Randomized, Open-Label Phase II Study Comparing Capecitabine-Cisplatin Every 3 Weeks with S-1-Cisplatin Every 5 Weeks in Chemotherapy-Naïve Patients with HER2-Negative Advanced Gastric Cancer: OGSSG1105, HERBIS-4A Trial

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Disclosures of potential conflicts of interest may be found at the end of this article.

TRIAL INFORMATION

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- Principal Investigator: Hisato Kawakami
- IRB Approved: Yes

LESSONS LEARNED

- Evidence has suggested that capecitabine-cisplatin is similar or possibly superior to S-1-cisplatin in terms of safety and efficacy for Japanese patients with advanced gastric cancer (AGC).
- As far as we are aware, our study is the first randomized trial of two regimens consisting of an oral fluoropyrimidine plus cisplatin in human epidermal growth receptor 2-negative AGC patients with measurable lesions.

ABSTRACT

Background. We performed a phase II study to evaluate the safety and efficacy of capecitabine plus cisplatin in comparison with S-1 plus cisplatin for first-line treatment of human epidermal growth receptor 2 (HER2)-negative advanced gastric cancer in Japan.

Methods. Eligible patients were randomly assigned to receive either capecitabine at 1,000 mg/m² twice daily for 14 days plus cisplatin at 80 mg/m² on day 1 every 3 weeks (n = 43) or S-1 at 40–60 mg twice daily for 21 days plus cisplatin at 60 mg/m² on day 8 every 5 weeks (n = 41). The primary endpoint of the study was response rate.

Results. Response rate did not differ significantly between the capecitabine-cisplatin and S-1-cisplatin groups (53.5% vs. 51.2%, respectively, p > .999). S-1-cisplatin tended to confer a better progression-free survival (PFS; median of 5.9 vs. 4.1 months, p = .284), overall survival (OS; median of 13.5 vs. 10.0 months, p = .290), and time to treatment failure (TTF; median of 4.5 vs. 3.1 months, p = .052) compared with capecitabine-cisplatin. Common hematologic toxicities of grade 3 or 4 included anemia and neutropenia in both groups. However, anorexia, fatigue, and hyponatremia of grade 3 or 4 occurred more frequently in the capecitabine-cisplatin group.

Conclusion. Capecitabine-cisplatin failed to demonstrate superior efficacy compared with S-1-cisplatin. The higher incidence of severe adverse events with capecitabine-cisplatin suggests that S-1-cisplatin should remain the standard first-line chemotherapy for HER2-negative advanced gastric cancer in Japan. The Oncologist 2018;23:1411–e147

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DISCUSSION

The response rate was 51.2% (95% CI, 35.1%–67.1%) in the S-1–cisplatin group and 53.5% (95% CI, 37.7%–68.8%) in the capecitabine-cisplatin group (\(p > .999\)). The DCR for the FAS was higher in the S-1–cisplatin arm (82.9%) than in the capecitabine-cisplatin arm (67.4%). A waterfall plot analysis revealed that patients in the S-1–cisplatin arm showed greater tumor shrinkage and that a larger proportion of patients in this arm experienced tumor shrinkage from baseline compared with the capecitabine-cisplatin arm (Fig. 1).

For survival analysis, the median follow-up time was 11.3 months. The median PFS was 5.9 months in the S-1–cisplatin group and 4.1 months in the capecitabine-cisplatin group (HR, 0.76; 95% CI, 0.485–1.24; \(p = .284\)) (Fig. 2A), whereas the corresponding values for median OS were 13.5 and 10.0 months (HR, 0.776; 95% CI, 0.485–1.244; \(p = .290\)) (Fig. 2B) and those for median TTF were 4.5 and 3.1 months (HR, 0.651; 95% CI, 0.421–1.006; \(p = .052\)) (Fig. 2C).

The most common all-grade hematologic adverse events were anemia (79% in the S-1–cisplatin group, 74% in the capecitabine-cisplatin group) and neutropenia (54% and 60%), each of which occurred at a similar frequency in the two groups. In contrast, anemia and neutropenia of grade 3 or 4 were more common in the capecitabine-cisplatin group than in the S-1–cisplatin group. With regard to nonhematologic toxicities, anorexia (67% and 72%) and malaise (46% and 49%) were common all-grade adverse events in both treatment groups. Anorexia, fatigue, and hyponatremia of grade 3 or 4 were more frequent in the capecitabine-cisplatin group (23%, 14%, and 16%) than in the S-1–cisplatin group (13%, 0%, and 5%). Peripheral
neuropathy and hand-foot syndrome of grade 3 or 4 were apparent in the capecitabine-cisplatin arm (5% and 2%) but not in the S-1–cisplatin arm. One death in the capecitabine-cisplatin group (2%, 1 of 43) was due to brain infarction, which was considered to be treatment related by the investigators.

