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Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: A randomised phase III trial (TCOG GI-0801/BIRIP trial)

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Abstract ***Purpose:*** We compared biweekly irinotecan plus cisplatin (BIRIP) with irinotecan alone as the second-line chemotherapy (SLC) for advanced gastric cancer (AGC).
Methods: Patients with metastatic or recurrent gastric cancer refractory to S-1-based first-line chemotherapy were randomly assigned to receive BIRIP (irinotecan 60 mg/m^2 plus cisplatin 30 mg/m^2, every 2 weeks) or irinotecan alone (irinotecan 150 mg/m^2, every 2 weeks). The primary end-point was to show the superiority of BIRIP to irinotecan in terms of progression free survival (PFS).
Results: 130 patients were enrolled. PFS was significantly longer in the BIRIP group (3.8 months [95% confidence interval (CI) 3.0–4.7]) than in the irinotecan group (2.8 months [2.1–3.3]; hazard

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ratio 0.68, 95% CI 0.47–0.98; $P = 0.0398$). Median overall survival was 10.7 months in the BIRIP group and 10.1 months in the irinotecan group (HR 1.00, 95% CI 0.69–1.44, $P = 0.9823$). The objective response rate was 22% in the BIRIP group and 16% in the irinotecan group ($P = 0.4975$). However, the disease control rate was significantly better in the BIRIP group (75%) than in the irinotecan group (54%, $P = 0.0162$). The incidences of grade 3 or worse adverse events did not differ between the two groups. Any grade elevation of serum creatinine was more common in the BIRIP group (25% versus 8%, $P = 0.009$), but any grade diarrhoea (17% versus 42%, $P = 0.002$) was more common in the irinotecan group.

Conclusion: BIRIP significantly prolonged PFS as compared with irinotecan alone and was tolerated as SLC, but did not demonstrate the survival benefit in this trial.

1. Introduction

Several randomised trials for patients with advanced gastric cancer (AGC) have shown that fluorouracil-based first-line chemotherapy can improve survival [1–3]. But standard first-line regimens vary among countries. In Eastern Asia, S-1 (consisting of tegafur, gimestat and otastat potassium in a molar ratio of one to 0.4 to one)-based regimens are most widely used for first-line chemotherapy [4,5]. In Japan, S-1 is used as standard postoperative adjuvant chemotherapy in patients with stages II–III gastric cancer who undergo curative surgery [6], and treatment strategies for patients with early recurrence are needed.

At the time of designing this trial, there was no established standard second-line chemotherapy (SLC) for patients with AGC. However, irinotecan alone and biweekly irinotecan plus cisplatin (BIRIP) were considered to be promising and were widely used as second-line treatment [7–9]. Recently, two randomised controlled trials showed a survival benefit of SLC as compared with best supportive care (BSC) [10,11]. In these trials, patients received irinotecan alone as SLC, and the results suggested that irinotecan alone might be an option for SLC.

In the phase II study of irinotecan alone as SLC in AGC after failure of cisplatin-based regimen, the response rate (RR) was 20.0% and median survival time (MST) was 5.2 months [7]. Because irinotecan alone frequently causes diarrhoea and febrile neutropenia, it is a toxic regimen for SLC. Several clinical studies have shown that a combination of irinotecan and cisplatin is effective in patients with AGC [5,12]. Furthermore, experimental studies have reported that irinotecan and cisplatin act synergistically [13,14]. BIRIP was developed as a less toxic regimen designed to reduce the incidences of diarrhoea and febrile neutropenia by decreasing the dose of irinotecan [8,9]. A phase I/II study of BIRIP as SLC for AGC showed promising efficacy and a manageable toxicity profile; the RR was 20.0% and MST was 9.0 months in the patients who had received prior chemotherapy (mainly fluoropyrimidine plus cisplatin-based regimen) [9].

