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Artigo Original

Meta-analysis of randomized phase II and phase III trials of gemcitabine with/without S-1 in Asian patients with advanced pancreatic cancer

Meta-análise de ensaios clínicos randomizados de fase II e III da gemcitabina com / sem S-1 em pacientes asiáticos com câncer pancreático avançado

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↗ Palavras-chave

gemcitabina; S-1; câncer pancreático; meta-análise; fase III

■ Resumo

Antecedentes: o câncer de pâncreas avançado (PC) é uma doença virulenta, onde gemcitabina é considerado o tratamento padrão de serviço. Recentemente, três estudos foram conduzidos, comparando com gemcitabina e sem S-1, um pró-fármaco por via oral 5-fluorouracil. Todos os três estudos demonstraram melhorias significativas na sobrevida livre de progressão (PFS), enquanto um estudo também mostrou uma melhoria estatisticamente significativa na sobrevida global (OS). Métodos: Foi realizada uma meta-análise dos três ensaios. Resultados: setecentos e setenta pacientes foram randomizados para receber gencitabina / S-1 (GS) versus gemcitabina; 75% tinham doença metastática e 65% tinham um status Cooperative Oncology Group Oriente desempenho (ECOG PS) de 0. GS foi associado com RR superiores (hazard ratio (HR) 0,348, p = 3,06 × 10-7), PFS (HR 0,64 , p = 7,26 × 10-9) e OS (HR 0,79, p = 2,47 × 10-2) em comparação com gemcitabina. Os pacientes que recebem GS eram mais propensos a sentir náuseas, diarreia, erupção cutânea e estomatite (principalmente de grau 1/2); neutropenia febril ocorreu em <2% dos pacientes. Um estudo demonstrou qualidade de vida superior para GS. Conclusão: GS deve ser considerada uma opção de primeira linha para o tratamento de PC avançado em pacientes asiáticos. Este regime deve servir como referência para estudos futuros e comparação com o regime FOLFIRINOX, o tratamento padrão-de-corrente, em pacientes com ECOG PS ≤ 1 se justifica.

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↗ Keywords

gemcitabine; S-1; pancreatic cancer; meta-analysis; phase III

■ Abstract

Background: Advanced pancreatic cancer (PC) is a virulent disease, where gemcitabine is considered the standard-of-care. Recently, three studies were conducted, comparing gemcitabine with and without S-1, an oral 5-fluorouracil prodrug. All three trials demonstrated significant improvements in progression-free survival (PFS) while one study also showed a statistically significant improvement in overall survival (OS). Methods: We performed a meta-analysis of the three trials. Results: Seven hundred and seventy patients were randomized to receive gemcitabine/S-1 (GS) vs. gemcitabine; 75% had metastatic disease and 65% had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0. GS was associated with superior RR (hazard ratio (HR) 0.348, p=3.06×10-7), PFS (HR 0.64, p=7.26×10-9) and OS (HR 0.79, p=2.47×10-2) compared to gemcitabine. Patients receiving GS were more likely to experience nausea, diarrhea, rash and stomatitis (mostly grade 1/2); neutropenic fever occurred in <2% of patients. One study demonstrated superior quality-of-life for GS. Conclusion: GS should be considered a first-line option for the treatment of advanced PC in Asian patients. This regimen should serve as the reference for future trials and comparison with the FOLFIRINOX regimen, the current standard-of-care, in patients with ECOG PS ≤ 1 is warranted.