| **Trial Information** |
|-----------------------|
| **Disease** | Gastric cancer |
| **Stage of Disease/Treatment** | Metastatic/advanced |
| **Prior Therapy** | None |
| **Type of Study – 1** | Phase II |
| **Type of Study – 2** | Randomized |
| **Primary Endpoint** | Overall response rate |
| **Secondary Endpoint** | Progression-free survival |
| **Secondary Endpoint** | Overall survival |
| **Secondary Endpoint** | Safety |
| **Secondary Endpoint** | Time to treatment failure |

**Additional Details of Endpoints or Study Design**

The trial was based on a randomized phase II screening design with a primary endpoint of response rate (RR). On the basis of an assumed RR of 40% in the S-1-cisplatin arm, the study was designed to detect an improvement in RR of 15 percentage points (i.e., to 55%) in the capecitabine-cisplatin arm. For primary analysis, 100 patients were required to detect such an improvement in RR with ≥80% power, with a one-sided significance level of 0.20 in Fisher’s exact test. However, as a result of slow accrual, the protocol was amended in December 2015 to reduce the planned sample size from 100 to 84 based on a one-sided significance level of 0.10 and power of 70%. Ultimately, enrollment was terminated after inclusion of 85 patients in April 2016.

The primary endpoint of the study was RR, with secondary end points including PFS, OS, TTF, and safety. Tumor response was assessed by investigators on the basis of RECIST version 1.1 at baseline and every 8 weeks after randomization until disease progression. The RR and disease control rate were defined as the proportion of patients who achieved a confirmed complete response (CR) or partial response (PR) or who achieved a confirmed CR, PR, or stable disease (SD), respectively. Tumor histology was based on the Japanese classification of gastric carcinoma, with differentiated-type tumors being defined as papillary or tubular adenocarcinoma and undifferentiated-type tumors as poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous adenocarcinoma. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

**Investigator’s Analysis**

Inactive because results did not meet primary endpoint.

**Drug Information for Phase II S-1 + CDDP**

| **Drug 1** |
|-----------------|
| **Generic/Working Name** | S-1 |
| **Trade Name** | TS-1 |
| **Company Name** | Taiho Pharmaceutical, Co, Ltd. |
| **Dose** | 80–120 mg/m² |
| **Route** | p.o. |
| **Schedule of Administration** | S-1 at 40–60 mg twice daily for 21 days every 5 weeks |

| **Drug 2** |
|-----------------|
| **Generic/Working Name** | Cisplatin (CDDP) |
| **Drug Class** | Platinum compound |
| **Dose** | 60 mg/m² |
| **Route** | IV |
| **Schedule of Administration** | Cisplatin at 60 mg/m² on day 8, every 5 weeks |

**Drug Information for Phase II Capecitabine + CDDP**

| **Drug 1** |
|-----------------|
| **Generic/Working Name** | Capecitabine |
| **Trade Name** | Xeloda |
| **Company Name** | Chugai Pharmaceutical, Co, Ltd. |
| **Dose**       | 2,000 mg/m² |
|---------------|-------------|
| **Route**     | p.o.        |
| **Schedule of Administration** | Capecitabine at 1,000 mg/m² twice daily for 14 days every 3 weeks |

**Drug 2**

| **Generic/Working Name** | Cisplatin (CDDP) |
|--------------------------|------------------|
| **Drug Class**           | Platinum compound |
| **Dose**                 | 80 mg/m²         |
| **Route**                | IV               |
| **Schedule of Administration** | Cisplatin at 80 mg/m² on day 1 every 3 weeks |

## PATIENT CHARACTERISTICS FOR PHASE II S-1 + CDDP

| **Number of Patients, Male** | 33 |
|-----------------------------|----|
| **Number of Patients, Female** | 8 |

### Stage

| **T factor** | **N factor** | **M factor** |
|--------------|--------------|--------------|
| TX           | NX           | MX/M0/M1      |
| T1 (SM)      | N0           | 2/6/33       |
| T2 (MP)      | N1           |               |
| T3 (SS)      | N2           |               |
| T4a (SE)     | N3a          |               |
| T4b (SI)     | N3b          |               |

### Age

**Median (range): 68 (38–77)**

### Number of Prior Systemic Therapies

**Median (range): 0**

### Performance Status: ECOG

| **ECOG** | **Number** |
|----------|------------|
| 0 — 22   | 22         |
| 1 — 19   | 19         |
| 2 — 0    | 0          |
| 3 — 0    | 0          |
| Unknown  | 0          |