This multicenter, open label, randomised phase III trial was designed to verify that progression free survival (PFS) is better with BIRIP than with irinotecan alone in patients with AGC who had received S-1-based first-line chemotherapy. This study was conducted by The Tokyo Cooperative Oncology Group (TCOG GI-0801/BIRIP trial).

2. Methods

2.1. Study design

The primary end-point was PFS. Secondary end-points were overall survival (OS), the time to treatment failure; defined as the time between study entry and the first evidence of disease progression, death due to any cause or protocol treatment discontinuation for a reason other than disease progression, tumour response, and safety. We recruited patients with AGC from 27 institutions in Japan between April 2008 and July 2011. We randomly assigned enrolled patients to either BIRIP or irinotecan alone in a one-to-one ratio by a minimisation method. The stratification factors were ECOG performance status (0/1/2), prior chemotherapy with or without cisplatin, and the presence or absence of adjuvant therapy with S-1.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the institutional review boards of each participating hospital. This study is registered with UMIN-CRT, number 000001028.

2.2. Patient selection

Patients were eligible if they had a histological diagnosis of adenocarcinoma of the stomach that was refractory to S-1-based first-line chemotherapy (excluding irinotecan plus S-1) for unresectable advanced or recurrent disease, or that recurred during or within 6 months after the completion of adjuvant therapy with S-1. Other eligibility criteria were as follows: the presence of measurable lesions or disease that could be serially evaluated to assess the response to treatment; no prior immunotherapy or

radiotherapy; prior S-1-based therapy completed at least 2 weeks before enrolment; previous surgery completed at least 4 weeks before enrolment; an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; an age of 20 years or older; an estimated life expectancy of at least 12 weeks; written informed consent; and following adequate organ functions as established by tests performed within the 14 d before enrolment; leucocyte count of $4.0–12.0 \times 10^9$/L; neutrophil count $\geqslant 2.0 \times 10^9$/L; platelets count $\geqslant 100 \times 10^9$/L; haemoglobin $\geqslant 80$ g/L; serum aspartate aminotransferase and alanine aminotransferase $\leqslant 100$ U/L; serum bilirubin $\leqslant 1.50$ mg/dL; serum creatinine $\leqslant$ upper limit of normal; and creatinine clearance $\geqslant 50$ mL/min. Patients could have no serious comorbidities.

2.3. Treatment plan

Patients randomly assigned to the BIRIP group received irinotecan 60 mg/m^2 as a 60 min intravenous infusion plus cisplatin 30 mg/m^2 as a 90 min intravenous infusion with adequate hydration on day 1 every 2 weeks. Those randomly assigned to the irinotecan group received irinotecan 150 mg/m^2 as a 90 min intravenous infusion on day 1 every 2 weeks. Treatment was continued until disease progression, unmanageable toxicity or withdrawal of consent.

2.4. Assessments

Computed tomographic (CT) scans were obtained within 2 weeks before study entry, and at 6 week intervals after the start of treatment. Treatment response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.0. All radiographic images of response to treatment were assessed by extramural review. All adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

2.5. Statistical analysis

PFS was defined as the time between study entry and the first evidence of disease progression or death from any cause. We assumed that median PFS would be 3.6 months in the BIRIP group and 2.1 months in the irinotecan group on the basis of the results of previous phase II studies [7,9]. Given an accrual period of 3.5 years and a minimum follow-up period of 1 year, we estimated that 122 patients (114 events) would be needed to detect a difference in PFS between the treatment groups on completion of follow-up, with a power of 80% and a type I error of 0.05 (two-sided log-rank test). We set the target number of enrolled patients at 130 to allow for factors such as ineligibility. Survival curves were estimated according to the Kaplan–Meier method and compared using the log-rank test. Fisher's exact test was used for analysis of the RR, the disease control rate (DCR; the rate of complete response plus partial response plus stable disease) and the incidence of adverse events. Univariate Cox proportional-hazards models were used for subgroup analysis of PFS. All data analyses were conducted with the use of SAS software, version 9.2.

