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# Phase II Study of S-1 plus Trastuzumab for HER2-positive Metastatic Breast Cancer (GBCCSG-01)

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**Abstract.** *Aim: Treatment strategies for patients with human epidermal growth factor 2 (HER2)-positive metastatic breast cancer (MBC) have significantly progressed. The use of trastuzumab, a monoclonal antibody targeting the HER2 (human epidermal growth factor 2) protein, in combination with chemotherapy improves survival in patients with HER2-positive breast cancer. S-1, an oral combination of fluorouracil derivatives, is widely used in Japan and is more convenient than intravenous drugs. However, little is known about the combination of S-1 and trastuzumab in patients with HER2-positive MBC. Patients and Methods: We conducted a single-arm, open-label, multicenter prospective phase II study to evaluate the efficacy of an S-1 plus trastuzumab regimen for HER2-positive MBC. S-1 was administered orally [80-120 mg, based on body surface area (BSA)] twice a day for 14 consecutive days in a 3-week cycle. Patients with BSA of <1.25 $m^2$ received a total of 80 mg of S-1, those with BSA ≥1.5 $m^2$ received 120 mg, and the remaining received 100 mg daily in two divided doses. Trastuzumab was administered intravenously at 8 mg/kg on day 1 of the first cycle and at 6 mg/kg on day 1 of subsequent cycles, i.e., every 3 weeks. Results: Between December 2008 and March 2013, 10 patients were enrolled and received a median of 17 (range=3-76) cycles of treatment. Overall response and clinical benefit rates were 60.0% and 90.0%, respectively. Progression-free survival was 15.8 (95% confidence interval=9.4-29.6) months and overall survival was 45.5 (95% confidence interval=37.1-62.2) months. Grade 3/4 adverse events included were neutropenia and hyperglycemia in one patient each (10.0%). There was no clinically significant cardiotoxicity. Conclusion: The combination of S-1 and trastuzumab was tolerable and had excellent efficacy with good response and disease control in this study. S-1 plus anti-HER2 therapy is a feasible treatment option for HER2-positive MBC.*

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Treatment strategies for patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer have significantly progressed in recent years (1-4). The use of trastuzumab, a monoclonal antibody targeting the HER2 protein, in combination with chemotherapy has improved survival of patients with HER2-positive breast cancer (1-3). Taxanes were the first established cytotoxic agent to be combined with trastuzumab (1). However, administration of taxanes causes various serious adverse events, including neutropenia, hair loss, edema, and peripheral neuropathy, which may affect health-related quality of life (HRQOL) (5, 6). The objective of treatment is to prolong survival and improve QOL (6-8). Thus, less toxic treatments are preferred and trastuzumab-based regimens that do not reduce HRQOL are needed for the management of HER2-positive MBC.

Orally administered drugs are generally more convenient than intravenous drugs (6, 9). S-1, an oral combination of fluorouracil derivatives, is widely used in Japan (6). It

combines tegafur (a prodrug of 5-fluorouracil) with gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, the rate-limiting enzyme in the catabolism of 5-fluorouracil) and potassium oxonate (an inhibitor of orotate phosphoribosyltransferase, which suppresses the gastrointestinal toxicity of 5-fluorouracil) in a molar ratio of 1.0:0.4:1.0 (8). S-1 led to an overall response rate (ORR) of 41.7% in Japanese phase II trials of patients with breast cancer (8, 10). A recent randomized phase III study reported that S-1 is non-inferior to taxane with respect to overall survival (OS) as a first-line treatment for MBC (6). As for adverse events, S-1 has shown a low incidence of myelosuppression, gastrointestinal toxicity and hair loss, and does not cause nausea, vomiting, alopecia, or peripheral neuropathy (8). Thus, S-1 was demonstrated to have high efficacy with low incidence of adverse events and is a promising new chemotherapy drug for MBC (6, 10). However, little is known about the efficacy of S-1 plus trastuzumab in patients with HER2-positive MBC and few data evaluating the efficacy are available in the existing literature (8, 11). We therefore carried out a phase II trial to verify the clinical efficacy of S-1 in combination with trastuzumab for HER2-positive MBC.