### Other

| **Metastatic/recurrent sites** | **Number** |
|------------------------------|------------|
| Lymph node                   | 33         |
| Peritoneum                   | 8          |
| Liver                        | 17         |
| Lung                         | 5          |
| Bone                         | 4          |
| Adrenal                      | 1          |
| Portal vein tumor thrombus   | 1          |
### Cancer Types or Histologic Subtypes

- HER2 unknown, 0
- HER2 negative 0/1+/2+ 23/14/4
- Papillary adenocarcinoma 0
- Tubular adenocarcinoma 23
- Poorly differentiated adenocarcinoma 14
- Signet ring cell carcinoma 3
- Mucinous adenocarcinoma 0
- Undetermined 1

### Patient Characteristics for Phase II Capecitabine + CDDP

|                          | 36 | 7 |
|--------------------------|----|---|
| Number of Patients, Male |    |   |
| Number of Patients, Female |  |   |

| Stage | T factor | TX | 1 |
|-------|----------|----|---|
|       | T1 (SM)  | 1  |
|       | T2 (MP)  | 1  |
|       | T3 (SS)  | 9  |
|       | T4a (SE) | 21 |
|       | T4b (SI) | 10 |
| N factor | NX | 2 |
|          | N0 | 5 |
|          | N1 | 7 |
|          | N2 | 15|
|          | N3a| 9 |
|          | N3b| 5 |
| M factor | MX/M0/M1 | 1/4/38 |

| Previous gastrectomy | Yes/No |
|----------------------|--------|
|                      | 2/41   |

| Age | Median (range): 64 (34–79) |
|-----|---------------------------|
| Number of Prior Systemic Therapies | Median (range): 0 |

| Performance Status: ECOG | 0 — 24 |
|--------------------------|--------|
|                          | 1 — 19 |
|                          | 2 — 0  |
|                          | 3 — 0  |
| Unknown — 0              |        |

| Other | Metastatic/recurrent sites |
|-------|---------------------------|
|       | Lymph node                | 37 |
|       | Peritoneum                 | 13 |
|       | Liver                      | 16 |
|       | Lung                       | 4  |
|       | Bone                       | 2  |
|       | Adrenal                    | 0  |
|       | Portal vein tumor thrombus | 0  |

| Cancer Types or Histologic Subtypes | HER2 unknown 1 |
|-------------------------------------|----------------|
|                                     | HER2 negative 0/1+/2+ 22/17/3 |
|                                     | Papillary adenocarcinoma 2    |
|                                     | Tubular adenocarcinoma 19     |
### Primary Assessment Method for Phase II S-1 + CDDP

| Title                                           | Total patient population |
|-------------------------------------------------|--------------------------|
| Number of Patients Screened                     | 41                       |
| Number of Patients Enrolled                     | 39                       |
| Number of Patients Evaluable for Toxicity       | 39                       |
| Number of Patients Evaluated for Efficacy       | 41                       |
| Evaluation Method                               | RECIST 1.1               |
| Response Assessment CR                          | \( n = 0 \) (0%)         |
| Response Assessment PR                          | \( n = 21 \) (51%)       |
| Response Assessment SD                          | \( n = 13 \) (32%)       |
| Response Assessment PD                          | \( n = 3 \) (7%)         |
| Response Assessment OTHER                       | \( n = 4 \) (10%)        |
| (Median) Duration Assessments PFS               | 179 days, CI: 136–225    |
| (Median) Duration Assessments OS                | 412 days, CI: 340–701    |

### Secondary Assessment Method for Phase II S-1 + CDDP

| Title                                           | Total patient population |
|-------------------------------------------------|--------------------------|
| (Median) Duration Assessments PFS               | 179 days, CI: 136–225    |
| (Median) Duration Assessments OS                | 412 days, CI: 340–701    |

### Primary Assessment Method for Phase II Capecitabine + CDDP

| Title                                           | Total patient population |
|-------------------------------------------------|--------------------------|
| Number of Patients Screened                     | 43                       |
| Number of Patients Enrolled                     | 43                       |
| Number of Patients Evaluable for Toxicity       | 43                       |
| Number of Patients Evaluated for Efficacy       | 43                       |
| Evaluation Method                               | RECIST 1.1               |
| Response Assessment CR                          | \( n = 0 \) (0%)         |
| Response Assessment PR                          | \( n = 23 \) (53%)       |
| Response Assessment SD                          | \( n = 6 \) (14%)        |
| Response Assessment PD                          | \( n = 10 \) (3%)        |
| Response Assessment OTHER                       | \( n = 4 \) (10%)        |
| (Median) Duration Assessments PFS               | 124 days, CI: 108–200    |
| (Median) Duration Assessments OS                | 305 days, CI: 218–474    |