3. Results

3.1. Patients characteristics

From April 9, 2008 through July 21, 2011, 130 patients were enrolled at 21 institutions in Japan. Sixty-four patients were randomly assigned to BIRIP and 66 patients to irinotecan (Fig. 1). Safety was analysed in these patients. In the irinotecan group, three patients were ineligible: one patient had no assessable lesions, one had double cancers and one had operable cancer but refused surgery. The full analysis set (FAS) thus comprised 127 patients (64 in the BIRIP group, and 63 in the irinotecan group). Efficacy was analysed in the FAS group of patients. Baseline patient characteristics were well balanced between the two treatment groups (Table 1). The number of patients who had received platinum agents as prior chemotherapy was 36 (56%) in the BIRIP group and 36 (57%) in the irinotecan group.

3.2. Treatment efficacy

The primary analysis of the FAS was done in September 2012, based on data up to 1 year after the last patient had been enrolled. At that time, study treatments had been discontinued in 64 patients in the BIRIP group and 63 patients in the irinotecan group, and a total of 114 PFS events had occurred. PFS was significantly longer in patients assigned to BIRIP (Median 3.8 months [95% confidence interval (CI) 3.0–4.7]) than in those assigned to irinotecan (2.8 months [2.1–3.3]; hazard ratio [HR] 0.68, 95% CI 0.47–0.98; $P = 0.0398$, Fig. 2). Median time to treatment failure was 3.3 months (95% CI 2.6–4.2) in the BIRIP group and 2.5 months (1.8–3.2) in the irinotecan group (HR 0.73, 95% CI 0.52–1.04; $P = 0.0817$). MST was 10.7 months (95% CI 8.9–13.8) in the BIRIP group and 10.1 months (95% CI 7.2–12.1) in the irinotecan group (HR 1.00, 95% CI 0.69–1.44, $P = 0.9823$, Fig. 3).

Table 2 shows the tumour response. The objective RR was 22% (95% CI 13–34) in the BIRIP group and 16% (8–27) in the irinotecan group ($P = 0.4975$). However, the DCR was significantly better in the BIRIP group (75% [95% CI 63–85]) than in the irinotecan group (54% [41–67], P = 0.0162).

Exploratory subgroup analyses of PFS, which were not preplanned in the protocol, showed favourable