■ Introduction

Advanced pancreatic cancer (PC) is a virulent disease associated with poor survival. While gemcitabine monotherapy has long been considered the standard-of-care,(Burris *et al*, 1997) multiple phase III evaluations that have attempted to combine additional cytotoxic drugs and targeted therapies with gemcitabine have been uniformly disappointing.(Stathis & Moore) The only other medication approved by the U.S. Food and Drug Administration is erlotinib; unfortunately, the combination only improves median overall survival (OS) by approximately two weeks compared to gemcitabine alone, without improving response rates (RRs) or progression-free survival (PFS).(Moore *et al*, 2007) A recent phase III evaluation did demonstrate superiority of FOLFIRINOX, a regimen of bolus and infusional 5-fluorouracil (5-FU), irinotecan and oxaliplatin, over gemcitabine.(Conroy *et al*) However, FOLFIRINOX is associated with significant toxicity and the study was restricted to patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤1.

At the 2011 Annual meeting of the American Society of Clinical Oncology (ASCO), the results of three trials comparing gemcitabine vs. gemcitabine/S-1 in East Asian patients with advanced PC were reported in abstract form and were subsequently published.(Ioka *et al*, 2011; Isayama *et al*, 2011; Omuro *et al*, 2011) S-1 is a mixture of tegafur (an oral 5-FU prodrug), gimeracil (a dihydropyrimidine dehydrogenase or DPD inhibitor that may potentiate the effect of 5-FU) and oteracil (which may reduce the gastrointestinal toxicity of 5-FU). The GEST is a phase III evaluation designed to detect an improvement in OS for gemcitabine/S-1 over gemcitabine. The GEMSAP and Japan Clinical Cancer Research Organization (JACCRO) studies are randomized phase II evaluations statistically powered to detect an improvement in PFS and RR respectively for the combination. The GEST and GEMSAP trials suggested a trend toward superior OS for gemcitabine/S-1 (with clear improvements in PFS in both studies) while the JACCRO study demonstrated clear RR, PFS and OS improvements for the combination. Both the GEMSAP and JACCRO studies met their primary end-points; the GEST study included a third arm of S-1 monotherapy, which met the co-primary end-point of non-inferiority compared to gemcitabine. We performed a meta-analysis of the three trials, based on the presented and published data.

■ Methods

Study selection

We performed search of several engines, including Pubmed, Embase, Lilacs and the Johns Hopkins University Medical Library using the keywords "pancreatic cancer", "gemcitabine" and "S-1", limiting the results to randomized clinical trials. This yielded no relevant searches. We then identified the three abstracts presented at the 2011 ASCO meeting and followed them until subsequent publication. These trials enrolled patients with either locally advanced/inoperable or metastatic PC. Patients in the GEST study had an ECOG PS of ≤1 while the GEMSAP and JACCRO studies enrolled patients with ECOG PS of ≤2.

All of the patients in the control arm received gemcitabine 1,000 mg/m^2 I.V. over 30 minutes on Days 1, 8 and 15 every 28 days. Patients in the experimental arm of the GEMSAP study received gemcitabine 1,000 mg/m^2 I.V. over 30 minutes on Days 1 and 15 of a 28-day cycle, along with S-1 40 mg/m^2 BID Days 1-14. The dose of S-1 was capped at 40, 50 or 60 mg BID if the body surface area (BSA) was <1.25 m^2, ≥1.25-<1.5 m^2 or ≥1.5 m^2 respectively. The experimental arms in the GEST and

JACCRO studies consisted of gemcitabine 1,000 mg/m^2 I.V. over 30 minutes on Days 1 and 8 of a 21-day cycle, along with S-1 40 mg/m^2 BID Days 1-14. In both studies, S-1 was administered at a dose of 30, 40 or 50 mg BID if the BSA was <1.25 m^2, ≥1.25-<1.5 m^2 or ≥1.5 m^2 respectively.

Statistical analysis

Woolf's test of heterogeneity was performed to determine if there was any heterogeneity across the studies in terms of RR, PFS, OS and adverse events rates. Data for RR, PFS and OS for the three trials were combined using the random effects model of DerSimonian and Laird. (DerSimonian & Laird, 1986) Overall log-odds ratios for adverse events were estimated using the Mantel-Haenszel procedure if there was not strong indication of heterogeneity. When there was evidence of heterogeneity in the odds ratios across the different studies, the Dersimonian and Laird model was used instead.

