Phase II Study of Ramucirumab Plus Irinotecan Combination Therapy as Second-Line Treatment in Patients with Advanced Gastric Cancer: HGCSG1603

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Abstract

Background: Ramucirumab is a human IgG1 monoclonal vascular endothelial growth factor receptor-2 antibody that inhibits tumor cell growth and affects the tumor cell microenvironment. We assessed the efficacy and safety of ramucirumab plus irinotecan combination therapy as second-line treatment in patients with previously treated advanced gastric cancer.

Materials and Methods: Patients with advanced gastric cancer refractory or intolerant to primary chemotherapy were included. Ramucirumab 8 mg/kg plus irinotecan 150 mg/m² combination therapy was administered every 2 weeks. The primary endpoint was progression-free survival rate at 6 months and secondary endpoints were overall survival, progression-free survival, response rate, safety, and dose intensity for each drug.

Results: Thirty-five patients were enrolled between January 2018 and September 2019. The progression-free survival rate at 6 months was 26.5% [95%CI, 13.2%–41.8%, P = .1353]. Median progression-free and overall survivals were 4.2 months (95%CI, 2.5-5.4 months) and 9.6 months (95%CI, 6.4-16.6 months), respectively. The overall response rate was 25.9% (95%CI, 11.1-36.3%) and disease control rate was 85.2% (95%CI, 66.3-95.8%). Grade ≥3 adverse events that occurred in >10% of patients included neutropenia, leucopenia, anemia, anorexia, and febrile neutropenia. No death or new safety signals with a causal relation to the study treatment were observed.

Conclusion: Although the primary endpoint was not achieved statistically, combination therapy of ramucirumab plus irinotecan showed anticancer activity and a manageable safety profile for second-line treatment of patients with advanced gastric cancer.

Keywords: gastric cancer; ramucirumab; irinotecan; second-line treatment

Implications for Practice

There have been no studies into the efficacy of ramucirumab plus irinotecan combination therapy for advanced gastric cancer. This single arm, phase II multicenter trial evaluated the efficacy and safety of ramucirumab plus irinotecan combination therapy as second-line treatment in patients with previously treated advanced gastric cancer. Although the primary endpoint was not achieved statistically, this regimen showed anticancer activity and a manageable safety profile. Ramucirumab plus irinotecan might be considered as an option for second-line treatment of patients with advanced gastric cancer for whom taxane is difficult to use.
**Introduction**

Gastric cancer was the fifth leading cause of cancer death worldwide in 2020. Approximately 60% of all patients diagnosed with gastric cancer are in East Asian countries, including Japan, Korea, and China. Systemic chemotherapy is the standard treatment for advanced or recurrent cases and was shown to prolong survival and provide clinically significant benefits in several randomized controlled trials that compared best supportive care with chemotherapy in patients with advanced gastric cancer. Several clinical trials examining the use of primary chemotherapy for unresectable advanced or recurrent gastric and esophagogastric junction cancer have reported standard chemotherapy of platinum-based and fluoropyrimidine-based combinations for human epidermal growth factor receptor 2 (HER2)-negative gastric cancer and platinum-based and fluoropyrimidine-based in combination with trastuzumab for HER2-positive gastric cancer. Recently, the efficacy of nivolumab, immune checkpoint inhibitor, plus chemotherapy (oxaliplatin plus fluoropyrimidine) for HER2-negative gastric or gastro-esophageal cancer was reported in CheckMate-649 and ATTRACTION-4. Chemotherapy can be used as second-line treatment for gastric cancer, and several clinical trials have shown survival benefits with its administration. Later lines of treatment have shown the efficacy of immune checkpoint inhibitors and trifluridine–tipiracil. In HER2-positive gastric cancer, the efficacy of trastuzumab deruxtecan has been reported in third-line DESTINY-Gastric01 and second-line DESTINY-Gastric02. However, treatment outcomes remain unsatisfactory and more effective treatment regimens are required.