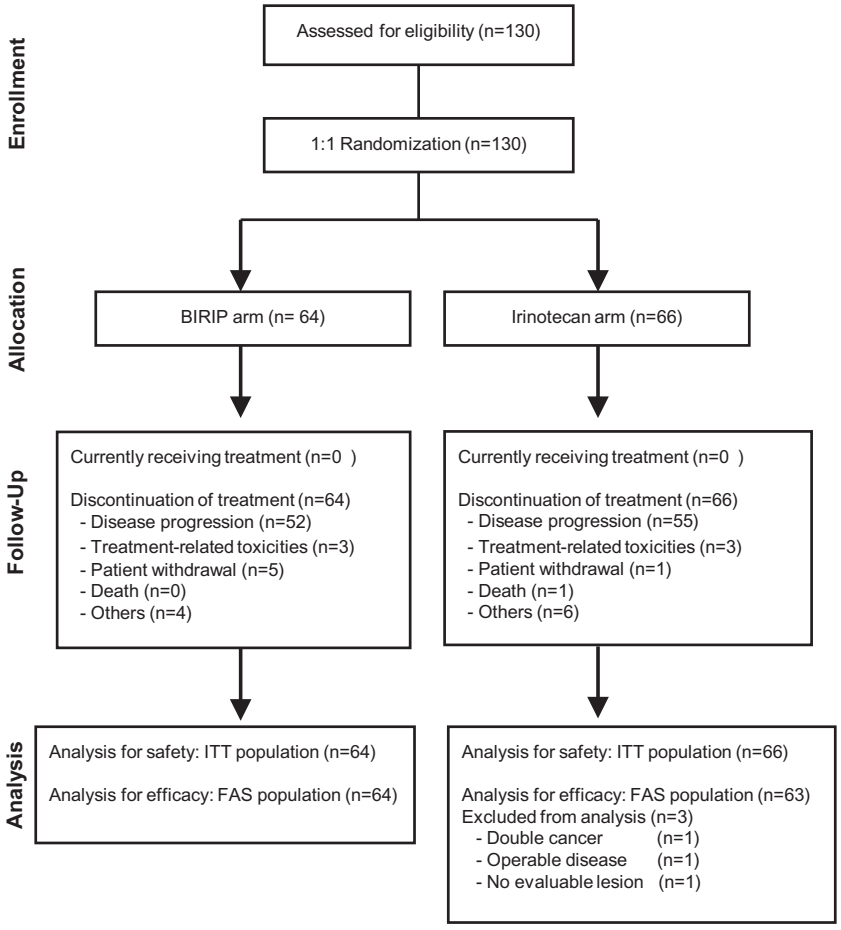

Fig. 1. CONSORT diagram. *Abbreviations:* BIRIP, bi-weekly irinotecan plus cisplatin; ITT, intention to treat; FAS, full analysis set.

trends for BIRIP in all subgroups except patients with peritoneal metastasis (Fig. 4). In the subgroup that had previously received platinum agents, median PFS was 2.8 (95% CI 2.3–3.6) months for patients assigned to BIRIP ($N = 36$) and 2.5 (95% CI 1.5–3.2) months for those assigned to irinotecan ($N = 36$; HR 0.80 [95% CI 0.49–1.28]; $P = 0.3511$). In the subgroup without prior platinum agents, median PFS was 6.4 (95% CI 4.4–7.5) months for patients assigned to BIRIP ($N = 28$) and 4.2 (95% CI 1.8–5.0) months for those assigned to irinotecan ($N = 27$; HR 0.60 [95% CI 0.33–1.08]; $P = 0.0786$).

3.3. Safety

Table 3 shows adverse events. The incidences of grade 3 or worse adverse events did not differ between the two groups. However, febrile neutropenia occurred in three patients (5%) in the irinotecan group, but did not occur in the BIRIP group. Any grade elevation of serum creatinine was more common in the BIRIP group (25% versus 8%, $P = 0.009$), and any grade diarrhoea (17% versus 42%, $P = 0.002$) was more common in the irinotecan group. There was no treatment-related death in either of the two study groups.

3.4. Treatment compliance and post-treatment

The median number of treatment cycles was six cycles (range 1–33) in the BIRIP group and five cycles (1–25) in the irinotecan group. Dose reductions were made for 19 (30%) patients in the BIRIP group and 21 (33%) in the irinotecan group. The most common cause for discontinuation of treatment was disease progression in both groups (81% in the BIRIP group versus 87% in the irinotecan group). At the time of the fifth cycle, the relative dose intensity of irinotecan was 85% (95% CI 39–100) in the irinotecan group, and the relative dose intensities of irinotecan and cisplatin were respectively 84% (46–100) and 83% (46–100) in the BIRIP group.

Forty-eight (75%) patients in the BIRIP group and 47 (75%) in the irinotecan group received third-line chemotherapy. The most common regimen of third-line chemotherapy was paclitaxel-based (mainly paclitaxel alone) in both groups (60% in the BIRIP group versus 77% in the irinotecan group).

4. Discussion

In this phase III trial, BIRIP as SLC significantly improved PFS as compared with irinotecan alone in

Table 1
Baseline characteristics (full analysis set population).

