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Original Research

TAS-118 (S-1 plus leucovorin) versus S-1 in patients with gemcitabine-refractory advanced pancreatic cancer: a randomised, open-label, phase 3 study (GRAPE trial)

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Abstract ***Background:*** In our previous randomised phase 2 study for patients with gemcitabine-refractory advanced pancreatic cancer, S-1 plus leucovorin improved progression-free survival compared with S-1 alone. Here, we evaluated the efficacy of TAS-118 (S-1 plus leucovorin) versus S-1 in overall survival (OS).

Patients and methods: This randomised, open-label, phase 3 study was conducted at 58 centres in Japan and Korea. Patients with metastatic pancreatic cancer that progressed during first-line gemcitabine-based chemotherapy or recurred during or after post-operative gemcitabine-based adjuvant treatment were randomly assigned (1:1) to receive either S-1 (40–60 mg, twice daily for 4 weeks in a 6-week cycle) or TAS-118 (S-1 40–60 mg plus leucovorin 25 mg, twice daily for 1 week in a 2-week cycle). The primary end-point was OS.

Results: A total of 603 patients were randomised, and 300 and 301 patients received TAS-118 and S-1, respectively. There was no difference in OS between groups (median OS for TAS-118 versus S-1, 7.6 months versus 7.9 months; hazard ratio [HR], 0.98 [95% confidence interval (CI), 0.82–1.16]; $P = 0.756$). Progression-free survival was significantly longer with TAS-118 than S-1 (median, 3.9 months versus 2.8 months; HR, 0.80 [95% CI, 0.67–0.95]; $P = 0.009$). There were interactions between Japan and Korea ($P = 0.004$) and between unresectable and recurrent disease ($P = 0.025$) in OS. Incidence, profile and severity of adverse events were similar between groups.

Conclusion: TAS-118 did not improve OS in patients with gemcitabine-refractory advanced pancreatic cancer compared to S-1. Further studies are needed to find patients who have benefit from adding leucovorin to S-1.

1. Introduction

Gemcitabine monotherapy was the standard first-line therapy for patients with advanced pancreatic cancer [1] until gemcitabine plus nab-paclitaxel and FOLFIRINOX were developed [2,3]. While these combination regimens are recommended as the standard first-line therapy for patients with good performance status (PS) [4], gemcitabine monotherapy is still used for patients with advanced pancreatic cancer to avoid severe toxicities as well as for patients in post-operative adjuvant settings.

Limited treatment options were available for gemcitabine-refractory advanced pancreatic cancer, although two regimens, oxaliplatin with fluorouracil and folinic acid in CONKO-003 study and nanoliposomal irinotecan with fluorouracil and folinic acid in NAPOLI-1 study, recently showed survival benefits [5,6]. Monotherapy with S-1, an oral fluoropyrimidine drug comprising tegafur, gimeracil and oteracil potassium, demonstrated non-inferiority to gemcitabine as first-line therapy for advanced pancreatic cancer, and favourable results were reported for its use in gemcitabine-refractory patients [7,8]. Since then, S-1 monotherapy has often been used for patients with gemcitabine-refractory pancreatic cancer in Japan and Korea.

Leucovorin enhances the efficacy of fluorouracil by stabilising the ternary complex with thymidylate synthase, fluorodeoxyuridine monophosphate and 5,10-methylenetetrahydrofolate, thereby strongly inhibiting DNA synthesis. S-1 plus leucovorin combination therapy (S-1/LV) has been studied in several clinical trials for gastrointestinal cancers [9–11] and improved progression-free survival (PFS) compared with S-1 monotherapy in a randomised phase 2 study for patients with gemcitabine-refractory advanced pancreatic cancer [12].

TAS-118 (Taiho Pharmaceutical, Tokyo, Japan) is an oral combination drug consisting of S-1 and leucovorin. In this phase 3 study, we assessed overall survival (OS) with TAS-118 compared to S-1 in patients with gemcitabine-refractory advanced pancreatic cancer.

2. Patients and methods

2.1. Study design and treatment

This randomised, open-label, multicenter, phase 3 study was conducted at 58 study sites in Japan and Korea. Patients were randomly assigned (1:1) to receive either TAS-118 or S-1 using stratification factors of pancreatic resection history (±), Eastern Cooperative Oncology Group PS (0/1) and country (Japan/Korea). Key eligibility criteria were histologically or cytologically confirmed pancreatic adenocarcinoma or adenosquamous carcinoma, refractory to gemcitabine (progression during first-line gemcitabine-based chemotherapy or recurrence during or within 6 months after post-operative gemcitabine-based adjuvant chemotherapy), no prior chemotherapy with fluoropyrimidine, at least one measurable or evaluable metastatic lesion, age 20–79 years, PS 0–1, serum albumin ≥3.5 g/dL and appropriate organ function. The study was approved by the institutional review board at each study site and was conducted in accordance with Good Clinical Practice Guidelines. All patients provided written informed consent.

S-1 was orally administered twice daily for 4 weeks in a 6-week cycle. TAS-118, which contains S-1 (30, 40, 50 or 60 mg) and leucovorin (25 mg), was orally administered twice daily for 1 week in a 2-week cycle. Initial doses of S-1 and TAS-118 were determined according to body surface area (as S-1, 40 mg for patients with body surface area <1.25 m^2; 50 mg for ≥1.25 to <1.5 m^2; 60 mg for ≥1.5 m^2). Patients continued the study treatment until disease progression, unacceptable toxicity or consent withdrawal.