Ramucirumab is a fully human IgG1 monoclonal vascular endothelial growth factor receptor-2 (VEGFR-2) antibody that prevents ligand binding of VEGF-A, VEGF-C, and VEGF-D as well as receptor-mediated pathway activation in endothelial cells, which subsequently inhibits neovascularization. Ramucirumab is an angiogenesis inhibitor that acts by inhibiting neogenesis and promoting the regression of tumor vessels, resulting in the normalization of residual blood vessels, which can then promote the delivery of anticancer drugs to the tumor. Therefore, ramucirumab inhibits tumor cell growth and affects the tumor cell microenvironment. The median overall survival in the ramucirumab monotherapy for previously treated advanced gastric or gastroesophageal junction adenocarcinoma (REGARD) study was 5.2 and 3.8 months in the ramucirumab and placebo groups, respectively [hazard ratio (HR), 0.776; 95% confidence interval (CI), 0.603-0.998; P = .0473]. Overall survival was longer in the ramucirumab plus paclitaxel group compared with placebo plus paclitaxel group in patients with previously treated advanced gastric or gastroesophageal junction adenocarcinoma (RAINBOW) trial in patients with disease progression at or within 4 months after first-line chemotherapy (platinum plus fluoropyrimidine) [median, 9.6 months; 95% CI, 8.5-10.8 versus 7.4 months; 95% CI, 6.3-8.4; HR, 0.807; 95% CI, 0.678-0.962; P = .017]. In addition, there is a report that ramucirumab plus paclitaxel has better response after immune checkpoint inhibitor therapy in advanced gastric cancer.

In contrast, there have been no studies into the efficacy of ramucirumab plus irinotecan combination therapy as second-line treatment for gastric cancer. The WJOG 4007 study demonstrated that the efficacy of irinotecan was equivalent to that of paclitaxel. Combination therapy of ramucirumab plus irinotecan has shown a favorable outcome in patients with colorectal cancer.

These results indicate that ramucirumab plus irinotecan combination therapy should show an improved efficacy. In addition, it is also considered that the patient who could not receive paclitaxel in the second-line treatment would increase by introduction of taxane to perioperative chemotherapy or first-line treatment and residual peripheral neuropathy by oxaliplatin of the first-line treatment. Therefore, the present trial, HGCGSG1603, examined the efficacy and safety of ramucirumab plus irinotecan combination therapy as second-line treatment in patients with previously treated advanced gastric cancer.

**Materials and Methods**

**Study Design and Participants**

This non-randomized, single arm, prospective, multicenter, phase 2 trial was conducted at 22 centers in Japan. The study included adults aged ≥20 years with confirmed unresectable advanced or recurrent gastric adenocarcinoma that was refractory or intolerant to initial chemotherapy. Further inclusion criteria were: Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; no history of irinotecan treatment; laboratory findings of adequate bone marrow, hepatic, and renal function 14 days prior to enrollment; and confirmation of progression or recurrence following initial treatment and the potential presence of an evaluable lesion <28 days prior to registration according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The presence or absence of a measurable lesion was not an inclusion criterion. Patients negative for HER-2/neu and those with unknown HER-2/neu status were eligible. HER-2/neu-positive patients were eligible if they had received treatment, including trastuzumab, and if disease progression was confirmed. Patients were excluded if they had undergone major surgery within 28 days prior to registration. Further exclusion criteria were: history of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism during the 3 months prior to the first dose of trial therapy; administration of anticoagulant therapy such as warfarin and low-molecular weight heparin; any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack within the previous 6 months; any grade 3-4 gastrointestinal bleeding within the previous 3 months; and pericardial or pleural effusion, or ascites requiring treatment. The Supplementary appendix provides the full inclusion and exclusion criteria.

The trial was conducted in accordance with the Declaration of Helsinki (October 2013 revision) and Ethics Guidelines 2014 of the Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labor, and Welfare notification tertiary for biomedical research on humans and was approved by the Institutional Review Boards of each participating institute. The trial received approval from the Hokkaido University Hospital Research Ethics Committee. All patients provided written informed consent prior to enrolling into the study. This trial was registered with the public database of the University Hospital Medical Information Network Clinical Trials Registry (UMIN000030372) and Japan Registry of Clinical Trials (jRCTs011180029).
Procedures

Patients received ramucirumab 8 mg/kg and irinotecan 150 mg/m² intravenously on day one of a 14-day cycle. Patients with UGT1A1 genetic polymorphisms who were homozygous or double heterozygous for UGT1A1*6 or UGT1A1*28 received 120 mg/m² irinotecan. Doses could be modified to manage treatment-related toxic effects. Criteria for dose reduction, dose delay or skip are presented in the Supplementary appendix.

The overall response rate was calculated based on the RECIST version 1.1 criteria. The progression-free survival and overall survival were determined using the Kaplan-Meier method. Safety was evaluated in the safety analysis group using the Common Terminology Criteria for Advanced Events version 4.0.

