The Oncologist, 2022, **27**, 251–e304
https://doi.org/10.1093/oncolo/oyab061
Clinical Trial Results

Three-Year Outcomes of a Phase II Study of Perioperative Capecitabine Plus Oxaliplatin Therapy for Clinical SS/SE N1-3 M0 Gastric Cancer (OGSG 1601)

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Abstract

Background: We previously reported the good feasibility and favorable efficacy of perioperative capecitabine plus oxaliplatin (CapeOx) in patients (pts) with clinical T3(SS)/T4a(SE) N1-3 M0 gastric cancer (GC) in a phase II study in which the pathological response rate, the primary endpoint, of 54.1% was demonstrated. Here, we report 3-year follow-up data.

Methods: The eligibility criteria included clinical T3(SS)/T4a(SE) N1-3 M0 GC according to the Japanese Classification of Gastric Carcinoma-3rd English Edition (JCGC). Three cycles of neoadjuvant CapeOx (capecitabine, 2000 mg/m^2 for 14 days; oxaliplatin, 130 mg/m^2 on day 1, every 3 weeks) were administered, followed by 5 cycles of adjuvant CapeOx after D2 gastrectomy. Three-year overall survival and relapse-free survival are presented here, and analyzed by cohorts based on pathologic response rate (pRR).

Results: Thirty-seven pts were enrolled from July 2016 to May 2017, and fully evaluated for efficacy and toxicity. Thirty-three pts (89.2%) completed the planned three cycles of neoadjuvant CapeOx and underwent gastrectomy, with an R0 resection rate of 78.4% (n = 29). The overall survival (OS) rate and relapse-free survival (RFS) rate at 3 years was 83.8% (95% CI, 72.7-96.5%) and 73.0% (95% CI, 60.0-88.8%), respectively. Further, the 3-year OS rate in pts with pathological response of grade 1a (n = 13) and grade 1b or higher (n = 20) was 69.2% (95% CI: 48.2-99.5%) and 100.0%, respectively, based on JCGC. Pathological response rate was classified according to JCGC as follows: grade 0, the tumor was not affected; grade 1a, less than one-third of the tumor was affected; grade 1b, one to two thirds of the tumor was affected; grade 2, greater than or equal to two thirds was affected; and grade 3, no residual tumor. A pathological response was defined as grade 1b or greater.

Conclusion: Perioperative CapeOx showed good feasibility and favorable prognosis, especially in pts with pathological response of grade 1b or higher and was found to be useful in predicting prognosis. The data obtained using this novel approach warrant further investigation (Trial ID: UMIN000021641, jRCTs051180109).

Key words: gastric cancer; capecitabine; oxaliplatin; perioperative chemotherapy.

Lessons Learned

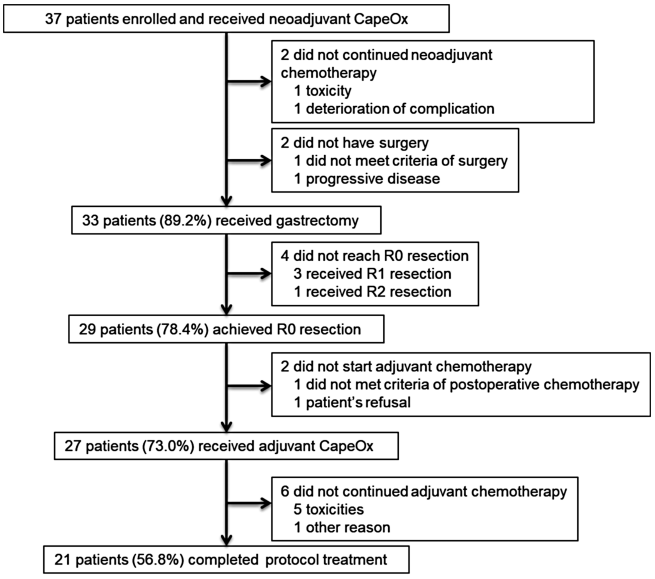
- Perioperative capecitabine plus oxaliplatin (CapeOx) therapy showed good feasibility and favorable prognosis, especially in patients with pathological response of grade 1b or higher, was found to be useful in predicting prognosis.
- Further studies with larger sample sizes are required to validate this novel approach.