### Secondary Assessment Method for Phase II Capecitabine + CDDP

| Title                                           | Total patient population |
|-------------------------------------------------|--------------------------|
| (Median) Duration Assessments PFS               | 124 days, CI: 108–200    |
| (Median) Duration Assessments OS                | 305 days, CI: 218–474    |
### Phase II S-1 + CDDP Adverse Events

| All Cycles Name       | NC/NA | 1  | 2  | 3  | 4  | 5  | All grades |
|-----------------------|-------|----|----|----|----|----|------------|
| Neutrophil count decreased | 46%   | 5% | 26%| 8% | 15%| 0% | 54%        |
| Platelet count decreased | 46%   | 21%| 15%| 15%| 3% | 0% | 54%        |
| Aspartate aminotransferase increased | 79%   | 18%| 0% | 3% | 0% | 0% | 21%        |
| Hypokalemia           | 79%   | 13%| 3% | 5% | 0% | 0% | 21%        |
| Hypoalbuminemia       | 48%   | 23%| 26%| 3% | 0% | 0% | 52%        |
| Febrile neutropenia   | 95%   | 0% | 0% | 5% | 0% | 0% | 5%         |
| Anemia                | 21%   | 28%| 28%| 23%| 0% | 0% | 79%        |
| Hyponatremia          | 64%   | 28%| 3% | 5% | 0% | 0% | 36%        |
| Peripheral sensory neuropathy | 97%   | 0% | 3% | 0% | 0% | 0% | 3%         |
| Fatigue               | 54%   | 28%| 18%| 0% | 0% | 0% | 46%        |
| Creatinine increased  | 61%   | 33%| 3% | 3% | 0% | 0% | 39%        |
| Anorexia              | 33%   | 26%| 28%| 13%| 0% | 0% | 67%        |
| White blood cell decreased | 49%   | 18%| 15%| 18%| 0% | 0% | 51%        |
| Abdominal pain        | 77%   | 18%| 5% | 0% | 0% | 0% | 23%        |
| Nausea                | 67%   | 28%| 5% | 0% | 0% | 0% | 33%        |
| Diarrhea              | 82%   | 10%| 8% | 0% | 0% | 0% | 18%        |
| Hyperkalemia          | 80%   | 15%| 0% | 5% | 0% | 0% | 20%        |
| Palmar-plantar erythrodysesthesi syndrome | 95%   | 5% | 0% | 0% | 0% | 0% | 5%         |
| Mucositis oral        | 87%   | 3% | 5% | 0% | 0% | 0% | 13%        |

Abbreviation: NC/NA, no change from baseline/no adverse event.

### Serious Adverse Events

| Name      | Grade | Attribution |
|-----------|-------|-------------|
| Sepsis    | 4     | Unlikely    |
| Syncope   | 3     | Unlikely    |

