical characteristics associated with long-term survival in AGC [15]. Conversely, new post-treatments, such as nivolumab, may affect our trial positively. In our trial, nivolumab was administered to eight patients. Post-treatment regimens are
Fig. 3  Kaplan–Meier curves for patients with HER2-positive advanced gastric cancer treated with trastuzumab in combination with S-1 and oxaliplatin (SOX100) therapy. (A) Progression-free survival, (B) overall survival.

**A**
Median PFS
7.6 months (95% CI 5.0-10.9)

**B**
Median OS
17.8 months (95% CI 10.5-22.9)
shown in Table 6. Nevertheless, we conclude that there were not so differences in efficacy among these trials.

The adverse events of combination therapy were tolerable (Table 3). In this study, they were generally low grade, and patients were mostly able to continue treatment after protocol-specified dose reductions. Major grade 3 or higher adverse events associated with this study included anorexia, peripheral sensory neuropathy, and diarrhea. Grade 3 or higher hematological adverse events were similar to those in other SOX130 plus trastuzumab regimens; however, grades 1 to 2 hematological adverse events in our trial were lower than those observed in SOX130 plus trastuzumab regimens. Gastrointestinal toxicities and peripheral sensory neuropathy in our trial were also similar to those observed in SOX130 plus trastuzumab regimens; however, grades 1 to 2 nausea and anorexia in our trial were lower [12, 13]. One patient showed grade 4 pneumonitis at the time of ILD diagnosis and died of respiratory failure within 1 month of diagnosis. Both oxaliplatin and trastuzumab can induce ILD. To our knowledge, there is no interaction between oxaliplatin and trastuzumab. Although the frequency of ILD is rare, this requires scrupulous attention because both drugs can result in lethal pneumonitis.

It is of interest whether 100 or 130 mg/m² of oxaliplatin is a more appropriate dose for the SOX plus trastuzumab regimen. The G-SOX study showed that 100 mg/m² of oxaliplatin was a suitable dose for AGC [7], whereas Takahari et al. and Yuki et al. showed SOX130 was suitable for HER2-positive AGC [12, 13]. Yuki et al. reported that some patients had a conversion to curative surgery with SOX130 plus trastuzumab, although the ORR in our trial was similar to that in previous trials. In our study with SOX100 plus trastuzumab, there were no patients who experienced conversion to curative surgery. A high dose of oxaliplatin, such as in SOX130, may be suitable for patients who want to aim for conversion to curative surgery [13]. We speculate that SOX100 plus trastuzumab is one of the alternative options for most patients with HER2-positive AGC because of low adverse events.

The limitation of our study is the lower number of enrolled subjects (25 cases). Originally, we planned to enroll 30 patients, so the reliability of the results may not be as high as anticipated. When we began this study, we estimated the 1-year survival rate; the primary end point of this study would be 65% with a 90% CI of ±15% (50–80%). The result of this phase II study was a 1-year survival rate of 70.8% with a 90% CI (55.5–86.1%). On

| Event                | Any grade (%) | Grade ≥ 3 (%) |
|----------------------|---------------|---------------|
| Leukopenia           | 9 (36)        | 2 (8)         |
| Neutropenia          | 8 (32)        | 2 (8)         |
| Febrile neutropenia  | 0             | 0             |
| Anemia               | 14 (56)       | 4 (16)        |
| Thrombocytopenia     | 14 (56)       | 1 (4)         |

**Hematological**

| Event                | Event Any grade (%) | Grade ≥ 3 (%) |
|----------------------|---------------------|---------------|
| Leukopenia           | 9 (36)              | 2 (8)         |
| Neutropenia          | 8 (32)              | 2 (8)         |
| Febrile neutropenia  | 0                   | 0             |
| Anemia               | 14 (56)             | 4 (16)        |
| Thrombocytopenia     | 14 (56)             | 1 (4)         |

**Non-hematological**

| Event                | Event Any grade (%) | Grade ≥ 3 (%) |
|----------------------|---------------------|---------------|
| Nausea               | 10 (40)             | 2 (8)         |
| Vomiting             | 5 (20)              | 1 (4)         |
| Anorexia             | 14 (56)             | 5 (20)        |
| Fatigue              | 8 (32)              | 1 (4)         |
| Peripheral sensory-neuropathy | 20 (80) | 4 (16) |
| Stomatitis           | 3 (12)              | 0             |
| Skin hyper pigmentation | 2 (8)           | 0             |
| Diarrhea             | 13 (52)             | 3 (15)        |
| AST increased        | 16 (64)             | 2 (8)         |
| ALT increased        | 12 (48)             | 0             |
| Creatinine increased | 2 (8)               | 0             |
| Total bilirubin increased | 6 (24)   | 0             |
| Ejection fraction decreased | 3 (12) | 1 (4) |
| Pneumonitis          | 0                   | 1             |