## Patients and Methods

*Study design and patients*. We conducted a single-arm, open-label, multicenter prospective phase II study to evaluate the efficacy of an S-1 plus trastuzumab regimen for HER2-positive MBC. HER2 overexpression was determined by immunohistochemistry (IHC) analysis and fluorescence in-situ hybridization (FISH) analysis. Women aged ≥20 years old with a histological diagnosis of HER2-positive (IHC 3+ or IHC 2+/FISH+) MBC were considered eligible for this study. Eligibility required measurable tumor based on Response Evaluation Criteria in Solid Tumors (RECIST) (12); left ventricular ejection fraction (LVEF) ≥55%; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or 2; expected survival >3 months; adequate organ function defined as leukocyte count 3,500-12,000/mm$^3$ (or neutrophil count >1500 /mm$^3$), platelet count >100,000/mm$^3$, hemoglobin >9 g/dl, serum aspartate aminotransferase and alanine aminotransferase levels less than 2.5× the upper level of normal at each institution, serum total bilirubin <1.5 mg/dl, and serum creatinine <1.2 mg/dl (or creatinine clearance >60 ml/min). Any treatment except for radiation was permitted for those with metastatic disease. Exclusion criteria included symptomatic central nervous system metastases, active systemic infectious disease, clinically significant cardiovascular impairment, serious concomitant illness, a second primary cancer, those who had received trastuzumab-containing therapy within the previous 6 months, and those who had received 5-fluorouracil-containing therapy within the previous 12 months.

From December 2008 to March 2013, a total of 10 patients were enrolled in this study. The demographic characteristics of the patients are shown in Table I. The median age was 57.5 years (range 47-82). Eight patients had recurrent disease and two patients had metastatic disease, stage IV. The study was carried out at the Gunma University, Japan. The study protocol was approved by the Ethics Committee of the participating institutions (approval number, 640), and written informed consent was obtained from all patients.

*Treatment procedure*. S-1 was administered orally (80-120 mg) based on body surface area (BSA) twice a day for 14 consecutive days in a repeating 3-week cycle (2 weeks on, 1 week off). Patients with BSA of <1.25 m$^2$ received a total of 80 mg of S-1, those with BSA ≥1.5 m$^2$ received 120 mg, and the remaining received 100 mg daily in two divided doses. Trastuzumab was administered intravenously at 8 mg/kg on day 1 of the first cycle and at 6 mg/kg on day 1 of the subsequent cycles, every 3 weeks. This regimen was continued until the occurrence of progressive disease (PD), as assessed by the investigator using RECIST criteria, or the appearance of unmanageable toxicity, or the patient's withdrawal of consent. Any concomitant medication could be given at the discretion of the investigator if it was considered necessary for the patient's welfare and was not expected to interfere with the evaluation of study treatment. Other antitumor therapies were not permitted.

*Assessments*. The primary endpoint was antitumor activity of S-1 plus trastuzumab, as assessed by ORR using RECIST criteria. Secondary endpoints included OS, progression-free survival (PFS), clinical benefit rate (CBR) and safety. Routine tumor assessments based on RECIST were performed 1 month after the first dose and then every month during treatment periods. The ORR was defined as the proportion of all patients with complete (CR) and partial (PR) response. The CBR was defined as the proportion of the patients with CR or PR or stable disease (SD) continuing longer than 4 weeks (28 days). CR and PR required confirmation at least 4 weeks after first being reported. The Kaplan–Meier approach was used to estimate median PFS and OS. OS was defined as the interval between the onset of study therapy and death, and the event as all-cause mortality.

Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, Version 3.0 and 4.0 (13). The incidence of adverse events was calculated according to grade. Hematological and biochemical assessments, physical examinations, and periodic measurement of vital signs were performed before the start of each treatment cycle.

## Results

*Patient characteristics*. From December 2008 through to March 2013, a total of 10 patients were enrolled from four institutions in Gunma, Japan. Ten patients received a median of 17 (range=3-76) cycles of treatment. The characteristics of patients are summarized in Table I. Of 10 patients, eight patients had recurrent cancer, and two patients had advanced cancer. The median age was 58 (range=47-82) years. Three patients had hormonal receptor (HR; estrogen or progesterone)-positive and the other seven patients had HR-negative tumors. No patients had received cytotoxic chemotherapy before registration, and hence all were receiving S-1 plus trastuzumab treatment as first-line chemotherapy. Three patients had received endocrine therapy for MBC before registration.