During the study treatment, adverse events (AEs) were evaluated based on the Common Terminology Criteria for Adverse Events version 4.03 every 2 weeks. Tumour response was evaluated by the investigators according to Response Evaluation Criteria in Solid Tumours version 1.1 every 6 weeks. Survival after discontinuation of the study was followed every 8 weeks.

2.2. Outcomes

The primary end-point was OS, defined as the time from randomisation to death due to any cause. The secondary end-points were safety, PFS (the time from randomisation to disease progression or death due to any cause, whichever came first), overall response rate (ORR) and disease control rate (DCR).

2.3. Statistical analysis

We anticipated median OS in the S-1 group to be 6.0 months for Japanese patients and 4.5 months for Korean patients [12,13]. To detect a 25% risk reduction for OS in the TAS-118 group compared to the S-1 group at a two-sided significance level of 0.05 with 90% power, 508 events were required. The planned sample size was 600 patients.

Two interim analyses by the independent data monitoring committee were planned to recommend early termination of this study; the first after 50 deaths to assess safety, and the second after 100 deaths to assess efficacy. Upon recommendations from the data monitoring committee at the two interim analyses, this study was completed without modification. The primary analysis used the stratified log-rank test and the Cox proportional hazards (CPH) model including treatment groups and stratification factors. A 5% significance level was adjusted by the O'Brien-Fleming method for multiple testing.

The efficacy was analysed on the full analysis set, consisting of the patients that met the following criteria: histologically or cytologically confirmed pancreatic cancer, refractory to gemcitabine, receiving the study drug at least once. OS and PFS were analysed by the Kaplan–Meier method. Safety was evaluated in all patients who received the study treatment at least once.

Before the data cut-off, Z score analysis was additionally preplanned because patient baseline characteristics were substantially different between the two countries under the blinded condition for treatment groups. Z score was calculated as hazard ratio (HR) divided by standard error by the CPH model using stratification factors as covariates and was analysed for the following patient subgroups: no history of pancreatic resection, prior chemotherapy gemcitabine alone, age <70 years, HbA1c <8.0% and C-reactive protein (CRP) < 2.0 mg/dL. Z scores of <−1.96 imply that TAS-118 is significantly superior to S-1 with a two-sided 5% significance level.

3. Results

3.1. Patients

Between July 2013 and August 2015, 603 patients were randomised to TAS-118 (n = 301) or S-1 (n = 302), and 296 patients in the TAS-118 group and 290 in the S-1 group were included in the full analysis set (Fig. 1).

Baseline characteristics were well balanced between treatment groups (Table 1). Some differences were observed between the two countries in age, PS and prior treatment (Supplementary Table S1). Baseline tumour burdens (target lesion, tumour diameter, number of metastatic sites and organs and CA19-9 level) tended to be larger in patients without pancreatic resection history than those with resection, especially among Japanese patients (Supplementary Table S2).

3.2. Efficacy

At the data cut-off date (10 May 2016), with a median follow-up time of 18.0 months, 514 events occurred (260