AST aspartate aminotransferase; ALT alanine aminotransferase

### Table 4 Previous clinical trials of chemotherapy combined with trastuzumab in HER2-positive advanced gastric cancer

| Regimen                | Phase | n  | ORR | PFS (m) | OS (m) | Ref |
|------------------------|-------|----|-----|---------|--------|-----|
| Toga                   | II    | 294| 47  | 6.7     | 13.8   | [10]|
| HERBIS-1               | II    | 53 | 68  | 7.8     | 16.0   | [16]|
| Ryu et al              | II    | 55 | 68  | 9.8     | 21.0   | [17]|
| CGOOG1001              | II    | 51 | 66.7| 9.2     | 19.5   | [18]|
| HERXO                  | II    | 45 | 46.7| 7.1     | 13.8   | [19]|
| HIGHSOX               | II    | 75 | 70.7| 8.8     | 18.1   | [12]|
| Yuki et al             | II    | 39 | 82.1| 7.0     | 27.6   | [13]|
| Our trial              | II    | 25 | 75.0| 7.6     | 17.8   |     |

ORR overall response rate, PFS progression-free survival, OS: overall survival, Ref reference, FP fluorouracil+cisplatin, Tmab trastuzumab, SP S-1+cisplatin, XELOX capecitabine+oxaliplatin, SOX130 S-1+oxaliplatin (130 mg/m²), SOX100 S-1+oxaliplatin (100 mg/m²)
the basis of these findings, we judged the reliability of this study to be sufficient. Overall, SOX100 plus trastuzumab showed good efficacy and was well tolerated in HER2-positive AGC. Therefore, SOX100 plus trastuzumab is an alternative option for the treatment of HER2-positive AGC.

### Table 6  Post-treatment regimens

| Post-treatment regimen | No. of patients (%) |
|------------------------|---------------------|
| PTX + RAM              | 13 (52)             |
| nabPTX + RAM           | 2 (8)               |
| PTX                    | 3 (12)              |
| Nivolumab              | 8 (32)              |
| S-1 + CDDP             | 1 (4)               |
| FOLFOX                 | 1 (4)               |
| FTD/TPI                | 1 (4)               |

*Post-treatment regimens*

**Acknowledgements** This work was supported by the Kidani Trust Memorial Foundation.
Author Contribution H.K., T.S., and E.K. conceived and designed the study. All authors collected the data. Y.M. and H.K. performed data analysis and wrote the manuscript. All authors have read and approved the final paper.

Funding This work was supported by the Kidani Trust Memorial Foundation.

Data Availability Applicable.

Code Availability Word, Microsoft Office 2019.

Declarations

Ethics Approval All patients provided written informed consent before enrollment. This study was approved by Institutional Review Board of all hospitals and registered with UMIN-CTR (UMIN000017182).

Consent to Participate and Publication All the authors have read the manuscript and have approved participation, this submission and publication in Journal of Gastrointestinal Cancer.

Competing Interests All authors declare no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021. https://doi.org/10.3322/caac.21660.

2. Shirasaka T. Development history and concept of an oral anti-cancer agent S-1 (TS-1): its clinical usefulness and future vistas. Jpn J Clin Oncol. 2009;39(1):2–15. https://doi.org/10.1093/jjco/hyn127.

3. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, Koizumi W, Saito H, Yamaguchi K, Takuchi H, Nasu J, Ohtsu A, Gastrointestinal Oncology Study Group of the Japan Clinical Oncology G. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 10 2009;(11):1063–1069. https://doi.org/10.1016/S1470-2045(09)70259-1.

4. Koizumi W, Narahara H, Harai Y, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Ochiai A, Morita S, Sano T, Kodera Y, Kakeji Y, Sakamoto J, Saji S, Yoshida K. Clinicopathological factors associated with HER2 status in gastric cancer: results from a prospective multicenter observational cohort study in a Japanese population (JFMC4-1101). Gastric Cancer. 2016;19(3):839–51. https://doi.org/10.1007/s10120-015-0518-8.

5. Matsusaka S, Nashimoto A, Nishikawa K, Miki A, Miwa H, Yamaguchi K, Yoshikawa T, Ochiai A, Morita S, Sano T, Kodera Y, Kakeji Y, Sakamoto J, Saji S, Yoshida K. Clinicopathological factors associated with HER2 status in gastric cancer: results from a prospective multicenter observational cohort study in a Japanese population (JFMC4-1101). Gastric Cancer. 2016;19(3):839–51. https://doi.org/10.1007/s10120-015-0518-8.