■ Results

Demographics

Overall, the three trials enrolled 389 patients with locally advanced or metastatic PC in the gemcitabine arms and 381 patients in the gemcitabine/S-1 arms. Patient demographics are listed in Table 1. The median age of patients ranged from 63 – 67 years in the three studies, the majority of patients was male (61%) and most had an ECOG PS of 0 (66%). While the GEMSAP and JACCRO studies permitted patients with ECOG 2, only four such patients were enrolled from both studies (H. Isayama and Y. Nakai, personal communication, July 2011). Seventy-five percent of patients had metastatic disease, with the liver being the most common site of metastasis (66% of patients with metastases).

Tabela 1. Patient demographics in the GEST, GEMSAP and JACCRO trials.

	Gemcitabine (n=389)	Gemcitabine/S-1 (n=381)
Age		
Median	64-67	63-65
Sex		
Male	237 (61%)	231 (61%)
Female	152 (39%)	150 (39%)
ECOG Performance status		
0	257 (66%)	248 (65%)
½	132 (34%)	133 (35%)
Stage		
Locally advanced	97 (25%)	97 (25%)
Metastatic	292 (75%)	284 (75%)
Metastatic sites*	(n=81)	(n=78)
Liver	56 (69%)	50 (64%)
Lymph node	28 (35%)	25 (32%)
Peritoneum	14 (17%)	16 (21%)
Lung	6 (7%)	5 (6%)

*Data on sites of metastases available only for GEMSAP and JACCRO studies.

ECOG, Eastern Cooperative Oncology Group performance status

Response rates (RRs)

Response and survival data are presented in Table 2.

Tabela 2. Response rates (RR), progression-free survival (PFS) and overall survival (OS) for the GEST, GEMSAP and JACCRO trials, as well as a phase III trial of gemcitabine vs. FOLFIRINOX.

Study	Drug	n	RR (%)	PFS* (mos)	OS (mos)
GEST (Ioka et al, 2011)	Gem	277	13	4.1	8.8
	Gem/S-1	275	29 (p<0.001)	5.7	10.1 (p=0.15)
GEMSAP (Isayama et al, 2011)	Gem	53	9.4	3.6	8.8
	Gem/S-1	53	18.9 (p=0.265)	5.4 (p=0.036)	13.5 (p=0.104)
JACCRO (Omuro et al, 2011)	Gem	59	6.8	4.7	8.3
	Gem/S-1	53	28.3 (p=0.005)	6.0 (p=0.001)	13.9 (p=0.033)

*In the JACCRO, time-to-progression was measured.

Gem, gemcitabine; mos, months; n, number

RRs for the gemcitabine arms ranged from 6.8 – 13% and were 18.9 – 29% in the gemcitabine/S-1 arms. In the individual studies, improvement in RR in the gemcitabine/S-1 arms was statistically significant in the GEST and JACCRO studies. Woolf's test of heterogeneity was performed and demonstrated a very low degree of heterogeneity in the odds ratios for RR (I^2 = 0%). When the odds ratios of the three studies were combined, the overall odds ratio estimate was 0.348 (95% CI 0.232-0.521; p=3.06×10^{-7}),

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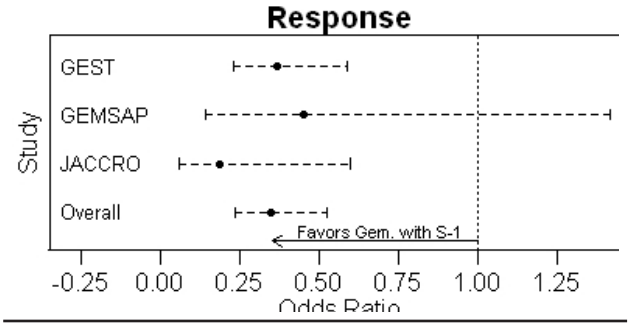
in favor of gemcitabine/S-1. Individual study and overall estimates and confidence intervals are summarized in Figure 1.