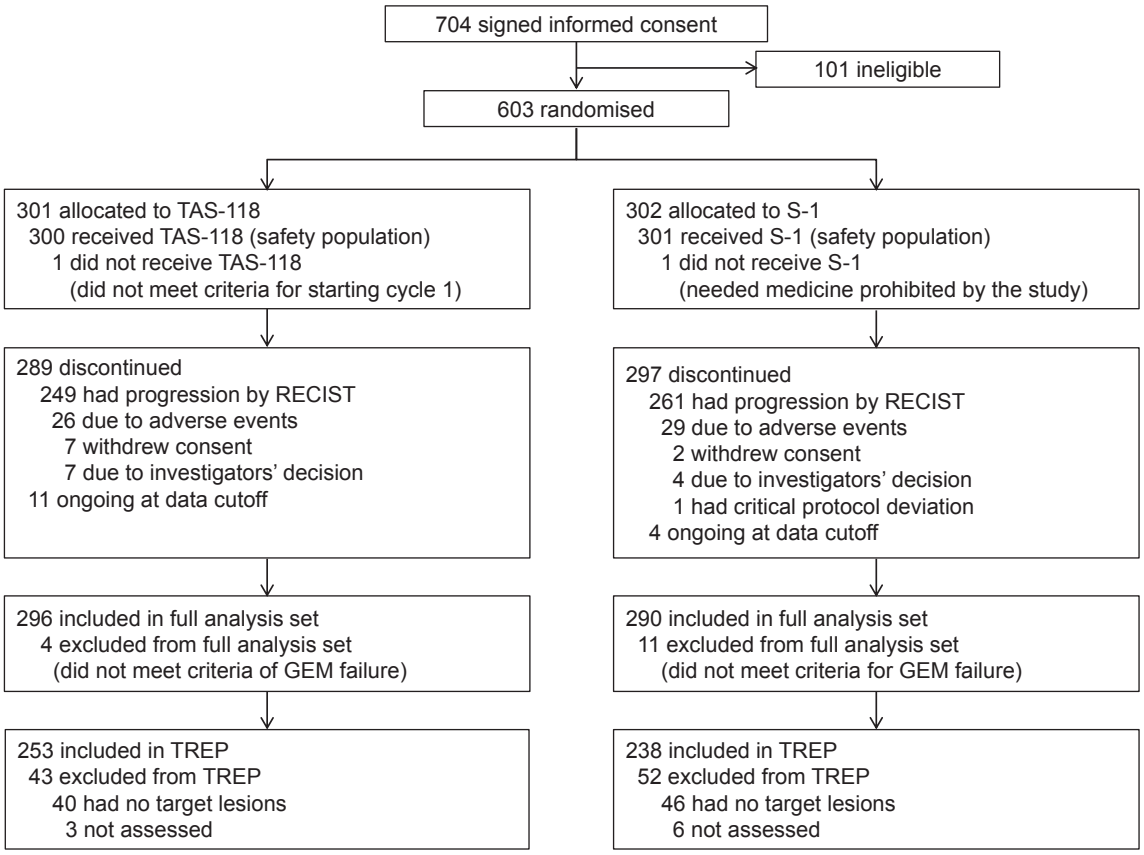

Fig. 1. Trial profile. GEM, gemcitabine; RECIST, Response Evaluation Criteria in Solid Tumours (version 1.1); TREP, tumour response-evaluable population.

and 254 in the TAS-118 and S-1 groups, respectively). Median OS was 7.6 months (95% confidence interval [CI], 7.0–8.2) in the TAS-118 group and 7.9 months (95% CI, 7.0–8.4) in the S-1 group (HR, 0.98 [95% CI, 0.82–1.16]; $P = 0.756$; Fig. 2A). PFS was significantly longer in the TAS-118 group than the S-1 group: 3.9 months (95% CI, 2.8–4.2) versus 2.8 months (95% CI, 2.7–2.9; HR, 0.80 [95% CI, 0.67–0.95]; $P = 0.009$; Fig. 2B). Post-study treatment was performed in 166 (56.1%) and 185 (63.8%) patients from the TAS-118 and S-1 groups, respectively (Supplementary Table S3). FOLFIRINOX was given to 24 (8.1%) and 28 (9.7%) patients, and gemcitabine plus nab-paclitaxel to 33 (11.1%) and 36 (12.4%) patients from the TAS-118 and S-1 groups, respectively. The proportion of patients with post-study treatment was smallest (42.6%) in the Korean TAS-118 group.

Forest plots of OS and PFS are shown in Fig. 3A and B. Factors favouring TAS-118 ($P < 0.1$) in terms of OS and PFS were country (Japan), age (<70 years), baseline CRP (<2.0 mg/dL) and HbA1c (<8%). The subgroup analyses of OS and PFS by country are summarised in Supplementary Tables S4–S5.

The prespecified subgroup analyses of OS and PFS by country (Japan/Korea) and history of pancreatic resection (±) are shown in Fig. 4A and B. Median OS of Japanese patients was 8.0 months (95% CI, 7.3–9.8) and 7.9 months (95% CI, 7.1–8.5) in the TAS-118 and S-1 groups, respectively (HR, 0.85 [95% CI, 0.70–1.04]; $P = 0.138$), while median OS of Korean patients was 6.0 months (95% CI, 5.0–7.0) and 7.4 months (95% CI, 5.4–8.8), respectively (HR, 1.57 [95% CI, 1.07–2.30]; $P = 0.027$; Fig. 4A). Median OS of patients without history of pancreatic resection was 7.3 months (95% CI, 6.4–7.9) and 7.4 months (95% CI, 6.4–8.1) in the TAS-118 and S-1 groups, respectively (HR, 0.85 [95% CI, 0.70–1.04]; $P = 0.129$), while median OS of patients with history of pancreatic resection was 8.7 months (95% CI, 7.1–11.2) and 9.4 months (95% CI, 8.1–12.6), respectively (HR, 1.51 [95% CI, 1.07–2.14]; $P = 0.050$; Fig. 4B). For Japanese patients without pancreatic resection, both OS and PFS showed trends favouring TAS-118 (Supplementary Table S6 and Supplementary Figs. S1a and S1b).

Z scores differed substantially between two countries, favouring TAS-118 in Japanese patients but S-1 in Korean patients (Supplementary Fig. S2). In Japanese patients, Z scores of OS were below the significance limit of −1.96 in any combination of prespecified factors. Z scores of OS decreased with increasing number of prespecified factors. In Korean patients, Z scores of OS and PFS were not correlated with the number of prespecified factors.

Table 1
Baseline characteristics.

Characteristics	TAS-118 (n = 296)	S-1 (n = 290)
Sex		
Male	173 (58.4%)	167 (57.6%)
Female	123 (41.6%)	123 (42.4%)
Age (y)		
Median (range)	65 (30–79)	64 (32–79)
Country		
Japan	235 (79.4%)	231 (79.7%)
Korea	61 (20.6%)	59 (20.3%)
ECOG performance status		
0	169 (57.1%)	161 (55.5%)
1	127 (42.9%)	129 (44.5%)
Site of primary lesion		
Head	128 (43.2%)	135 (46.6%)
Other	168 (56.8%)	155 (53.4%)
Pancreatic resection		
No	211 (71.3%)	209 (72.1%)
Yes	85 (28.7%)	81 (27.9%)
Measurable lesion[a]		
No	40 (13.5%)	46 (15.9%)
Yes	256 (86.5%)	244 (84.1%)
Number of metastatic sites[b]		
0	1 (0.3%)	0 (0.0%)
1	136 (45.9%)	117 (40.3%)
2	100 (33.8%)	103 (35.5%)
≥3	59 (19.9%)	70 (24.1%)
Metastatic site		
Liver	194 (65.5%)	185 (63.8%)
Lung	82 (27.7%)	99 (34.1%)
Peritoneum	71 (24.0%)	67 (23.1%)
Previous treatment		
Gemcitabine-based chemotherapy	212 (71.6%)	209 (72.1%)
Resection plus gemcitabine-based chemotherapy	84 (28.4%)	81 (27.9%)
Albumin (g/dL)		
Median (range)	4.0 (3.1–4.9)	3.9 (3.1–4.9)
C-reactive protein		
<2.0 mg/dL	269 (90.9%)	271 (93.4%)
≥2.0 mg/dL	27 (9.1%)	19 (6.6%)
Baseline HbA1c		
<8%	263 (89.5%)	269 (93.4%)
≥8%	31 (10.5%)	19 (6.6%)