Received: 23 June 2021; Accepted: 17 September 2021.

Discussion

Our phase II study is the first to demonstrate the efficacy and safety of perioperative capecitabine plus oxaliplatin (CapeOx) in clinical T3(SS)/T4a(SE) N1-3 M0 GC. The sample size of this study was 34 pts, which was calculated on the hypothesis that the expected pRR was 65% and the threshold was 40%, with a one-sided α of 0.05 and a β of 0.1, according to exact *P*-value methods. The total sample size was set at 37 patients to account for deviation (Figure 1). Perioperative CapeOx showed acceptable feasibility and favorable survival benefits as demonstrated by 3-year overall survival (OS) rate of 83.8%, although pRR value of 54.1% (*P* = .058; 90% CI: 39.4-68.2) did not reach the commonly accepted cutoff of 0.05. Phase II study of neoadjuvant S-1 plus oxaliplatin (SOX) therapy for gastric cancer (GC), previously conducted in Japan, showed a high histological response rate of 85.7%, but the efficacy of neoadjuvant SOX therapy was not sufficiently verified due to the small sample size of 14 patients [Surg Today 2016;46:1076-1082].

Regarding survival outcome in the present study, the 3-year OS and RFS showed favorable results of 83.8% and 73.0%, respectively. In particular, 3-year OS rate in patients with pathological response of grade 1a (*n* = 13) and grade 1b or higher (*n* = 20) were 69.2% (95% CI: 48.2-99.5%) and 100.0%, respectively. In addition, 3-year RFS rate in the same cohorts were 46.2% (95% CI: 25.7-83.0%) and 95.0% (95% CI: 85.9-100.0%), respectively. Comparing the prognosis in patients with pathological response of grade 1b or higher with other perioperative studies, perioperative CapeOx treatment showed favorable efficacy. This is the rare study of perioperative chemotherapy for resectable GC with pathological response rate as the endpoint. We have thus clarified that the good pathological response of neoadjuvant CapeOx contributed to a better prognosis. In conclusion, perioperative CapeOx showed good feasibility and favorable prognosis, especially in patients with pathological response of grade 1b or higher, and was found to be useful in predicting prognosis. Nevertheless, further studies with larger sample size are required to validate this novel approach.



CapeOx; capecitabine plus oxaliplatin

Figure 1. Treatment delivery.

Author disclosures and references available online.

Trial Information	
Disease	Gastric cancer, advanced cancer
Stage of disease/treatment	Neo-adjuvant
Prior therapy	None
Type of study	Phase II, single arm
Primary endpoint	Pathological response rate
Secondary endpoints	3-year recurrence-free survival rate, percentage completion of the protocol treatment, relative dose intensity (RDI) of neoadjuvant chemotherapy, RDI of adjuvant chemotherapy, 3-year overall survival rate, percentage completion of adjuvant chemotherapy, and overall response rate, safety, surgical complications
Investigator's Analysis	Correlative endpoints not met but clinical activity observed

Additional Details of Endpoints or Study Design

Primary endpoint was a pathological response rate (pRR) classified according to the third English Edition JCGC[1] as follows: grade 0, the tumor was not affected; grade 1a, less than one-third of the tumor was affected; grade 1b, one to two thirds of the tumor was affected; grade 2, greater than or equal to two thirds was affected; and grade 3, no residual tumor. A pathological response was defined as grade 1b or greater. While the pathologist at each institute confirming a pathologic diagnosis by resected specimen, the pathological response for the tumor was evaluated by largest section of cancer tissue, submitted from each institute, in which the cancer lesion was considered to be present and in which the cancer lesion was likely to remain, via independent central review by 2 pathologists according to the JCGC and Becker regression criteria.[2]

Becker regression criteria included the following categories: grade 1a, complete regression; grade 1b, subtotal regression(<10% residual tumor); grade 2, partial regression(10-50% residual tumor); grade 3, minor or no regression(>50% residual tumor). A pathological response was defined as grade 2 or lesser. It should be noted that this scale lies in an opposite direction from the JCGC criteria.