Figura 1. Individual study and overall estimates and confidence intervals for response rates.

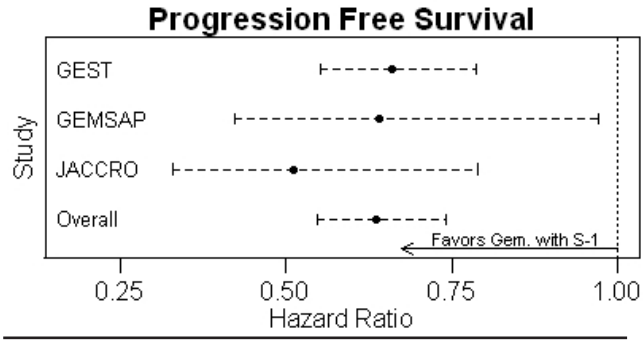


Progression-free survival (PFS)

The GEST and GEMSAP studies reported PFS, while the JACCRO study reported time-to-progression (TTP). In the gemcitabine arms, PFS/TTP was between 3.6 – 4.7 months; in the gemcitabine/S-1 arms, it ranged between 5.4 – 6 months. This difference was statistically significant in all three studies. Woolf's test of heterogeneity revealed a very low degree of heterogeneity in the odds ratios for PFS/TTP ($I^2 = 0\%$).

Analysis of PFS/TTP revealed an overall hazard ratio estimate of 0.64 (95% CI 0.55-0.74, $p=7.26\times10^{-9}$) in favor of gemcitabine/S-1 (Figure 2).

Figura 2. Individual study and overall hazard ratio estimates and confidence intervals for progression-free survival.

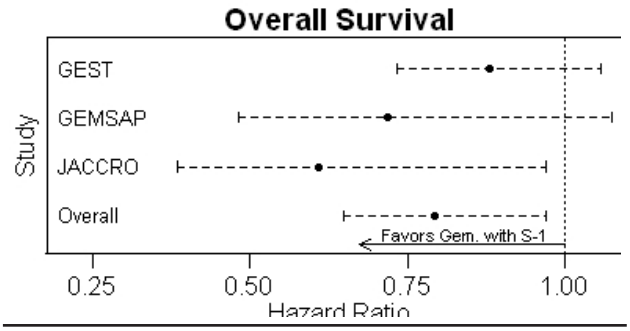


Overall survival (OS)

OS in the gemcitabine and gemcitabine/S-1 arms were between 8.3 – 8.8 months and 10.1 – 13.9 months respectively. The difference in OS between the treatment arms was significant in the JACCRO study but only showed a non-significant trend in the GEST and GEMSAP studies (p=0.15 and p=0.104 respectively). Woolf's test of heterogeneity revealed a small degree of heterogeneity in the odds ratios for OS between the three studies ($I^2 = 21.2\%$).

When OS data were combined, the overall hazard ratio estimate was 0.79 (95% CI 0.65-0.79, $p=2.47\times10^{-2}$) in favor of gemcitabine/S-1 (Figure 3).

Figura 3. Individual study and overall hazard ratio estimates and confidence intervals for overall survival.



Adverse events

Toxicities from the three studies are presented in Table 3.

In general, the toxicities seen in the gemcitabine/S-1 arms of the three studies were additive and are consistent with the expected toxicities of the individual drugs. Patients who received gemcitabine/S-1 were more likely to experience nausea, diarrhea, rash and stomatitis (mostly grade 1/2). Grade 3/4 neutropenia was reported in 33.3 – 62.2% of patients receiving gemcitabine/S-1 but neutropenic fever was extremely uncommon (<2% of patients in the GEST study) and not statistically different compared to the gemcitabine arm.