ECOG, Eastern Cooperative Oncology Group; HbA1c, glycated hemoglobin; RECIST, Response Evaluation Criteria in Solid Tumours.
Data are n (%), unless otherwise stated.
Analysis set: full analysis set.
[a] Assessed according to RECIST version 1.1.
[b] Including target lesions and non-target lesions assessed according to RECIST version 1.1.

ORRs were 20.6% and 15.1% (P = 0.127), and DCRs were 67.2% and 59.2% (P = 0.075) in the TAS-118 and S-1 groups, respectively.

3.3. Safety

Common AEs (≥10%) are listed in Table 2. The most common AEs in the TAS-118 group were decreased appetite (58.0%), stomatitis (50.3%) and diarrhoea (48.7%), and those in the S-1 group were decreased appetite (54.8%), diarrhoea (42.5%) and nausea (40.5%). The numbers of patients who discontinued the study treatment due to AEs were 26 (8.7%) and 29 (9.6%) in the TAS-118 and S-1 groups, respectively (Fig. 1). Dose reduction due to AEs was reported in 108 (36.0%) and 45 (15.0%) patients from the TAS-118 and S-1 groups, respectively. AEs leading to death were observed in 16 (5.3%) and 12 (4.0%) patients from the TAS-118 and S-1 groups, respectively; only one event (hepatic dysfunction) in the TAS-118 group was judged to be treatment related.

Median relative dose intensity was 90.7% and 94.0% in the TAS-118 and S-1 groups, respectively. No differences were observed between the countries (Supplementary Table S7).

4. Discussion

This study was one of the largest phase 3 studies of patients with gemcitabine-refractory advanced pancreatic cancer. TAS-118 did not significantly improve OS, but modestly improved PFS. There are some possible reasons for not meeting the primary objective.

OS in both treatment groups was longer than expected, decreasing the statistical power. Median OS in this study was longer than reported in other studies of second-line chemotherapy [5,6], including our previous phase 2 study [12]. Baseline characteristics in this study were better than those in other studies. For example, the eligibility criteria of this study required serum albumin ≥3.5 g/dL compared to ≥3.0 g/dL in the NAPOLI-1 study and our previous phase 2 study [6,12]. Also, measurable lesions were required in our previous phase 2 study, but not in this study. Only one prior chemotherapy was allowed in this study, while over 30% of patients received two or more lines of prior chemotherapies in NAPOLI-1. These differences may partially explain the longer OS in this study. Post-study treatment might contribute to prolonged OS. Approximately 60% of patients received post-study treatment, compared with <40% in NAPOLI-1 [6]. Furthermore, approximately 10% of patients were treated with FOLFIRINOX and gemcitabine plus nab-paclitaxel. Hence, the significant prolongation of PFS with TAS-118 might not be translated into OS improvement.

There was a substantial interaction in the counties regarding the efficacy of TAS-118 and S-1 on OS; survival benefit of TAS-118 was suggested in the Japanese patients but not in the Korean patients. OS appeared to be shorter in the Korean patients than the Japanese patients as we expected when designed this study (Fig. 4A). Korean patients showed worse PS and higher CRP levels than Japanese patients at baseline. Treatment history with gemcitabine differed slightly between the two countries; more Japanese patients received treatment for initially unresectable disease, more