Outcomes and Statistical Analysis

The primary endpoint was the progression-free survival rate at 6 months. The secondary endpoints were overall survival, progression-free survival, overall response rate, safety, and dose intensity for each drug.

The median progression-free survival with irinotecan monotherapy as second-line treatment for gastric cancer was 2.3-4.2 months. Furthermore, the median progression-free survival with ramucirumab in combination with paclitaxel in the RAINBOW study was 4.4 months. Based on these results, the target progression-free survival at 6 months was set with a threshold of 16% (median progression-free survival, 2.3 months) and an expected value of 39% (median progression-free survival, 4.4 months). A 2-sided significance level was set to 5%, a registration period was 24 months, and a follow-up period was 12 months. The minimum sample size required to achieve a detection power of 80% was found to be 31. A total of 35 patients were planned for registration to allow for potential dropout (eg, due to ineligibility).

The progression-free survival and overall survival were estimated using Kaplan-Meier method and their 95% CIs were calculated with a complementary log-log transformation. Univariate and multivariate analyses using Cox proportional hazards models were performed to evaluate the association between clinical features (ie, age, sex, ECOG performance status, HER2, liver metastasis, peritoneum metastasis, and measurable lesion) and progression-free survival or overall survival. All statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM, Armonk, NY).

Results

Thirty-five patients were enrolled between January 2018 and September 2019. All patients received at least one cycle study treatment and were included in the full analysis set and safety population.

Table 1. Baseline characteristics.

| Characteristic                        | N = 35 (%) |
|---------------------------------------|------------|
| Age, years                            | N = 35 (%) |
| Median (range)                        | 70 (47-80) |
| <70                                   | 16 (46%)   |
| ≥70                                   | 19 (54%)   |
| Sex                                   | N = 35 (%) |
| Female                                | 10 (29%)   |
| Male                                  | 25 (71%)   |
| ECOG performance status               | N = 35 (%) |
| 0                                     | 22 (63%)   |
| 1                                     | 13 (37%)   |
| Primary tumor site                    | N = 35 (%) |
| Gastroesophageal junction              | 4 (11%)    |
| Stomach                               | 31 (89%)   |
| Histological subtype                  | N = 35 (%) |
| Intestinal                            | 17 (49%)   |
| Diffuse                               | 13 (37%)   |
| Mixed                                 | 5 (14%)    |
| HER2 status                           | N = 35 (%) |
| Negative                              | 24 (69%)   |
| Positive                              | 9 (26%)    |
| Not tested                            | 2 (6%)     |
| UGT1A1 status (*6/*28)                | N = 35 (%) |
| Wild type                             | 14 (40%)   |
| Single heterozygous                   | 13 (37%)   |
| Double variant                        | 1 (3%)     |
| Not tested                            | 7 (20%)    |
| Metastatic site                       | N = 35 (%) |
| Lymph node                            | 23 (66%)   |
| Peritoneum                            | 18 (51%)   |
| Liver                                 | 12 (34%)   |
| Lung                                  | 2 (6%)     |
| Measurable lesion                     | N = 35 (%) |
| Present                               | 27 (77%)   |
| Absent                                | 8 (23%)    |
| First-line treatment                  | N = 35 (%) |
| S-1 + oxaliplatin                     | 17 (49%)   |
| Capecitabine + oxaliplatin            | 7 (20%)    |
| FOLFOX                                | 6 (17%)    |
| Nab-paclitaxel + S-1 + oxaliplatin    | 1 (3%)     |
| Docetaxel + S-1 + CDDP               | 1 (3%)     |
| S-1 + CDDP                            | 1 (3%)     |
| Capecitabine + CDDP                   | 1 (3%)     |
| S-1 + docetaxel                       | 1 (3%)     |
| Prior trastuzumab                     | N = 35 (%) |
| Yes                                   | 9 (26%)    |
| No                                    | 26 (74%)   |
| Prior ramucirumab                     | N = 35 (%) |
| Yes                                   | 0 (0%)     |
| No                                    | 35 (100%)  |
| Previous gastrectomy                  | N = 35 (%) |
| Yes                                   | 8 (23%)    |
| No                                    | 27 (77%)   |

Data are presented as N (%) or median (range).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; S-1, tegafur, oteracil, and gimeracil; CDDP, cisplatin; FOLFOX, leucovorin, fluorouracil, and oxaliplatin.