Secondary endpoints included the percent completion of the protocol treatment, relative dose intensity (RDI) of neoadjuvant chemotherapy, RDI of adjuvant chemotherapy, 3-year overall survival (OS) rate, 3-year relapse free survival (RFS) rate, 3-year progression-free survival (PFS) rate, percent completion of adjuvant chemotherapy, overall response rate (RR),[3] and safety. The OS was defined as the number of days from enrollment to death due to any cause and was censored at the last day of the patient's life. Relapse-free survival and PFS were defined as the number of days from enrollment to the date of recurrence and progression, respectively, of the original GC or death. Response rate was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0), and surgical complications were evaluated using the Clavien–Dindo criteria. The planned dose was defined as the total dose if three cycles of CapeOx as neoadjuvant chemotherapy and 5 cycles as adjuvant chemotherapy had been completed without dose reduction. We also assessed the RDI, which was defined as the ratio of delivered dose intensity to the planned dose intensity. Dose intensity was calculated as the ratio of the cumulative dose to the treatment duration per 21 days.

OGSG 1601 (OGSG: Osaka Gastrointestinal Cancer Chemotherapy Study Group) was a multicenter phase II study to examine efficacy and safety of perioperative CapeOx therapy in patients with GC. The sample size of this study was 34 patients, which was calculated on the hypothesis that the expected pRR was 65% and the threshold was 40%, with a one-sided α of 0.05 and a β of 0.1, according to exact *P*-value methods. The total sample size was set at 37 patients to account for deviation. Efficacy and safety analysis sets consisted of the patients who were enrolled in this study and received at least 1 cycle of CapeOx therapy. The RR was analyzed based on the efficacy analysis set with measurable lesions. OS, RFS, and PFS were analyzed based on the efficacy analysis set and estimated using Kaplan-Meier method, and 95% CI of OS, RFS, and PFS rate at 3-year were also estimated. Based on the safety analysis set, the incidence of adverse events and that of 95% CI were calculated using a binomial distribution.

All statistical analyses were conducted at the OGSG Statistical Analysis Department. Statistical analyses were conducted with R, version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Drug Information	
Capecitabine	
Generic/working name	Capecitabine
Drug type	Small molecule
Drug class	Antimetabolite
Dose	2000 mg/m^2 per
Route	Oral (p.o.)
Schedule of administration	Days 1-14, every 3 weeks. Three cycles of neoadjuvant chemotherapy and 5 cycles of adjuvant chemotherapy were administered

Oxaliplatin	
Generic/working name	Oxaliplatin
Company name	Yakult Honsha Co., Ltd.
Drug type	Small molecule
Drug class	Platinum compound
Dose	130 mg/m^2 per
Route	i.v.
Schedule of administration	Day 1, every 3 weeks. Three cycles of neoadjuvant chemotherapy and 5 cycles of adjuvant chemotherapy were administered.

Patient Characteristics

Number of patients, male	28	
Number of patients, female	9	
Stage	cT factor (third English edition JCGC)	*n* (%)
	3 (SS)	14 (37.8)
	4a (SE)	23 (62.2)
	cN factor	
	1	20 (54.1)
	2	15 (40.5)
	3	2 (5.4)
	Clinical stage	
	IIB	9 (24.3)
	IIIA	13 (35.1)
	IIIB	13 (35.1)
	IIIC	2 (5.4)
Age	Median (range): 65 (38-81) years	
Number of prior systemic therapies	Median (range): none	
Performance Status: ECOG	0—29 1—8 2—0 3—0 Unknown—0	
Other	Baseline characteristics of patients	*n* (%)
	Tumor location	
	Upper third	11 (29.7)
	Middle third	12 (32.4)
	Lower third	14 (37.8)
	Macroscopic type (third English edition JCGC)	
	1	1 (2.7)
	2	6 (16.2)
	3	29 (78.4)
	4	0 (0)
	5	1 (2.7)

Primary Assessment Method

Title	**Pathological response**
Number of patients screened	37
Number of patients enrolled	37
Number of patients evaluable for toxicity	37
Number of patients evaluated for efficacy	37
Evaluation method	JCGC, Becker regression criteria