### Phase II Capecitabine + CDDP Adverse Events

| All Cycles Name       | NC/NA | 1  | 2  | 3  | 4  | 5  | All grades |
|-----------------------|-------|----|----|----|----|----|------------|
| Neutrophil count decreased | 40%   | 2% | 23%| 21%| 14%| 0% | 60%        |
| Platelet count decreased | 40%   | 21%| 15%| 15%| 3% | 0% | 54%        |
| Aspartate aminotransferase increased | 87%   | 9% | 2% | 2% | 0% | 0% | 13%        |
| Hypokalemia           | 79%   | 12%| 0% | 7% | 2% | 0% | 21%        |
| Hypoalbuminemia       | 56%   | 21%| 23%| 0% | 0% | 0% | 44%        |
| Febrile neutropenia   | 93%   | 0% | 0% | 7% | 0% | 0% | 7%         |
| Anemia                | 25%   | 19%| 28%| 28%| 0% | 0% | 75%        |
| Hyponatremia          | 63%   | 21%| 0% | 14%| 2% | 0% | 37%        |
| Peripheral sensory neuropathy | 85%   | 5% | 5% | 5% | 0% | 0% | 15%        |
| Fatigue               | 51%   | 19%| 30%| 0% | 0% | 0% | 49%        |
| Vomiting              | 95%   | 5% | 0% | 0% | 0% | 0% | 5%         |
| White blood cell decreased | 47%   | 7% | 28%| 16%| 2% | 0% | 53%        |
| Creatinine increased  | 72%   | 9% | 14%| 5% | 0% | 0% | 28%        |
| Anorexia              | 28%   | 19%| 30%| 23%| 0% | 0% | 72%        |
| Abdominal pain        | 98%   | 0% | 0% | 2% | 0% | 0% | 2%         |
Gastric cancer is the fifth most common malignant disease and the second leading cause of cancer deaths worldwide [1], with an especially high incidence in East Asia. Individuals newly diagnosed with gastric cancer often present with unresectable or metastatic disease, known as advanced gastric cancer (AGC). Trastuzumab in combination with unresectable or metastatic disease, known as HER2-negative AGC, represents the standard therapy for such patients in practice, given that the addition of docetaxel [6] or epirubicin [7] was associated with a limited improvement in survival but substantial hematologic toxicity [6,7]. Adverse events were generally mild, with the most common events of grade 3 or 4 being neutropenia, anemia, anorexia, and nausea. Similar efficacy and safety profiles for capcitabine-cisplatin in Japanese AGC patients were also apparent in a retrospective study [12]. These data have suggested that capcitabine-cisplatin is similar or possibly superior to S-1-cisplatin in terms of safety and efficacy for Japanese patients with AGC. However, capcitabine-cisplatin has not been prospectively compared with S-1-cisplatin in patients with HER2-negative AGC to date. We have therefore now conducted a phase II study to assess the efficacy and safety of capcitabine-cisplatin versus S-1-cisplatin in Japanese patients with HER2-negative AGC.

In our trial, however, capcitabine-cisplatin failed to show a superior efficacy relative to S-1-cisplatin. Although RR, the primary endpoint of our trial, did not differ significantly between the two treatment groups, disease control rate (DCR) was higher in the S-1-cisplatin arm, with this benefit being confirmed by waterfall analysis. The benefit of S-1-cisplatin with regard to its high DCR likely reflects the observed trend toward a better PFS and OS in the S-1-cisplatin arm than in the capcitabine-cisplatin arm.
With respect to adverse events, both regimens in the present study showed similar hematologic toxicity profiles, with anemia and neutropenia being most frequently observed. In contrast, the overall incidence of nonhematologic toxicities of grade 3 or 4 was higher in the capecitabine-cisplatin group than in the S-1-cisplatin group. A meta-analysis comparing S-1 with capecitabine in AGC found no overall difference in terms of serious adverse events [13]. In the present study, however, anorexia, fatigue, and hyponatremia of grade 3 or 4 occurred more frequently in the capecitabine-cisplatin arm than in the S-1-cisplatin arm. Moreover, brain infarction of grade 5 occurred in one patient of the capecitabine-cisplatin group, possibly as a result of the high dose intensity of cisplatin, which is known to be associated with venous thromboembolism [14]. Indeed, most of the differences in nonhematologic toxicity between the two groups were likely due to the higher dose of cisplatin administered in the capecitabine-cisplatin arm, which was also associated with a shorter time to treatment failure. Together, our findings suggest that, at least in the setting of the present trial, administration of cisplatin at 80 mg/m² every 3 weeks in combination with capecitabine did not increase efficacy but was more toxic compared with that at 60 mg/m² every 5 weeks in combination with S-1.

In conclusion, although our study was a phase II trial and our results thus need confirmation, capecitabine-cisplatin failed to demonstrate superior efficacy over S-1-cisplatin. The higher incidence of severe nonhematologic adverse events observed with capecitabine-cisplatin suggests that S-1-cisplatin should remain the standard first-line chemotherapy for HER2-negative AGC with measurable lesions, at least in Japan.

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DISCLOSURES
Hisato Kawakami: Chugai Pharmaceutical, Eli Lilly & Co., Taiho Pharmaceutical, Takeda Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Bayer (H); Takao Tamura: Chugai Pharmaceutical, Taiho Pharmaceutical, Roche (RF, H); Daisuke Sakai: Chugai Pharmaceutical (RF, H); Yukinori Kurokawa: Taiho Pharmaceutical (H); Taroh Satoh: Takara Bio, Inc (SAB), Yakult Honsha, Chugai Pharmaceutical, Eli Lilly & Co., Merck-Serono, Takeda Pharmaceutical, Taiho Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Bayer (H); Yakult Honsha, Ono Pharmaceutical, Eli Lilly & Co., Chugai Pharmaceutical, Merck Sharp & Dohme, Daiichi-Sankyo, Giliad Science, Bristol-Myers Squibb, Sanofi-Aventis (RF). The other authors indicated no financial relationships.

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

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