![Figure 1. Flow chart of HGCSG1603. Thirty-five patients were enrolled during the planned registration period. All patients received at least one cycle study treatment and were included in the full analysis set and safety population.](image-url)
treatment and were included in the full analysis set and safety population (Fig. 1). The baseline characteristics of the patients are listed in Table 1. No patients received ramucirumab treatment prior to the study. Thirty-one patients received oxaliplatin in their first-line treatment regimen. Thirteen patients had single-heterozygous UGT1A1 and one had a double variant in UGT1A1 status. The 35 patients received a median of 5 cycles (range, 1-24+). The median relative dose intensity of ramucirumab and irinotecan was 96.6% and 88.3%, respectively.

Twenty-six patients discontinued study treatment due to disease progression and 4 discontinued due to adverse events.

![Figure 2](image.png)

**Figure 2.** Progression-free survival (A) and overall survival (B) of HGCSG1603. Progression-free survival rate at 6 months was 26.5% (95%CI, 13.2%-41.8%, \( P = .1353 \)). Median progression-free survival and overall survival were 4.2 months (95%CI, 2.5-5.4 months) and 9.6 months (95%CI, 6.4-16.6 months).

| Table 2. Univariate and multivariate analyses of progression-free survival. |
|-----------------------------|-----------------------------|-----------------------------|
| Age, years                  | N              | Univariate          | \( P \)       | Multivariate | \( P \)       |
| <70                         | 16             | 1 (ref)             | .187          | 1 (ref)      | .128          |
| ≥70                         | 19             | 0.617 [0.302-1.263] | .052          | 0.522 [0.226-1.205] | .128 |
| Sex                         |                |                    |               |              |               |
| Female                      | 10             | 1 (ref)             | .123          | 1 (ref)      | .153          |
| Male                        | 25             | 1.901 [0.841-4.296] | .053          | 1.830 [0.798-4.196] | .068 |
| ECOG performance status     |                |                    |               |              |               |
| 0                           | 22             | 1 (ref)             | 1 (ref)       |              |               |
| 1                           | 13             | 2.113 [0.990-4.507] | .053          | 2.238 [0.941-5.322] | .068 |
| HER2                        |                |                    |               |              |               |
| Negative + not tested       | 26             | 1 (ref)             | 1 (ref)       |              |               |
| Positive                    | 9              | 2.139 [0.955-4.787] | .065          | 1.981 [0.829-4.736] | .124 |
| Liver metastasis            |                |                    |               |              |               |
| Absent                      | 23             | 1 (ref)             | 1 (ref)       |              |               |
| Present                     | 12             | 1.431 [0.676-3.027] | .349          | 1.209 [0.461-3.170] | .699 |
| Peritoneum metastasis       |                |                    |               |              |               |
| Absent                      | 17             | 1 (ref)             |              |              |               |
| Present                     | 18             | 1.181 [0.590-2.365] | .639          |              |               |
| Measurable lesion           |                |                    |               |              |               |
| Absent                      | 8              | 1 (ref)             |              |              |               |
| Present                     | 27             | 0.968 [0.414-2.265] | .940          |              |               |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.
One patient received curative resection and one continued the study treatment at the data cutoff for analysis. The other 3 patients discontinued study treatment at the discretion of the attending physician.

Progression-free survival rate at 6 months was 26.5% (95%CI, 13.2%–41.8%, \( P = .1353 \)). Median progression-free survival and overall survival were 4.2 months (95%CI, 2.5–5.4 months) and 9.6 months (95%CI, 6.4–16.6 months), respectively (Fig. 2). Univariate and multivariate analyses of progression-free survival and overall survival according to Cox proportional hazards models are presented in Tables 2 and 3. Analysis of patients aged <70 years and ≥70 years revealed progression-free survival of 2.8 and 4.2 months, and overall survival of 5.1 and 15.6 months, respectively. The efficacy of this therapy was even shown in the elderly. The overall response rate was 25.9% (95%CI, 11.1%–36.3%) and the