Outcome Notes

Pathological response	*n* (%)
JCGC	
Grade 0	0 (0)
Grade 1a	13 (35.1)
Grade 1b	8 (21.6)
Grade 2	11 (29.7)
Grade 3	1 (2.7)
No. of surgery	4 (10.8)
pRR 20	(54.1) (90% CI: 39.4-68.2)
Becker regression criteria	
Grade 1a	1 (2.7)
Grade 1b	2 (54.1)
Grade 2	16 (43.2)
Grade 3	14 (37.8)
No. of surgery	4 (10.8)
pRR 19	(51.4) (95% CI: 34.4-68.1)

Pathological response rate was classified according to the third English edition JCGC as follows: grade 0, the tumor was not affected; grade 1a, less than one third of the tumor was affected; grade 1b, one to two thirds of the tumor was affected; grade 2, greater than or equal to two thirds was affected; and grade 3, no residual tumor. A pathological response was defined as grade 1b or greater. Becker regression criteria included the following categories: grade 1a, complete regression; grade 1b, subtotal regression; <10% residual tumor; grade 2, partial regression; 10-50% residual tumor; grade 3, minor or no regression; >50% residual tumor. A pathological response was defined as grade 2 or greater. Abbreviations: JCGC; Japanese Classification of Gastric Carcinoma, pRR; pathological response rate.

Adverse Events

See Tables 1 and 2.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Correlative endpoints not met but clinicalactivity observed

Gastric cancer (GC) is the second leading cause of cancer deaths worldwide.[4] Although the mainstay of treatment for GC is surgical resection, many patients suffer from recurrent disease.[5-7] Since the prognoses of patients with recurrent GC are still poor, more effective chemotherapy should be developed. At present, perioperative and postoperative chemotherapy improve overall survival in patients with resectable GC.[8-11] The recommended therapeutic strategy is generally selected according to anticipated locoregional control after surgery, and tends to vary by geographic region. Postoperative radiotherapy with 5-FU plus leucovorin has become the standard adjuvant regimen in the US,[8] whereas the perioperative triplet regimen of epirubicin, cisplatin, and 5-FU in the UK.[9] Two large randomized controlled trials demonstrated in Japan and Korea have showed the efficacy of adjuvant chemotherapy after D2 gastrectomy versus D2 gastrectomy alone for patients with resectable GC.[10,11] The ACTS-GC trial reported a hazard ratio for 5-year overall survival (OS) of 0.67 (95% confidence interval [CI]: 0.54-0.83) for surgery and adjuvant chemotherapy treated with the oral fluoropyrimidine S-1 for 1 year versus surgery alone.[12] However, the efficacy of S-1 is limited, with a 5-year OS rate of 67.1% in patients with stage IIIA disease and 50.2% in patients with stage IIIB disease according to Japanese Classification of Gastric Carcinoma (JCGC; second English Edition).[13] Furthermore, the treatment benefits of S-1 during stage IIIA or IIIB appear to be lower than that in stage II, as suggested by ACTS-GC.[12] On the other hand, the CLASSIC trial investigated the use of adjuvant capecitabine plus oxaliplatin (CapeOx) for 6 months after D2 gastrectomy versus surgery alone for patients with stage II or III GC.[11] The adjuvant CapeOx regimen demonstrated significant survival benefits over surgery alone, with the hazard ratio for 5-year OS of 0.75 (95% CI: 0.52-1.10) in stage IIIA GC and 0.67 (95% CI: 0.39-1.13) in stage IIIB GC, respectively[14]; hence, this therapy was considered as one of the standard of care for stage III GC in Japan.[15] Subsequently, the JACCRO GC-07 trial designed to prove the superiority of adjuvant S-1 plus docetaxel over S-1 alone for pathologic stage III GC demonstrated significant benefits with the hazard ratio for 3-year RFS of 0.632 (99.99% CI: 0.400-0.998; $P < .001$).[16]