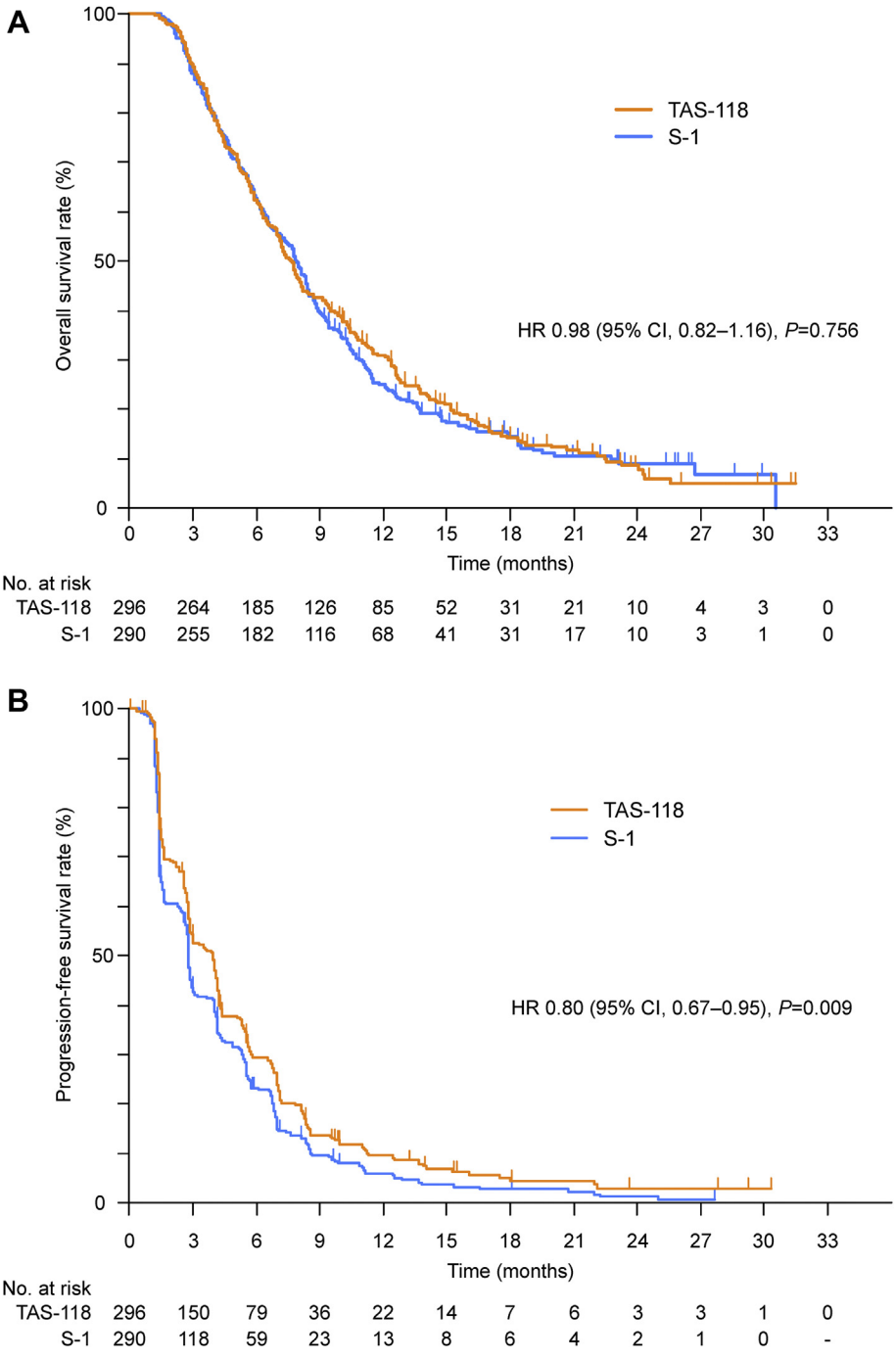

Fig. 2. Kaplan–Meier curve of (A) overall survival and (B) progression-free survival. CI, confidence interval; HR, hazard ratio.

Korean patients received adjuvant chemotherapy after pancreatic resection and more Korean patients received combination therapy as first-line treatment. These differences would be associated with shorter survival in Korean patients, and some factors might generate an interaction of efficacy in the two countries.

Pancreatic resection history is known to be a prognostic factor [14]. Patients with initially unresectable disease generally have larger tumour burdens than those with recurrent disease. Indeed, OS was longer in patients with prior pancreatic resection than those with initially unresectable patients (Fig. 4b). This trend was observed in both countries. The subgroup of Japanese patients without pancreatic resection showed significant OS improvement with TAS-118 compared to S-1, whereas the subgroup with pancreatic resection showed no improvement in OS with TAS-118 (Supplementary Fig. S1a). There was no difference of OS between TAS-118 and S-1 in the Korean patients without pancreatic resection, while OS in TAS-118 was rather