### Table 3. Univariate and multivariate analyses of overall survival.

|                          | Univariate | P     | Multivariate | P     |
|--------------------------|------------|-------|--------------|-------|
| **Age, years**           |            |       |              |       |
| <70                      | 16         | 1 (ref) |              | 1 (ref) |
| ≥70                      | 19         | 0.430 [0.186–0.996] | 0.049 | 0.253 [0.091–0.702] | 0.008 |
| **Sex**                  |            |       |              |       |
| Female                   | 10         | 1 (ref) |              | 1 (ref) |
| Male                     | 25         | 1.401 [0.555–3.537] | 0.476 | 1.289 [0.494–3.360] | 0.604 |
| **ECOG performance status** |       |       |              |       |
| 0                        | 22         | 1 (ref) |              | 1 (ref) |
| 1                        | 13         | 1.701 [0.756–3.829] | 0.199 | 2.122 [0.886–5.084] | 0.091 |
| **HER2**                 |            |       |              |       |
| Negative + not tested    | 26         | 1 (ref) |              | 1 (ref) |
| Positive                 | 9          | 1.891 [0.749–4.773] | 0.178 | 1.320 [0.484–3.597] | 0.587 |
| **Liver metastasis**     |            |       |              |       |
| absent                   | 23         | 1 (ref) |              | 1 (ref) |
| present                  | 12         | 1.860 [0.800–4.323] | 0.150 | 2.610 [0.938–7.258] | 0.066 |
| **Peritoneum metastasis** |        |       |              |       |
| absent                   | 17         | 1 (ref) |              | 1 (ref) |
| present                  | 18         | 1.031 [0.459–2.314] | 0.941 |
| **Measurable lesion**    |            |       |              |       |
| absent                   | 8          | 1 (Ref) |              | 1 (Ref) |
| present                  | 27         | 1.121 [0.416–3.021] | 0.821 |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.

![Figure 3. Waterfall plot of maximum percentage in tumor size from baseline. Change in tumor size was assessed by Response Evaluation Criteria in Solid Tumors version 1.1. The overall response rate was 25.9% (95%CI, 11.1%-36.3%) and the disease control rate was 85.2% (95%CI, 66.3%-95.8%) in 27 patients with at least one measurable lesion.](image-url)
The response rate was 25.9%, which was also comparable since more elderly patients were enrolled in the present trial. The success of neoadjuvant and adjuvant chemotherapy as second-line therapy has been previously reported in advanced gastric cancer.33-35 The phase III trial comparing ramucirumab plus irinotecan with ramucirumab plus paclitaxel, the standard second-line therapy, might be considered as an option for second-line treatment of gastric cancer and the populations that are likely to benefit from using this combination therapy of ramucirumab plus irinotecan showed an acceptable safety profile and no new or unexpected toxicities were observed in this trial. The most common grade ≥3 adverse events included neutropenia, leucopenia, anemia, and thrombocytopenia. Myelosuppression was slightly more frequent than in RAINBOW trial. The large number of elderly patients in this trial may be influential. However, all of them were manageable with appropriate supportive care.

The present trial has some limitations. First, this was a single arm phase II trial with a small sample size. A phase III trial comparing ramucirumab plus irinotecan with ramucirumab plus paclitaxel, the standard second-line therapy, may be considered. Second, immune checkpoint inhibitors are transitioning to first-line treatment of gastric cancer and the consequences in patients receiving immune checkpoint inhibitors as first-line therapy remain unknown. No patients used immune checkpoint inhibitors as first-line treatment in this trial. Third, no biomarker studies were conducted in this trial and the populations that are likely to benefit from using this regimen were not identified.

**Conclusion**

Although the primary endpoint was not achieved statistically, combination therapy of ramucirumab plus irinotecan showed anticancer activity and a manageable safety profile. Although larger further explore studies are warranted, this therapy might be considered as an option for second-line treatment of patients with advanced gastric cancer for whom taxane administration is inappropriate due to prior treatment or residual peripheral neuropathy.

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**Table 4.** Adverse events occurring in ≥10% of the patients, irrespective of causality.

| All grade | ≥Grade 3 |
|-----------|----------|
| n | % | n | % |
| **Non-hematological adverse events** |
| Hypertension | 32 | 91 | 3 | 9 |
| Fatigue | 24 | 69 | 1 | 3 |
| Anorexia | 22 | 63 | 5 | 14 |
| Proteinuria | 18 | 51 | 3 | 9 |
| Diarrhea | 17 | 49 | 3 | 9 |
| Alopecia | 15 | 43 | — | — |
| Nausea | 12 | 34 | 0 | 0 |
| Vomiting | 9 | 26 | 0 | 0 |
| Epistaxis | 4 | 11 | 0 | 0 |
| **Hematological adverse events** |
| Neutrophil count decreased | 29 | 83 | 18 | 51 |
| Anemia | 29 | 83 | 7 | 20 |
| White blood cell count decreased | 27 | 77 | 15 | 43 |
| Platelet count decreased | 22 | 63 | 2 | 6 |
| Febrile neutropenia | 4 | 11 | 4 | 11 |