Characteristics	BIRIP ($n = 64$)	Irinotecan ($n = 63$)
Age, median (range)	66 (29–80)	67 (49–78)
Gender, *N* (%)		
Male	49 (77)	55 (87)
Female	15 (23)	8 (13)
Histology, *N* (%)		
Intestinal	32 (50)	32 (51)
Diffuse	32 (50)	31 (49)
Gastrectomy, *N* (%)		
–	42 (66)	39 (62)
+	22 (34)	24 (38)
Disease status, *N* (%)		
Metastatic	44 (69)	40 (63)
Recurrent	20 (31)	23 (37)
Peritoneal metastasis, *N* (%)		
+	13 (20)	20 (32)
–	51 (80)	43 (68)
Prior chemotherapy, *N* (%)		
S-1	19 (30)	19 (30)
S-1 + Cisplatin	28 (44)	30 (48)
S-1 + Docetaxel	8 (13)	6 (10)
S-1 + Cisplatin + Docetaxel	4 (6)	5 (8)
S-1 + Oxaliplatin	3 (5)	1 (2)
Other	2 (3)	2 (3)
ECOG PS, *N* (%)		
0	44 (69)	43 (68)
1	20 (31)	20 (32)
2	0	0
Prior chemotherapy with platinum, *N* (%)		
+	36 (56)	36 (57)
–	28 (44)	27 (43)
Prior adjuvant therapy with S-1, *N* (%)		
+	15 (23)	17 (27)
–	49 (77)	46 (73)

Abbreviations: BIRIP, biweekly irinotecan plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status.

patients with AGC refractory to S-1-based first-line chemotherapy. We observed that BIRIP was associated with a risk reduction of disease progression or death by 32% (HR, 0.68; $P = 0.0398$) in the FAS population, improving median PFS from 2.8 months in the irinotecan group to 3.8 months. To our knowledge, our study is the first to report the superiority of combination chemotherapy to mono-therapy as SLC in terms of PFS in the phase III trial. However, neither OS nor RR differed between the two groups. The DCR which was not preplanned in the protocol was significantly better in the BIRIP group (75%) than in the irinotecan group (54%, $P = 0.0162$). The incidences of grade 3 or worse adverse events did not differ between the two groups. However, BIRIP had a good tolerability profile and was associated with no febrile neutropenia and less diarrhoea.

Several clinical studies have shown that combination therapy with irinotecan and cisplatin is active in the patients with AGC. A combination of irinotecan and cisplatin, reported by Ajani et al. [12] and Boku et al. [5], was developed as a first-line regimen. Grade 3 or worse nausea occurred in 16–21% of patients, diarrhoea in 9–22% and febrile neutropenia in 4–9%, indicating that the regimen is toxic. BIRIP was developed as a less toxic, second-line regimen. The use of irinotecan in a low dose of 60 mg/m^2 every 2 weeks was expected to reduce the incidences of toxic effects such as diarrhoea and febrile neutropenia [9].

When our study began, the results of randomised phase III trials of SLC in AGC were unavailable. However, the results of several trials were reported during the course of our study (Table 4). Then, the survival benefits of SLC over BSC were demonstrated [10,11,16,17]. In