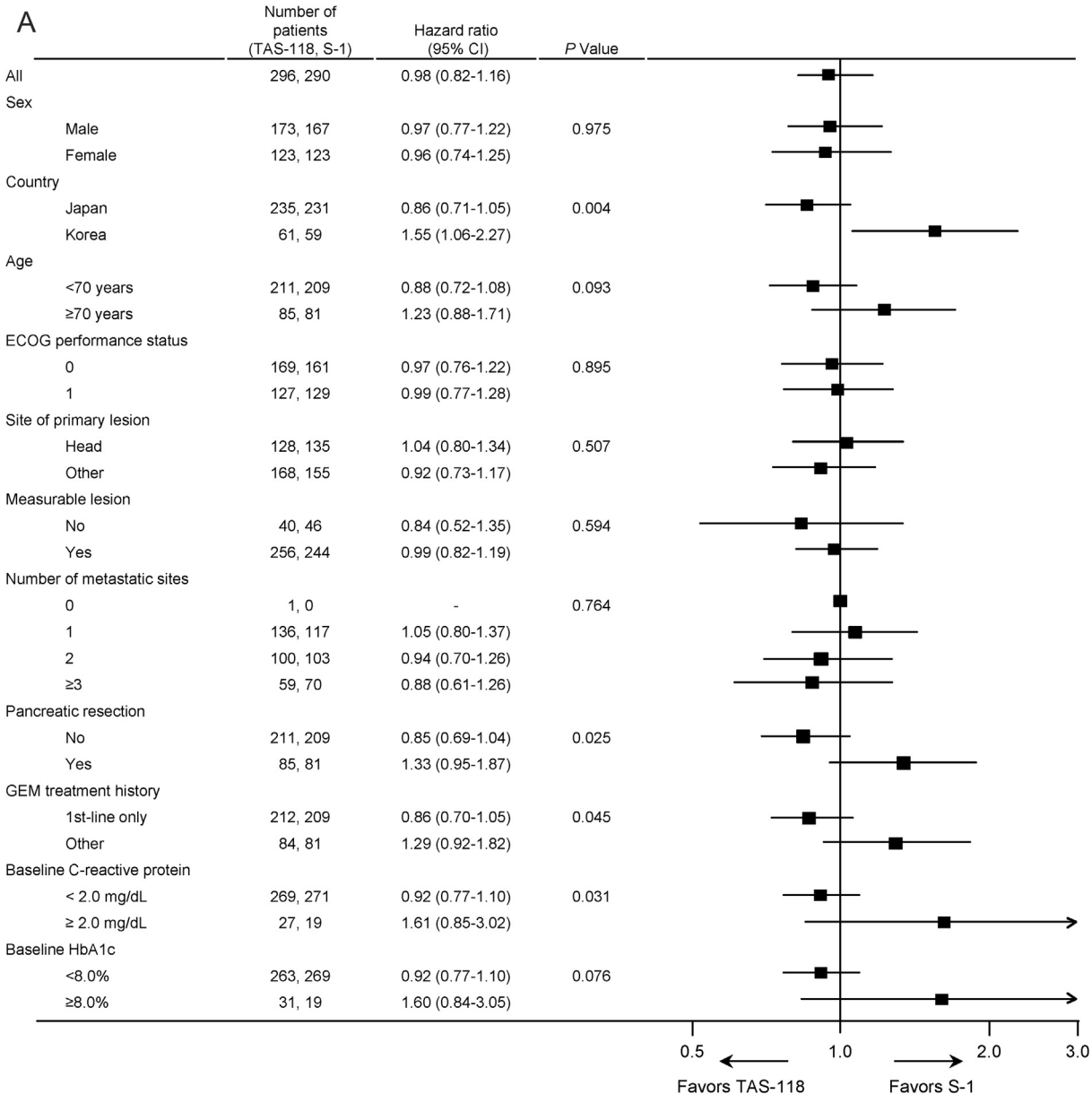

Fig. 3. Forest plot of (A) overall survival and (B) progression-free survival. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; HbA1c, glycated hemoglobin.

worse in those with pancreatic resection (Supplementary Fig. S1b). NAPOLI-1 also reported that OS in the experimental nanoliposomal irinotecan arm was shorter than in the control arm (HR = 1.23) in patients with pancreatic resection [6]. In our study, half of the Korean patients had undergone pancreatic resection, compared to only 23% of the Japanese patients. This might account for efficacy differences between the two countries, although persuasive explanation is difficult why such efficacy differences occurred between patients with and without pancreatic resection. Considering such a similar result in different trials, intensive chemotherapy may have adverse impacts on survival of patients with pancreatic resection. In future study designs, pancreatic resection history should be considered as an important factor that influences treatment efficacy.

The Z score analysis was preplanned to explore the reasons for regional differences in the efficacy of TAS-118 versus S-1. Z scores of Japanese patients with TAS-118 showed longer OS and PFS in all subgroups classified by combination of the prespecified factors, and Korean patients showed even shorter OS and PFS in all subgroups. Thus, there might be other factors than those expected affecting the efficacy of TAS-118.

The safety profiles of TAS-118 and S-1 were consistent with previous reports of S-1/LV or S-1 alone [10–12], and both treatments were well tolerated. The toxicities of TAS-118 were well managed by appropriate