The phase II RAMIRIS study showed that second-line paclitaxel plus ramucirumab was less effective in patients pretreated with docetaxel.34 In addition, the use of oxaliplatin has become the mainstay of first-line treatment for gastric cancer. Oxaliplatin is increasingly used in the control arms of recent first-line clinical trials, and has been administered in most of the first-line therapies even in general practice. In the present trial, 89% of patients also received oxaliplatin in their pretreatment. It is anticipated that patients who are taxane refractory to prior therapy or transition to second-line therapy in an inappropriate condition due to residual peripheral neuropathy by oxaliplatin would remain constant and may be an important second-line treatment option for these patients.

It is unclear why better results have been obtained in people aged 70 years or older in univariate and multivariate analyses. This trial had a small sample size and may include some potential bias. Rather than better results at age 70 years or older, it is also considered that patients younger than 70 years may have had a poor prognosis that was refractory to treatment.

Although 26% of HER2-positive patients were included in this trial, according to the findings of DESTINY-Gastric 02 study, HER2-positive patients may become the mainstay of treatment with trastuzumab-deruxtecan in the second-line setting in the future.20 Combined treatment using ramucirumab plus irinotecan showed an acceptable safety profile and no new or unexpected toxicities were observed in this trial. The most common grade ≥3 adverse events included neutropenia, leucopenia, anemia, febrile neutropenia, hypertension, proteinuria, and thrombocytopenia. No death or new safety signals with a causal relation to the study treatment were observed.

**Discussion**

This single arm, phase II multicenter trial evaluated the efficacy and safety of ramucirumab plus irinotecan combination therapy as second-line treatment in patients with advanced gastric cancer. The progression-free survival rate at 6 months was 26.5% and the trial did not meet its primary endpoint. However, the secondary endpoints of median overall survival and progression-free survival were comparable to those reported in the RAINBOW trial,16 and the antitumor activity was effective. These results are clinically encouraging, particularly since more elderly patients were enrolled in the present trial. The response rate was 25.9%, which was also comparable to that reported in the RAINBOW trial.16 Despite a median progression-free survival comparable to that of RAINBOW trial, the reasons why the progression-free survival rate at 6 months for the primary endpoint was not statistically hypothesized were high expectation setting and smaller sample size. Expected value was estimated from Kaplan-Meyer curve of causality.
ject to the conflict of interest policies of their institutions. The authors would like to thank Enago (www.enago.jp) for the English language review.

Conflict of Interest

Yasuyuki Kawamoto: Eli Lilly Japan, Merck Biopharma, Daiichi Sankyo, Taiho Pharma, Takeda Pharma and Yakult Honsha (H), Takeda Pharma (RF); Satoshi Yukita: Eli Lilly Japan, and Yakult Honsha (H); Kentaro Sawada: Chugai Pharma, Ono Pharma, Taiho Pharma, Merck Biopharma, and Takeda Pharma (H); Michio Nakamura: Eli Lilly Japan, Takeda Pharma, Sanofi, Daiichi Sankyo, Taiho Pharma, Chugai Pharma, Bayer Holding, and Bristol-Myers Squibb (H); Yasushi Tsujii: Eli Lilly Japan (H); Yuh Sakata: Eli Lilly Japan, Yakult Honsha, Taiho Pharma, and Bristol-Myers Squibb (H), Delta-Fly Pharma (OI—family); Yoshito Komatsu: Chugai, Eli Lilly Japan, Taiho Pharma, Takeda Pharma, Daiichi-Sankyo, and Ono Pharma (H), Taiho Pharma, and Chugai Pharma (RF). The other authors indicated no financial relationships.

Author Contributions

Conception/Design: Y.K., S.Y., Y.S., N.S., and Y.K. Provision of study material/patients: Y.K., S.Y., K.S., M.N., Y.T., Y.S., and Y.K. Collection and/or assembly of data: Y.K., S.Y., M.S., Y.S., N.S., and Y.K. Data analysis and interpretation: Y.K., S.Y., K.O., Y.M.I., Y.S., N.S., and Y.K. Manuscript writing: Y.K., S.Y., Y.S., N.S., and Y.K. Final approval of manuscript: All authors.

Data Availability

The data underlying this article cannot be shared publicly because informed consent has not been obtained from the study subjects for secondary use of the data in the study. The data will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at The Oncologist online.

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