*Tumor responses and survival*. The overall response was CR in three patients (30%), PR in three (30%), SD in three

Table I. *Patient characteristics and clinicopathological features.*

| Characteristic | Value |
|---|---|
| Age median (range), years | 58 (47-82) |
| ECOG performance status, (n) | |
| 0 | 9 |
| 1 | 0 |
| 2 | 1 |
| ER status, n | |
| Positive | 3 |
| Negative | 7 |
| PgR status, n | |
| Positive | 2 |
| Negative | 8 |
| Metastatic sites, n | |
| Liver | 4 |
| Lung | 3 |
| Bone | 1 |
| Lymph node | 4 |
| Other | 2 |
| Priory surgery, n | |
| Yes | 7 |
| No | 3 |
| Adjuvant therapy, n | |
| Chemotherapy | 7 |
| Endocrine therapy | 3 |
| Trastuzumab | 1 |

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor.

Table II. *The common adverse events of any grade and grade 3/4 experienced by patients.*

| Adverse event | All grade, (n) | Grade 3/4, (n) |
|---|---|---|
| Leukopenia | 2 | 0 |
| Neutropenia | 1 | 1 |
| Anemia | 6 | 0 |
| Platelet count decreased | 3 | 0 |
| Hypoalubuminrmia | 1 | 0 |
| Bilirubin increased | 6 | 0 |
| AST inceased | 8 | 0 |
| ALT increased | 6 | 0 |
| ALP increased | 1 | 0 |
| Stomatitis | 3 | 0 |
| Anorexia | 2 | 0 |
| Nausea | 4 | 0 |
| Vomiting | 1 | 0 |
| Diarrhea | 2 | 0 |
| Constipation | 2 | 0 |
| Skin rash | 1 | 0 |
| Skin pigmentation | 4 | 0 |
| Alopecia | 1 | 0 |
| Fatigue | 3 | 0 |
| Peripheral neuropathy | 1 | 0 |
| Fever | 2 | 0 |
| Hyperglycemia | 1 | 1 |
| Dysphasia | 1 | 0 |

n: Number of patients; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

(30%), and PD in one (10%). Therefore, the ORR and CBR were 60.0% (6/10) and 90.0% (9/10), respectively. By the time of data cut-off, PFS events had been observed in seven patients (70%). Three out of 10 patients died from breast cancer and one died from perforated peritonitis of the stomach. The mean PFS for the patient population was 15.8 months (95% confidence interval=9.4-29.6 months) and OS was 45.5 months (95% confidence interval=37.1-62.2 months) (Figure 1).

*Safety.* All patients were assessed for toxicities during the treatment cycles. The adverse events are shown in Table II. Regarding hematological toxicity, leukopenia occurred in two (20%) patients, hemoglobinemia in six (60%), and thrombocytopenia in three (30%). Only one patient had grade 3 neutropenia, but no patients had grade 4 hematological toxicity. With regard to non-hematological toxicities, the most common events were diarrhea and elevation of serum aminotransferase. Grade 3/4 adverse events included neutropenia and hyperglycemia, in one patient each (10.0%). There was no clinically significant cardiotoxicity and there was no treatment-related mortality.

## Discussion

As noted in the introduction section, treatment strategies for patients with HER2-positive MBC have significantly improved in recent years (1-4). The use of trastuzumab in combination with chemotherapy improves survival in patients with HER2-positive breast cancer (1-3). Furthermore, the combination of docetaxel with pertuzumab and trastuzumab was established as a first-line treatment for HER2-positive MBC in the CLEOPATRA study, showing a significantly prolonged PFS and OS compared with the placebo arm (docetaxel with placebo and trastuzumab) (14). In this study, we were unable to not administer pertuzumab as treatment procedure because pertuzumab had not yet been approved in Japan during this study. Taxanes were the first established cytotoxic agent to be combined with trastuzumab (1) and combined with pertuzumab and trastuzumab (14). However, taxanes can cause cumulative toxicities, such as peripheral neuropathy, hair loss, and edema (6). The goals of treatment for MBC are prolonging survival and maintaining adequate QOL or HRQOL. Trastuzumab-based chemotherapy regimens that do not reduce QOL or HRQOL