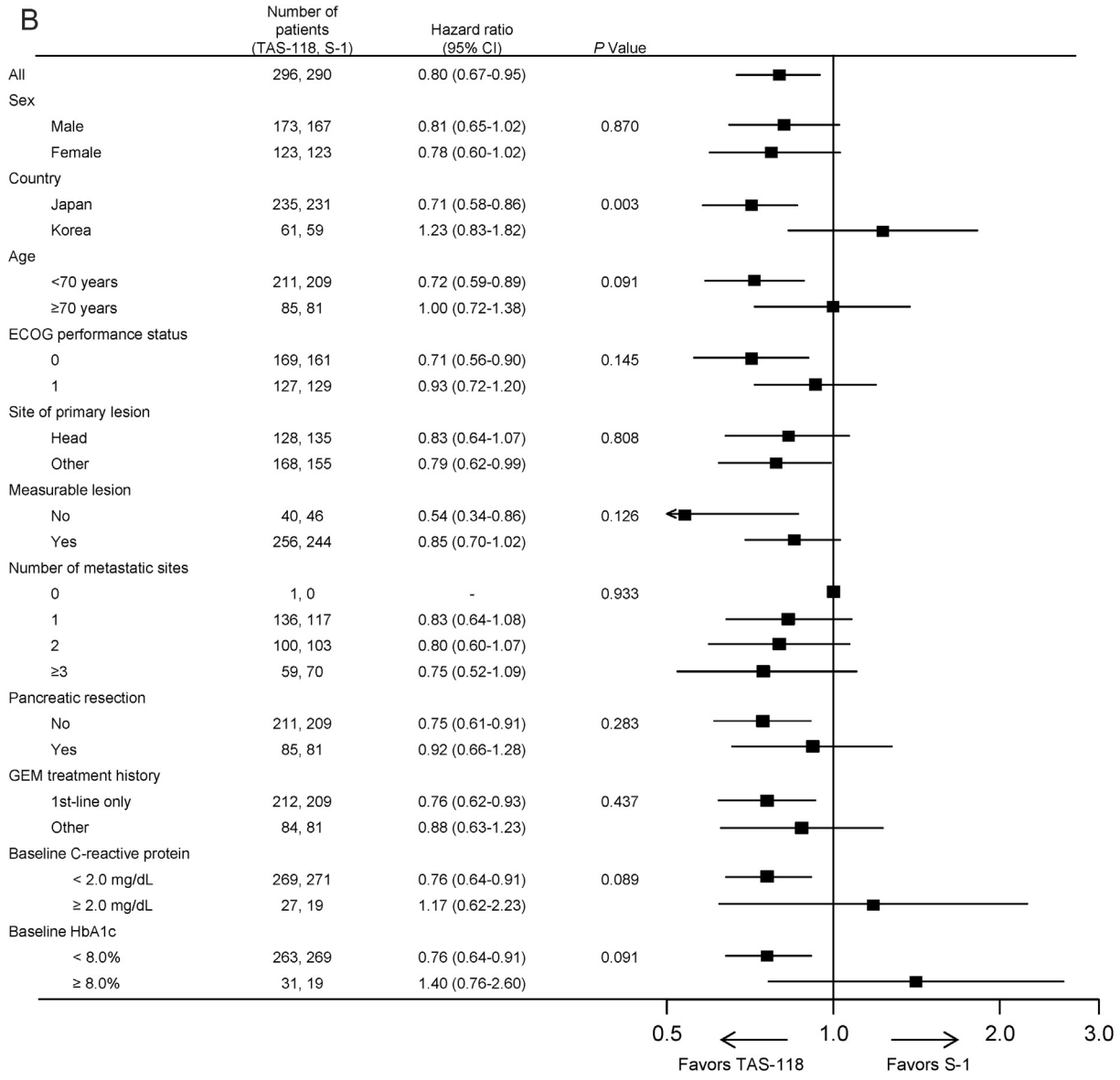

Fig. 3. (*continued*).

dose reduction. Given the increasing number of patients who receive intensive first-line treatment with nab-paclitaxel- or oxaliplatin-containing regimens, a less toxic regimen with substantial efficacy can be an option for second-line treatment.

In conclusion, despite the modestly prolonged PFS obtained with TAS-118, OS was not improved. The subgroup analyses suggested that TAS-118 might be more effective than S-1 in some populations. Further studies are warranted to determine optimal use of TAS-118.

Conflict of interest

T.I. reports honoraria from Shire, Daiichi-Sankyo, Taiho, AstraZeneca, Otsuka, Chugai, Yakult and Mochida; and research funding from AstraZeneca, Sumitomo Dainippon, Baxalta/Shire, Eisai, Taiho and Incyte. M.U. reports honoraria from Taiho, Eli Lilly, Yakult, Teijin, Shire, Novartis, AstraZeneca, Ono and Eisai and research funding from Taiho, Shire, Daiichi-Sankyo, Eisai, AstraZeneca, Ono, MSD, Merck Serono, NanoCarrier, Sumitomo Dainippon and Incyte. H.U. reports honoraria from Taiho, Chugai and Yakult and research funding from Taiho, Eli Lilly, NanoCarrier and Baxalta. J.O.P. reports honoraria from Celgene and research funding from Celgene and AstraZeneca. H.M.C. reports honoraria and travel fee from Taiho and research funding from Celgene, Pharmacyclics, Taiho and Novartis. N.S. reports honoraria from Toshiba, Cook Medical and Boston Scientific and research funding from Zeria, Eisai, Kyowa Hakko Kirin, Baxalta and Taiho. M.K. reports stock ownership and patents from TheraBioPharma and honoraria and