6. Hidu CA. Trastuzumab–mechanism of action and use in clinical practice. N Engl J Med. 2007;357(1):39–51. https://doi.org/10.1056/NEJMra043186.

7. Yamada Y, Higuchi K, Nishikawa K, Gotoh M, Fuse N, Sugimoto N, Nishina T, Amagai K, Chin K, Niwa Y, Tsuji A, Imamura H, Tsuda M, Yasui H, Fujii H, Yamaguchi K, Yasui H, Hironaka S, Shimada K, Miwa H, Hamada C, Hyodo I. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naive patients with advanced gastric cancer. Ann Oncol. 2015;26(1):141–8. https://doi.org/10.1093/annonc/mdu472.

8. Kataoka H, Mori Y, Shimura T, Nishie H, Natsume M, Mochizuki H, Hirata Y, Sobue S, Mizushima T, Sano H, Mizuno Y, Nakamura M, Hirano A, Tsuichida K, Adachi K, Seno K, Kitagawa M, Kawai T, Joh T. A phase II prospective study of the trastuzumab combined with 5-weekly S-1 and CDDP therapy for HER2-positive advanced gastric cancer. Cancer Chemother Pharmacol. 2016;77(5):957–62. https://doi.org/10.1007/s00280-016-3013-y.

9. Matsuura S, Hagiwara K, Ito K, Saito H, Sumida T, Fujimori K, Oshita O, Asaka Y, Otsuka S, Hironaka Y, Kakeji Y, Sakamoto J, Saji S, Yoshida K. Clinicopathological factors associated with HER2 status in gastric cancer: results from a prospective multicenter observational cohort study in a Japanese population (JFMC4-1101). Gastric Cancer. 2016;19(3):839–51. https://doi.org/10.1007/s10120-015-0518-8.

10. Baba H, Mori M. Multicenter phase II study of SOX plus trastuzumab for chemotherapy-naive, HER2-positive advanced gastric cancer. Ann Oncol. 2018;29(5):1238–46. https://doi.org/10.1093/annonc/mdy121.

11. Kataoka H, Mori Y, Shimura T, Nishie H, Natsume M, Mochizuki H, Hirata Y, Sobue S, Mizushima T, Sano H, Mizuno Y, Nakamura M, Hirano A, Tsuichida K, Adachi K, Seno K, Kitagawa M, Kawai T, Joh T. A phase II prospective study of the trastuzumab combined with 5-weekly S-1 and CDDP therapy for HER2-positive advanced gastric cancer. Cancer Chemother Pharmacol. 2016;77(5):957–62. https://doi.org/10.1007/s00280-016-3013-y.

12. Kadoiwa K, Ishizuka N, Takashima A, Minashi K, Kadowaki S, Mishina T, Nakajima TE, Amagai K, Machida N, Goto M, Taka K, Watauki T, Shoji H, Hironaka S, Boku N, Yamaguchi K. Multicenter phase II study of trastuzumab with 5-fluorouracil plus oxaliplatin for chemotherapy-naive, HER2-positive advanced gastric cancer. Gastric Cancer. 2019;22(6):1238–46. https://doi.org/10.1007/s10120-019-00973-5.

13. Yuki S, Shinozaki K, Kashiwada T, Kusumoto T, Iwatsuki M, Satake H, Kobayashi K, Esaki T, Nakajima Y, Kawanaka H, Emi Y, Komatsu Y, Shimokawa M, Makiyama A, Saeki H, Okinaka Y, Ito K, Takenouchi M, Oshida K, Otsuka S, Yamada Y, Higuchi K, Nishikawa K, Gotoh M, Fuse N, Sugimoto N. Multicenter phase II study of trastuzumab for patients with HER2(+) metastatic or recurrent gastric cancer: KSCC/HC0SG/CCOG/PerSeUS 1501B. Cancer Chemother Pharmacol. 2020;85(1):217–23. https://doi.org/10.1007/s00280-019-03991-3.

14. Kanda Y. Investigation of the freely available easy-to-use software “EZAR” for medical statistics. Bone Marrow Transplant. 2013;48(3):452–8. https://doi.org/10.1038/bmt.2012.244.

15. Kadowaki S, Komori A, Takahara D, Ura T, Ito S, Tajika M, Niwa Y, Oze I, Muro K. Clinical characteristics associated with long-term survival in metastatic gastric cancer after systemic chemotherapy. Asian Pac J Cancer Prev. 2015;16(13):5433–8. https://doi.org/10.7314/ápjc.2015.16.13.5433.