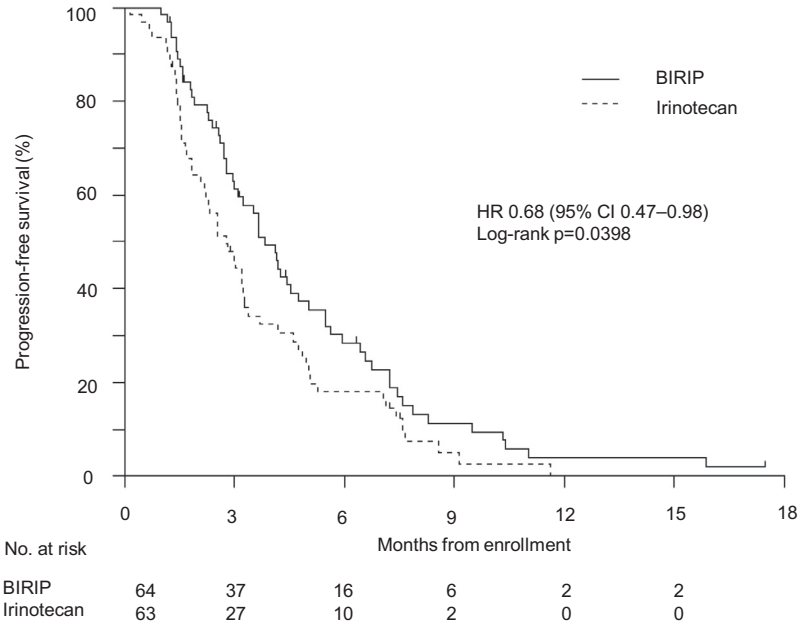

Fig. 2. Kaplan–Meier curves of progression-free survival after random assignment. *Abbreviations:* HR, hazard ratio.

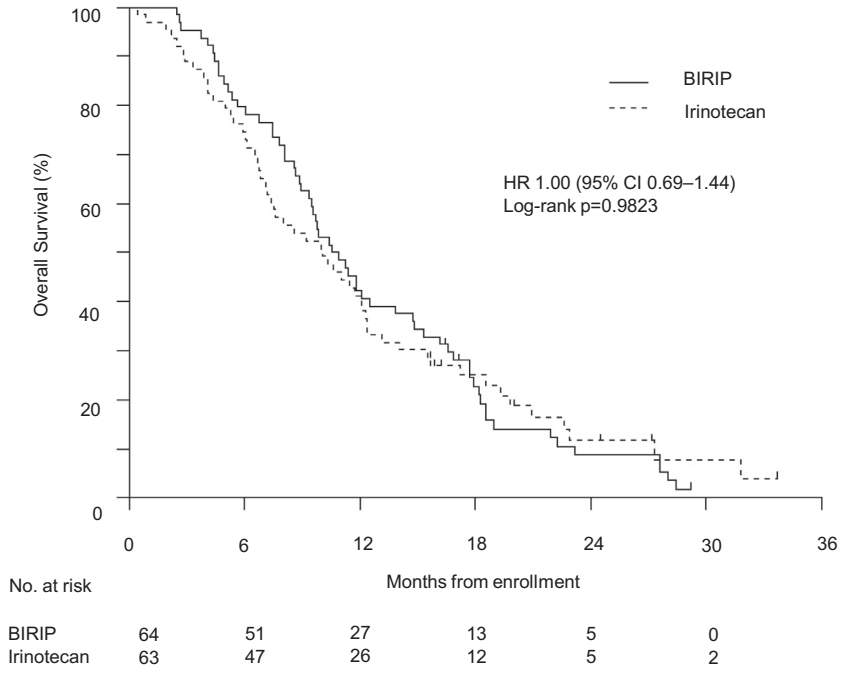

Fig. 3. Kaplan–Meier curves of overall survival after random assignment.

Table 2
Tumour response.

	BIRIP ($n = 64$)	Irinotecan ($n = 63$)	P-value
Tumour response, number of patients (%)			
Complete response	0	0	
Partial response	14 (22)	10 (16)	
Stable disease	34 (53)	24 (38)	
Progressive disease	15 (23)	27 (43)	
Not evaluable	1 (2)	2 (3)	
Response rate	14 (22)	10 (16)	$P = 0.4975$
Disease control rate	48 (75)	34 (54)	$P = 0.0162$

Abbreviation: BIRIP, biweekly irinotecan plus cisplatin. P values were calculated with Fisher's exact test.

the Arbeitsgemeinschaft Internistische Onkologie (AIO) trial comparing irinotecan alone with BSC as SLC in gastric cancer, OS was significantly longer in the irinotecan alone group [10]. In Korean trial comparing chemotherapy (irinotecan or docetaxel) with BSC, OS was significantly longer in the chemotherapy group [11]. In the WJOG4007 trial comparing paclitaxel with irinotecan as SLC in Japanese patients with AGC, neither OS nor PFS differed significantly between the paclitaxel group and the irinotecan group [15]. On the basis of these results, SLC using irinotecan alone or taxane alone has been recognised as the standard of care for patients with AGC.