However, postoperative adjuvant therapy has the limitation of drug compliance for more toxic regimens. In contrast, neoadjuvant strategies allow for intensive chemotherapy because the general condition of most preoperative patients is better than postoperative status. To administer intensive chemotherapy for stage III GCs which have a poor prognosis, neoadjuvant chemotherapies are currently being developed. In addition, perioperative chemotherapy has been the standard of care for resectable GC in Europe.[9] From these backgrounds, we conducted a phase II study to evaluate the clinical outcomes including efficacy, safety and survival benefits of perioperative CapeOx in clinical T3(SS)/T4a(SE) N1-3 M0 GC according to the JCGC third English Edition.[1] This is the second published report from

this study; the primary efficacy analysis and safety data from OGSG1601 (OGSG: Osaka Gastrointestinal Cancer Chemotherapy Study Group) have been reported previously.[17] The pRR, the primary endpoint, was 54.1% (P = .058; 90% CI: 39.4-68.2), although the survival data were immature. We report here an updated analysis of relapse-free survival and overall survival from OGSG1601 after a median follow-up of 3 years.

The pRR was set as the primary endpoint in this study, given that resectable GC rarely have measurable lesions, although the RECIST criteria is the current gold standard for the evaluation of tumor response. The pathological response, grade 1b or greater according to JCGC, has been adopted as the best surrogate endpoint for OS for GC in this setting.[18] Furthermore, a pathological response of grade 1b or greater according to JCGC predicted the survival.[19] Thus, a pathological response equivalent to or higher than grade 1b according to the JCGC criteria was determined as the primary endpoint. In fact, as a result of using this endpoint, survival data was favorable, although the sample size was small in this study. Furthermore, in the 2 criteria of JCGC[1] and Becker regression criteria,[2] there were 20 patients of grade 1b or higher in JCGC and 19 patients of grade 2 or lower in Becker criteria. Only 1 patient was evaluated to have the residual tumor between 33% and 50%, but it was actually difficult to determine exact ratio of the residual tumor even by performing a central review. Both criteria could be used to determine prognosis cut off points. Moreover, pRR may become important as an endpoint of study on neoadjuvant chemotherapy in future.

With regard to safety, both neoadjuvant and adjuvant CapeOx therapies showed good tolerability (Table1). In the neoadjuvant treatment, the hematologic and nonhematological toxicities were comparable with neoadjuvant S-1 plus oxaliplatin (SOX),[20] where the incidences of grades 3-4 adverse events of neutropenia, thrombocytopenia, anorexia, and diarrhea were found in 8% each of patients in this study and 7.1%, 21.4%, 14.3%, and 7.1% in patients with neoadjuvant SOX, respectively. In addition, the major complications of surgery were comparable to neoadjuvant SOX, where the incidences of grade 3b complication of postoperative ileus, grade 3a intra-abdominal abscess, and grade 3a anastomotic leakage were found in 3% of patients (Table 2) in this study, whereas grades 3-4 (CTCAE ver. 4.0) pancreatic fistula and pulmonary infection were found in 21.4% and 7.1% of patients in neoadjuvant SOX, respectively.[20] In the adjuvant CapeOx phase, fewer incidences of nonhematological toxicities were noted when compared with the J-CLASSIC trial, a phase II trial of adjuvant CapeOx therapy conducted for pathological stage II/III GC in Japan.[15] The incidences of grades 3-4 diarrhea, anorexia, vomiting, and fatigue in this study were 4%, 4%, 0%, and 0%, respectively, while 2%, 17%, 5%, and 6%, respectively, in the J-CLASSIC trial. This discordance is possibly due to the starting dose of the adjuvant perioperative CapeOx regimen, which was adjusted according to the last dose of the neoadjuvant CapeOx or the body surface area after gastrectomy, whichever was lower, making the adjuvant CapeOx therapy more feasible even after gastrectomy. In the present study, RDI of adjuvant CapeOx was maintained regardless of the surgical technique used and was comparable to the RDI of previously reported adjuvant CapeOx trials,[11,15] such as RDI of 80.9% and 65.1% for capecitabine and oxaliplatin, respectively, in this study, while the RDI for 2 drugs were 67.2% and 73.4%, respectively, in the J-CLASSIC trial. The eligibility criteria in these past studies included patients who were in good condition with adequate oral intake after surgery.[11,13] Therefore, in adjuvant chemotherapy with gastrectomy, the strategy of perioperative chemotherapy may be good from the viewpoint of improving the completion rate and RDI.