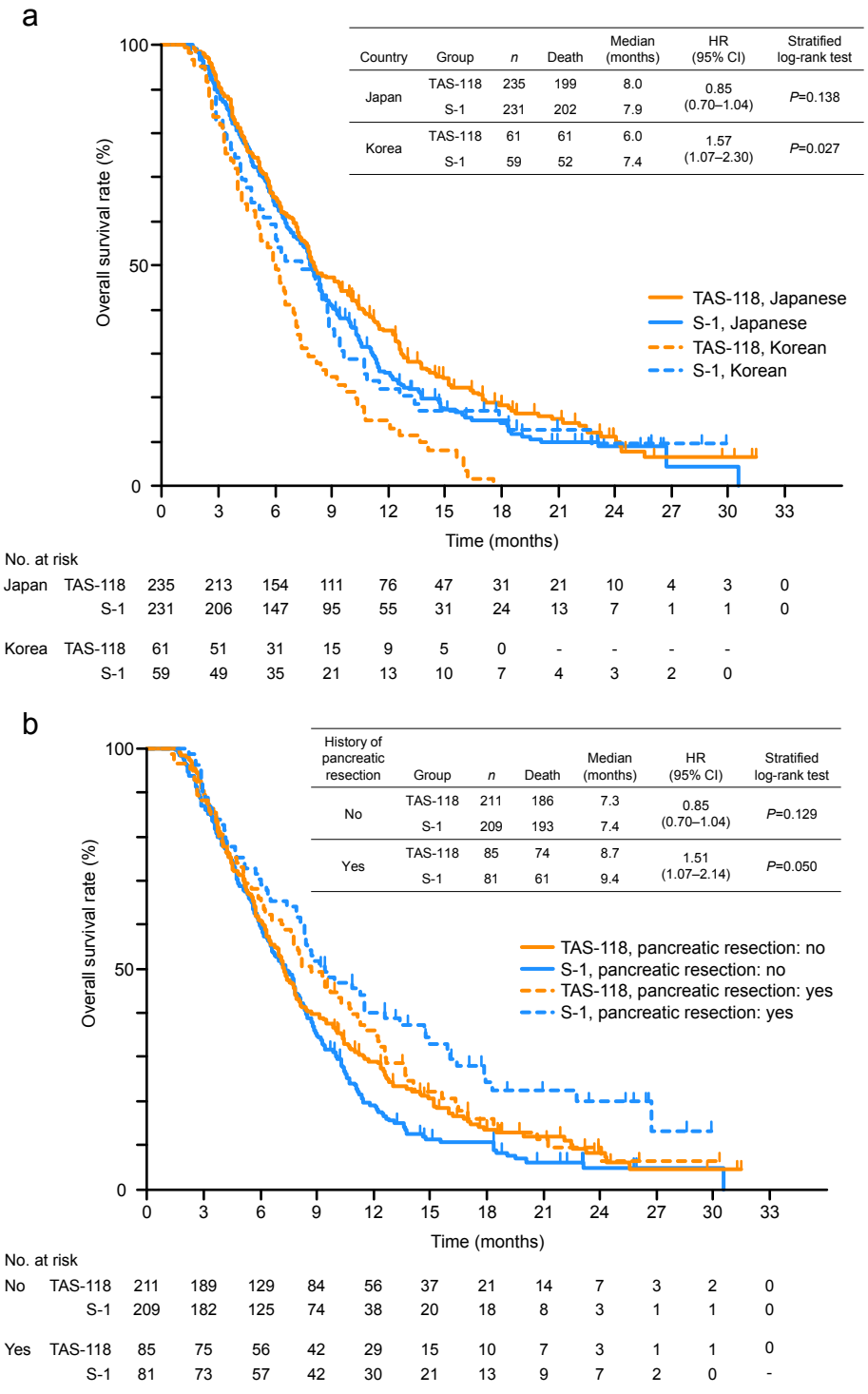

Fig. 4. Kaplan–Meier curves of overall survival by (A) country and (B) history of pancreatic resection. CI, confidence interval; HR, hazard ratio.

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Table 2
Commonly reported adverse events (≥10% of patients in either treatment group).

Adverse events	TAS-118 (n = 300)				S-1 (n = 301)			
	Any grade		≥Grade 3		Any grade		≥Grade 3	
Any event	300	(100.0%)	188	(62.7%)	293	(97.3%)	161	(53.5%)
Haematologic								
Anaemia	53	(17.7%)	18	(6.0%)	57	(18.9%)	26	(8.6%)
Neutropaenia	35	(11.7%)	5	(1.7%)	35	(11.6%)	10	(3.3%)
Leucocytopenia	35	(11.7%)	4	(1.3%)	38	(12.6%)	3	(1.0%)
Thrombocytopenia	33	(11.0%)	5	(1.7%)	46	(15.3%)	5	(1.7%)
Non-haematologic								
Decreased appetite	174	(58.0%)	28	(9.3%)	165	(54.8%)	21	(7.0%)
Stomatitis	151	(50.3%)	20	(6.7%)	84	(27.9%)	2	(0.7%)
Diarrhoea	146	(48.7%)	22	(7.3%)	128	(42.5%)	24	(8.0%)
Skin hyperpigmentation	122	(40.7%)	0	(0.0%)	85	(28.2%)	0	(0.0%)
Nausea	120	(40.0%)	5	(1.7%)	122	(40.5%)	2	(0.7%)
Malaise	101	(33.7%)	4	(1.3%)	85	(28.2%)	1	(0.3%)
Palmar-plantar erythrodysesthesia syndrome	72	(24.0%)	5	(1.7%)	35	(11.6%)	0	(0.0%)
Vomiting	71	(23.7%)	6	(2.0%)	70	(23.3%)	2	(0.7%)
Lacrimation increased	65	(21.7%)	1	(0.3%)	47	(15.6%)	1	(0.3%)
Dysgeusia	64	(21.3%)	0	(0.0%)	50	(16.6%)	0	(0.0%)
Fatigue	55	(18.3%)	3	(1.0%)	53	(17.6%)	2	(0.7%)
Pyrexia	51	(17.0%)	1	(0.3%)	52	(17.3%)	0	(0.0%)
Weight decreased	49	(16.3%)	6	(2.0%)	38	(12.6%)	3	(1.0%)
Constipation	41	(13.7%)	4	(1.3%)	42	(14.0%)	3	(1.0%)
Rash	37	(12.3%)	2	(0.7%)	21	(7.0%)	1	(0.3%)
Epistaxis	35	(11.7%)	0	(0.0%)	15	(5.0%)	0	(0.0%)
Hypoalbuminaemia	32	(10.7%)	10	(3.3%)	33	(11.0%)	5	(1.7%)
Abdominal pain	31	(10.3%)	7	(2.3%)	35	(11.6%)	4	(1.3%)
Oedema peripheral	31	(10.3%)	0	(0.0%)	20	(6.6%)	0	(0.0%)
Dry skin	31	(10.3%)	0	(0.0%)	18	(6.0%)	0	(0.0%)
Insomnia	30	(10.0%)	0	(0.0%)	20	(6.6%)	0	(0.0%)

Analysis set: safety population.

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Appendix A. Supplementary data

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