In present study, MST was 10.7 months in the BIRIP group and 10.1 months in the irinotecan group. The relatively good OS was probably related to the high proportion of patients who received post-treatment and the good general condition of the patients at enrolment. In both treatment groups, about 75% of the patients received third-line chemotherapy, which was mainly taxane-based. All patients had good ECOG performance status, and there were relatively few patients with peritoneal metastasis as compared with previous phase III trials.

The primary end-point of our study was superiority in terms of PFS, not overall survival. In Japan, more than 70% of patients with AGC receive third-line chemotherapy. Besides overall survival is strongly affected by the type of first-line regimen, it was considered difficult to demonstrate superiority of a second-line regimen in terms of overall survival. We therefore designated superior PFS as the primary end-point of this phase III study. Recent phase III studies comparing chemotherapies each other as SLC did not demonstrate the superiority in terms of either OS or PFS [15,18]. The development of a more effective regimen such as the combination chemotherapy with molecular target agents is required as SLC for patients with AGC.

In our study, patients who had previously received platinum agents could be enrolled because good results were obtained in a phase I/II trial of BIRIP in patients with AGC previously treated with cisplatin, i.e. Koizumi et al. reported that among 21 patients who had received cisplatin, four (19.1%) had a partial response, and eight (38.1%) had stable disease [9]. In our study, at least 56% of the patients in both groups had previously received platinum-based chemotherapy. In the subgroup with or without prior chemotherapy with

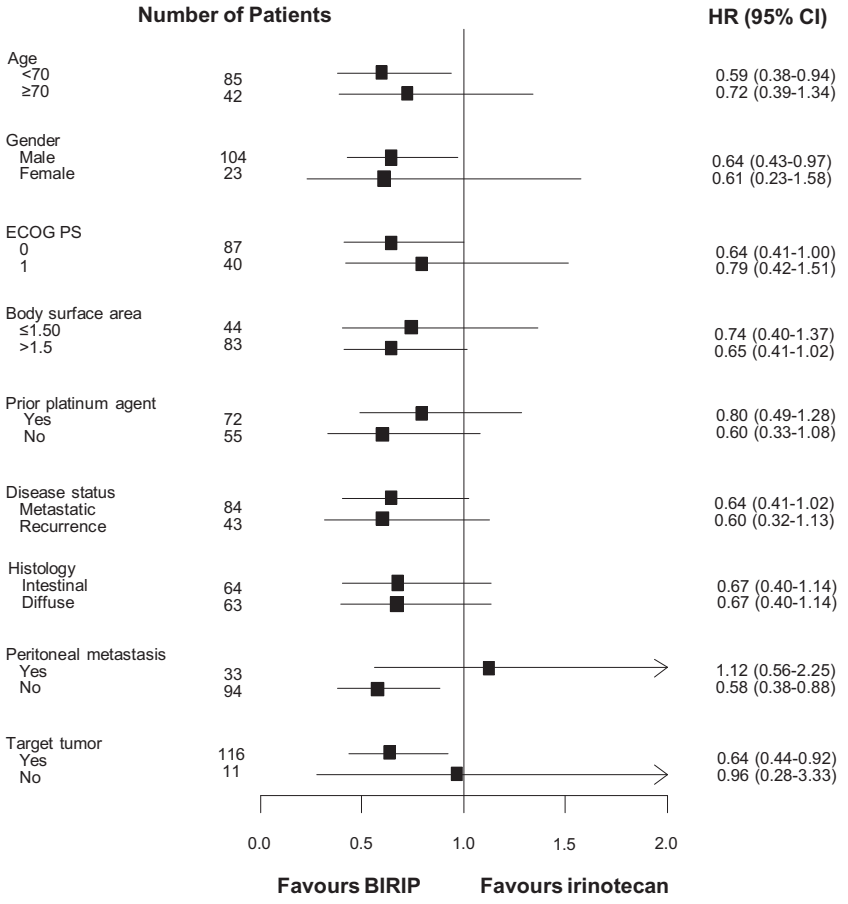

Fig. 4. Subgroup analysis for progression free survival. *Abbreviations:* ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 3
Adverse events (CTCAE version 3.0).