So far, the more intensive triplet regimens, such as docetaxel, oxaliplatin, plus S-1 (DOS) and docetaxel, oxaliplatin, fluorouracil, and plus leucovorin (FLOT), have demonstrated high rates of complete regression (14.6% and 16%, respectively), with considerably high incidence of severe neutropenia (65.8% and 52%, respectively).[21,22] Given the severe toxicities, these regimens are likely to be suitable for only selected patients with GC, underscoring the importance of the development of a highly efficacious treatment strategy with fewer toxicities. These regimens may be effective for patients who are expected to have a low histological response, but selecting these patients remains a future issue. Since type 4 GC was excluded in this study, it may have been easier to obtain a pathological response. The completion rate of neoadjuvant chemotherapy, the starting rate of adjuvant chemotherapy, and the completion rate of adjuvant chemotherapy were 89.8%, 59.8%, and 45.5%, respectively, in perioperative FLOT study,[22] whereas 89.2%, 73.0%, and 56.8%, respectively, in this perioperative CapeOx study. The less toxic CapeOx regimen resulted in a higher treatment continuation rate (Fig. 1).

The present study has several limitations. First, this trial was a single-arm study performed in a limited number of patients. Second, in this trial, staging laparoscopy was not regulated; hence, peritoneal cytology or metastasis was not completely excluded before enrollment. Three patients achieved R1 resection, although the presence of peritoneal cytology or metastasis during enrollment was not evaluated in these patients (Fig. 2).

In conclusion, perioperative CapeOx showed good feasibility and favorable prognosis, especially in patients with pathological response of grade 1b or higher and was found to be useful in predicting prognosis. Nevertheless, further studies with larger sample size are required to validate this novel approach.

Acknowledgments

This work was sponsored by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG). We thank the patients, their families, and the investigators who participated in the OGSG 1601 trial. We are grateful to Dr Yoshinobu Hirose and Dr Yoshitaka Kurisu for pathological central reviewing for the study. We thank Akemi Morita, Mieko Nakai, Nami Yoshida, and Chihiro Sawano for their help in the data management. We are also grateful to Toshimasa Tsujinaka for helpful advice. This study was financially supported by Yakult Honsha Co., Ltd.

Conflict of Interest

Tetsuji Terazawa: Daiichi-Sankyo Co. Ltd. (C/A), CHUGAI Pharmaceutical Co., Eli Lilly Co. Ltd., Taiho Pharmaceutical Co. Ltd., Sanofi Co. Ltd. (H), Shionogi Co. Ltd. (E); **Hisato Kawakami:** Bristol-Myers Squibb Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co. Ltd., Daiichi-Sankyo Co. Ltd., Taiho Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Merck Biopharma Co. Ltd., Takeda Pharmaceutical

Co. Ltd., Yakult Pharmaceutical Industry, Teijin Pharma Ltd., Glaxo Smith Kline K.K. (H), Bristol-Myers Squibb Co. Ltd., Daiichi-Sankyo Co. Ltd., Taiho Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Kobayashi Pharmaceutical. Co. Ltd., Eisai Co. Ltd. (RF); **Yukinori Kurokawa**: Taiho Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., MSD Co. Ltd. (RF), Taiho Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., Eli Lilly Co. Ltd., Yakult Honsha Co. Ltd., Nippon Kayaku Co. Ltd., Bristol-Myers Squibb Co. Ltd., Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd. (lecture fees); **Daisuke Sakai**: Chugai Pharmaceutical Co. Ltd. (H), Chugai Pharmaceutical Co. Ltd., Yakult Honsha Co. Ltd. (RF), **Taroh Saroh**: Ono Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Yakult Honsha Co. Ltd. (Endorsed Chair), Ono Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Yakult Honsha Co. Ltd., Elli Lilly Co. Ltd., Bristol Myers Squib Co. Ltd., Daiichi Sankyo Co. Ltd., MSD Co. Ltd., Taiho Pharmaceutical Co. Ltd. (OI), Ono Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Yakult Honsha Co. Ltd., Eli Lilly Co. Ltd., Bristol Myers Squib Co. Ltd., Daiichi Sankyo Co. Ltd., MSD Co. Ltd., Taiho Pharmaceutical Co. Ltd., Elli Lilly Co. Ltd., Bristol Myers Squib Co. Ltd., Daiichi Sankyo Co. Ltd., MSD Co. Ltd., Taiho Pharmaceutical Co. Ltd., Giliad Sciences Co. Ltd., Palexell Co. Ltd., Astellas Co. Ltd., HUTCHMED Co. Ltd. (RF), Takara Bio Co. Ltd. (SAB). 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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Figures and Tables