16. Kurokawa Y, Sugimoto N, Miwa H, Tsuda M, Nishina S, Okuda H, Yamaguchi H, Gamoh M, Sakai D, Shimokawa T, Komatsu Y, Doki Y, Tsujinaka T, Furukawa H. Phase II study of trastuzumab in combination with S-1 plus cisplatin in HER2-positive gastric cancer (HERBIS-1). Br J Cancer. 2014;110(5):1163–8. https://doi.org/10.1038/bjc.2014.18.

17. Ryu MH, Yoo C, Kim JG, Ryoo BY, Park YS, Park SR, Han HS, Chung JJ, Song EK, Lee KH, Kang SY, Kang YK. Multicenter phase II study of trastuzumab in combination with capecitabine and oxaliplatin for advanced gastric cancer. Eur J Cancer. 2015;51(4):482–8. https://doi.org/10.1016/j.ejca.2014.12.015.
18. Gong J, Liu T, Fan Q, Bai L, Bi F, Qin S, Wang J, Xu N, Cheng Y, Bai Y, Liu W, Wang L, Shen L. Optimal regimen of trastuzumab in combination with oxaliplatin/ capecitabine in first-line treatment of HER2-positive advanced gastric cancer (CGOG1001): a multicenter, phase II trial. BMC Cancer. 2016;16:68. https://doi.org/10.1186/s12885-016-2092-9.

19. Rivera F, Romero C, Jimenez-Fonseca P, Izquierdo-Manuel M, Salud A, Martinez E, Jorge M, Arrazubi V, Mendez JC, Garcia-Alfonso P, Reboredo M, Barriuso J, Munoz-Unceta N, Jimeno R, Lopez C. Phase II study to evaluate the efficacy of Trastuzumab in combination with Capecitabine and Oxaliplatin in first-line treatment of HER2-positive advanced gastric cancer: HERXO trial. Cancer Chemother Pharmacol. 2019;83(6):1175–81. https://doi.org/10.1007/s00280-019-03820-7.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Yoshinori Mori1 · Hiromi Kataoka2 · Masahide Ebi3 · Kazunori Adachi3 · Yoshiharu Yamaguchi3 · Noriyuki Hayashi4 · Yoshikazu Hirata4 · Satoshi Sobue5 · Ryo Ishihara5 · Yuta Suzuki5 · Takashi Mizushima5 · Yusuke Inoue6 · Izumi Hasegawa6 · Satoshi Ono1,3 · Atsuyuki Hirano1 · Yoshihide Kimura1 · Koji Seno1 · Keiji Ozeki1 · Takaya Shimura2 · Eiji Kubota2

Yoshinori Mori
ysnmori@yahoo.co.jp
Masahide Ebi
mebi@aichi-med-u.ac.jp
Kazunori Adachi
k.adachi@aichi-med-u.ac.jp
Yoshiharu Yamaguchi
yamaguchi.yoshiharu.902@mail.aichi-med-u.ac.jp
Noriyuki Hayashi
nori53412@yahoo.co.jp
Yoshikazu Hirata
yskzhtm4@gmail.com
Satoshi Sobue
ssobae@nn.iiij4u.or.jp
Ryo Ishihara
ishihara-ryo@tajimi-hospital.jp
Yuta Suzuki
suzuki-yuta@tajimi-hospital.jp
Takashi Mizushima
mizushima-takashi@tajimi-hospital.jp
Izumi Hasegawa
izumi.hasepyon@gmail.com
Satoshi Ono
ono.satoshi.667@mail.aichi-med-u.ac.jp
Atsuyuki Hirano
a.hirano.20@west-med.jp
Kojo Seno
k.seno.20@west-med.jp
Keiji Ozeki
keozeki@med.nagoya-cu.ac.jp
Takaya Shimura
tshimura@med.nagoya-cu.ac.jp
Eiji Kubota
kkuboan@gmail.com

1 Department of Gastroenterology, Nagoya City University West Medical Center, 1-1-1 Hirate-cho, Kita-ku, Nagoya, Aichi 462-8508, Japan
2 Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan
3 Department of Gastroenterology, Aichi Medical University School of Medicine, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan
4 Department of Gastroenterology, Kasugai Municipal Hospital, 1-1-1 Takaki-cho, Kasugai, Aichi 486-8510, Japan
5 Gifu Prefectural Tajimi Hospital, 5-161, Maehata-cho, Tajimi, Gifu 507-8522, Japan
6 Department of Gastroenterology, Japan Community Health Care Organization Chukyo Hospital, 1-1-10 Sanjo, Minami-ku, Nagoya, Aichi 457-8510, Japan