Adverse events, *N* (%)	BIRIP ($n = 64$)		Irinotecan ($n = 66$)	
	Any grade	Grades 3–4	Any grade	Grades 3–4
Neutropenia	48 (75)	25 (39)	39 (59)	24 (36)
Anaemia	37 (58)	10 (16)	30 (46)	12 (18)
Thrombocytopenia	17 (27)	0	9 (14)	1 (2)
Diarrhoea	11 (17)	1 (2)	28 (42)*	4 (6)
Nausea	31 (48)	3 (5)	24 (36)	3 (5)
Vomiting	18 (28)	0	15 (23)	0
Anorexia	38 (59)	4 (6)	30 (46)	7 (11)
Bilirubin	6 (9)	1 (2)	8 (12)	0
Creatinine	16 (25)**	1 (2)	5 (8)	1 (2)
Abdominal pain	5 (8)	0	13 (20)	0
Fatigue	27 (42)	2 (3)	28 (42)	4 (6)
Febrile neutropenia	0	0	3 (5)	3 (5)

Abbreviations: BIRIP, biweekly irinotecan plus cisplatin; CTCAE, the Common Terminology Criteria for Adverse Events.
P values were calculated with Fisher's exact test.
* $P = 0.002$.
** $P = 0.009$.

platinum agent, there was a trend towards better PFS in the BIRIP group. In other subgroups except for patients with peritoneal metastasis, there was also a trend towards better PFS in the BIRIP group. However, our study was conducted solely in Japanese patients, more than 40% of whom had received no platinum therapy before study entry. Western patients nearly invariably receive a platinum-based regimen as first-line chemotherapy for AGC, and we therefore recommend caution in extrapolating our results to Western patients in the absence of an adequately powered subgroup analysis.

Table 4
PFS and OS in recent randomised phase III trials as SLC for AGC.

Trial	Regimens	*N*	PFS		OS	
AIO trial [10]	Irinotecan	21	2.5 M	–	4.0 M	HR 0.48
	BSC	19	–	–	2.4 M	$P = 0.023$
Korean trial [11]	Irinotecan or docetaxel	133	–	–	5.3 M	HR 0.657
	BSC	69	–	–	3.8 M	$P = 0.007$
COUGAR-02 [16]	Docetaxel	84	–	–	5.2 M	HR 0.67
	BSC	84	–	–	3.6 M	$P = 0.01$
REGARD [17]	Ramucirumab	238	2.1 M	HR 0.483	5.2 M	HR 0.776
	Placebo	117	1.3 M	$P < 0.0001$	3.8 M	$P = 0.047$
WJOG4007 [15]	Irinotecan	111	2.3 M	HR 1.14	8.4 M	HR 1.13
	Paclitaxel	108	3.6 M	$P = 0.33$	9.5 M	$P = 0.38$
TyTAN [18]	Lapatinib plus paclitaxel	132	5.4 M	HR 0.85	11.0 M	HR 0.84
	paclitaxel	129	4.4 M	$P = 0.2441$	8.9 M	$P = 0.2088$
TCOG GI-0801/BIRIP trial	Irinotecan plus cisplatin	64	3.8 M	HR 0.68	10.7 M	HR 1.00
	Irinotecan	63	2.8 M	$P = 0.0398$	10.1 M	$P = 0.9823$

Abbreviations: AIO, Arbeitsgemeinschaft Internistische Onkologie; PFS, progression free survival; OS, overall survival; SLC, second-line chemotherapy; AGC, advanced gastric cancer; BSC, best supportive care; M, months; HR, hazard ratio.

In conclusion, BIRIP significantly prolonged PFS as compared with irinotecan alone and was tolerated as SLC for AGC, but did not demonstrate the survival benefit in this trial.

Conflict of interest statement

None declared.

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