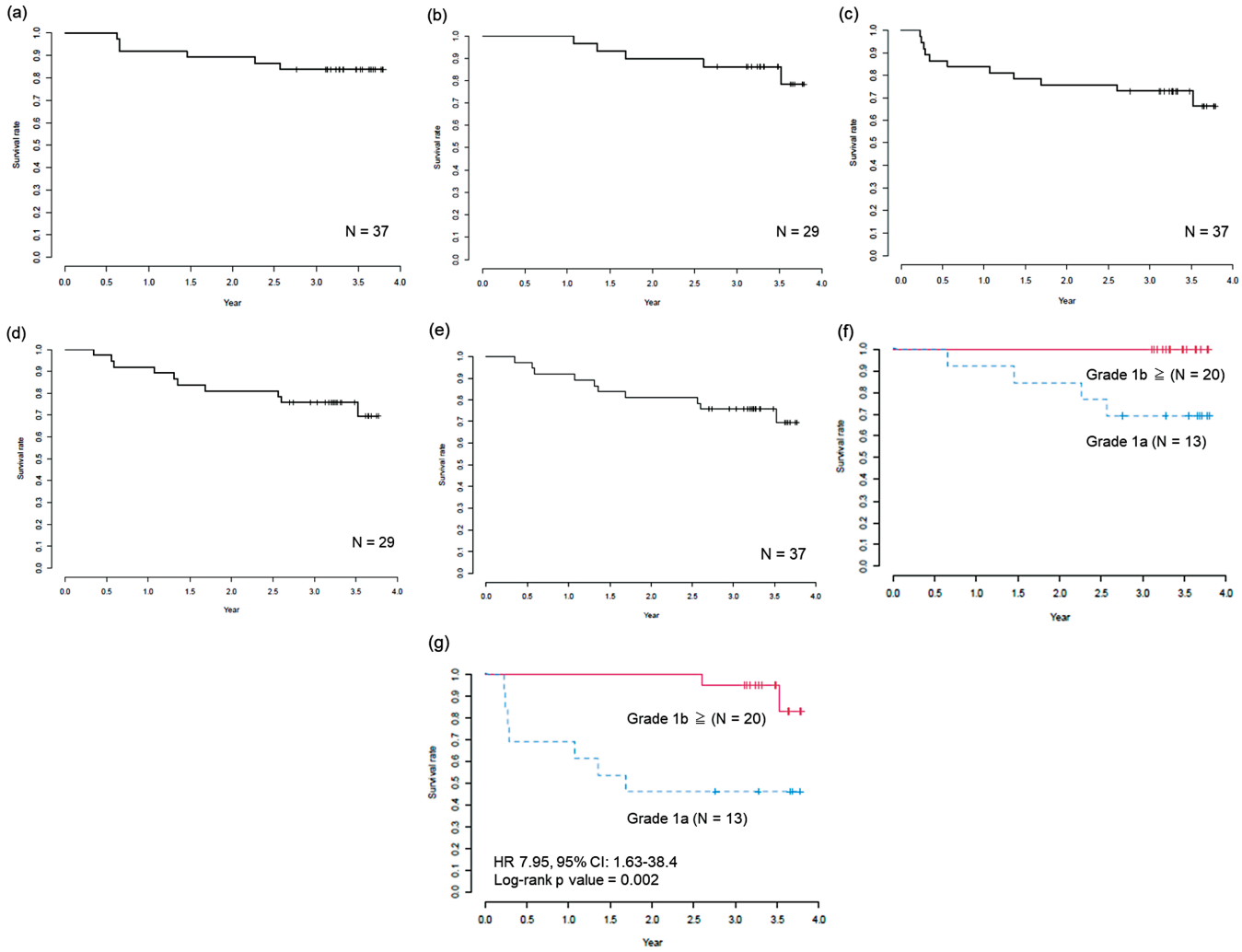

Figure 2. Kaplan-Meier overall survival (**a**), subclass analysis of OS according to R0 resection (**b**), relapse-free survival (**c**), subclass analysis of RFS according to R0 resection (**d**), progression-free survival (**e**), subclass analysis of OS according to pathological response (**f**), subclass analysis of RFS according to pathological response (**g**) at median follow-up period of 3.1 year.

Table 1. Adverse events of neoadjuvant and adjuvant chemotherapy.

Adverse event	Neoadjuvant chemotherapy, *n* = 37, *n* (%)					Adjuvant chemotherapy, *n* = 27, *n* (%)				
	G1	G2	G3	G4	%G3–G4	G1	G2	G3	G4	%G3–G4
Leukopenia	8 (21.6)	6 (16.2)	2 (5.4)	0 (0)	2 (5.4)	5 (18.5)	8 (29.6)	0 (0)	0 (0)	0 (0)
Neutropenia	6 (16.2)	8 (21.6)	2 (5.4)	1 (2.7)	3 (8.1)	3 (11.1)	7 (25.9)	9 (33.3)	1 (3.7)	10 (37)
Anemia	10 (27)	5 (13.5)	1 (2.7)	0 (0)	1 (2.7)	11 (40.7)	4 (14.8)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	8 (21.6)	2 (5.4)	2 (5.4)	1 (2.7)	3 (8.1)	12 (44.4)	2 (7.4)	0 (0)	0 (0)	0 (0)