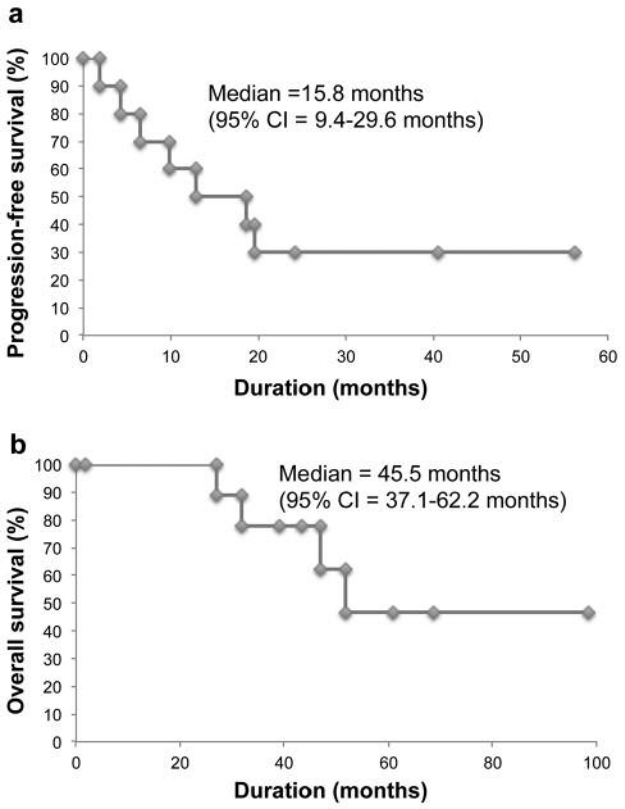


Figure 1. *Kaplan–Meier estimates of progression-free (a) and overall survival (b) rates. Bars represent patients whose data were censored.*

are required for the management of HER2-positive MBC, and less toxic treatments should be chosen as the first-line chemotherapy, as long as the treatment can control disease progression (11). S-1 chemotherapy, which is used in Japan, was recently shown to be non-inferior to taxane with respect to OS and better than taxane with regard to HRQOL as a first-line treatment for patients with HER2-negative MBC in a SELECT BC trial (6). Therefore, S-1, rather than taxane, with trastuzumab or another anti-HER2 treatment, should be an effective and less toxic regimen for HER2-positive MBC.

In this study, ORR and CBR were 60% and 90%, respectively. PFS was 15.8 months and OS was 45.5 months. Grade 3/4 adverse events included neutropenia and hyperglycemia in one patient each (10%, respectively). Thus, this study strongly suggests that combination therapy with S-1 and trastuzumab is an effective treatment option with a manageable toxicity profile for patients with HER2-positive MBC. As for S-1 plus trastuzumab combination treatment, one phase II study in Japan has already reported the efficacy of this regimen (11). Our phase II study results are consistent with the ORR of 53.6% and CBR of 75.0% in that phase II study (11). However, grade 3 leukopenia and neutropenia was observed 25% of patients in that study (11), which is relatively high compared with our results. There are often patients who cannot continue with S-1 therapy, and adverse effects may have been particularly high because of that study's 4-week administration with a 2-week rest schedule (11). In our study, that 6-week regimen was changed to a 3-week schedule of 2 weeks of administration and 1 week of rest, and this change appeared to reduce toxicity and to be consistent with tri-weekly trastuzumab. Adverse events such as hair loss, peripheral neuropathy, or edema, which are commonly observed in patients with taxane treatment, were rare in this study. To our knowledge, this is the first prospective clinical trial evaluating the efficacy of a 3-week regimen of S-1 plus trastuzumab for HER2-positive MBC.

This study has potential limitations, the major one being the small number of cases. However, the combination of docetaxel with pertuzumab and trastuzumab had already been established as first-line treatment for HER-2 positive MBC. Additional research is needed to explore the efficacy of S-1 plus pertuzumab and trastuzumab, or other anti-HER2 regimens, in larger numbers of patients to confirm the effects of S-1 combined with anti-HER2 therapy.

In conclusion, the combination of S-1 and trastuzumab was tolerable and had excellent efficacy with good response and disease control in this study. S-1 plus anti-HER2 therapy is a feasible treatment option for HER2-positive MBC.

## Competing Interest Statement

The Authors declare that they have no competing financial interests in regard to this study.

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