Febrile neutropenia	—	—	0 (0)	0 (0)	0 (0)	—	—	0 (0)	0 (0)	0 (0)
Nausea	7 (18.9)	7 (18.9)	1 (2.7)	0 (0)	1 (2.7	7 (25.9)	4 (14.8)	0 (0)	0 (0)	0 (0)
Vomiting	5 (13.5)	1 (2.7)	0 (0)	0 (0)	0 (0)	4 (14.8)	0 (0)	0 (0)	0 (0)	0 (0)
Stomatitis	2 (5.4)	1 (2.7)	1 (2.7)	0 (0)	1 (2.7)	2 (7.4)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	7 (18.9)	4 (10.8)	3 (8.1)	0 (0)	3 (8.1)	9 (33.3)	3 (11.1)	1 (3.7)	0 (0)	1 (3.7)
Anorexia	6 (16.2)	10 (27)	3 (8.1)	0 (0)	3 (8.1)	5 (18.5)	9 (33.3)	1 (3.7)	0 (0)	1 (3.7)
Fatigue	6 (16.2)	4 (10.8)	1 (2.7)	0 (0)	1 (2.7)	4 (14.8)	5 (18.5)	0 (0)	0 (0)	0 (0)
Peripheral neuropathy	14 (37.8)	3 (8.1)	0 (0)	0 (0)	0 (0)	9 (33.3)	8 (29.6)	0 (0)	0 (0)	0 (0)
Hand-foot syndrome	3 (8.1)	2 (5.4)	0 (0)	0 (0)	0 (0)	2 (7.4)	2 (7.4)	0 (0)	0 (0)	0 (0)

Source: CTCAE Ver. 4.0.

Table 2. Surgical complications (n = 33).

Surgical complications	I	II	IIIa	IIIb	Iva
Ileus	0	1 (3.0)	0	1 (3.0)	0
Paralytic ileus	0	1 (3.0)	0	0	0
Weight loss	1 (3.0)	0	0	0	0
Intra-abdominal abscess	0	0	1 (3.0)	0	0
Anastomotic leakage	0	0	1 (3.0)	0	0
Pancreatic fistula	0		0	0	0

Clavien–Dindo criteria, n (%).