Quality-of-life (QoL)

QoL analyses performed in the GEST study demonstrate that patients treated with gemcitabine/S-1 had statistically significant superior QoL (assessed using the EQ-5D questionnaire) and quality-adjusted life years compared to those who received gemcitabine alone. (Ohashi et al, 2011)

■ Discussion

The results of this meta-analysis confirm the observations of the individual studies and suggest that gemcitabine/S-1 is associated with superior RR, PFS and OS compared to gemcitabine alone. The magnitude of the OS difference in the statistically significant JACCRO trial (5.6 months) is also highly clinically relevant and nearly identical to the OS difference in the GEMSAP trial, which only showed a non-significant trend toward improved OS (p=0.104). The largest of the three trials, the GEST study, demonstrated a non-significant trend toward a 1.3 month improvement in OS. One possibility for the lack of an OS benefit in the GEMSAP study for combination chemotherapy is that 58% of patients who

Tabela 3. Adverse events reported in the GEST, GEMSAP and JACCRO studies.

Adverse Event	GEST		GEMSAP (Nakai et al, 2010)		JACCRO study		Heterogeneity*	Odds ratio+ (95% CI; p-value)
	Gem	Gem/S-1	Gem	Gem/S-1	Gem	Gem/S-1		
Anorexia								
Any grade	57.8%	65.2%	51.9%	62.7%	33.9%	35.8%	p=0.81	0.74 (0.55-1.00; p=0.06)
Grade 3/4	7%	9%	9.6%	3.9%	1.7%	1.9%	p=0.40	0.90 (0.51-1.58; p=0.81)
Diarrhea								
Any grade	20.9%	37.8%	11.5%	33.3%	3.4%	18.9%	p=0.32	**0.38** (0.27-0.54; p <0.001)
Grade 3/4	1.1%	4.9%	0%	2%	0%	1.9%	p=0.80	**0.19** (0.05-0.65; p=0.007)
Fatigue								
Any grade	45.1%	65.9%	48.1%	39.2%	27.1%	32.1%	p=0.01	0.74‡ (0.34-1.58; p=0.43)
Grade 3/4	4.0%	4.9%	3.8%	2.0%	3.4%	0%	p=0.02	1.04 (0.50-2.20; p=0.91).
Neutropenia								
Any grade	68.1%	83.1%	61.5%	56.9%	33.9%	66.0%	p=0.02	0.51‡ (0.24-1.07; p=0.07)
Grade 3/4	41.0%	62.2%	34.6%	33.3%	18.6%	52.8%	p=0.02	**0.45**‡ (0.21-0.95; p=0.04)
Neutropenic fever	0.4%	1.9%	N/A				0.19 (0.004-1.74)	
Nausea								
Any grade	42.9%	55.1%	34.6%	35.3%	15.3%	22.6%	p=0.58	**0.65** (0.48-0.88; p=0.006)
Grade 3/4	1.8%	4.9%	0%	2.0%	1.7%	0%	p=0.26	0.41 (0.15-1.07; p=0.10)
Rash								
Any grade	27.8%	40.8%	9.6%	21.6%	13.6%	50.9%	p=0.03	**0.34**‡ (0.15-0.79; p=0.01)
Grade 3/4	1.1%	4.1%	0%	3.9%	0%	1.9%	p=0.67	**0.20** (0.06-0.71; p=0.01)
Stomatitis								
Any grade	13.9%	34.1%	9.6%	25.5%	3.4%	26.4%	p=0.36	**0.28** (0.19-0.42; p <0.001)
Grade 3/4	0%	1.9%	0%	5.9%	0%	0%	N/A	**0** (0-0.57; p=0.003)

*Heterogeneity was determined using Woolf's test; +Unless otherwise indicated, dds ratios were combined using the Mantel-Haenszel procedure;
‡Odds ratios were combined using the DerSimonian and Laird model because of the heterogeneity in odds ratios across studies.
Odds ratios in **bold** are statistically significant

were treated with gemcitabine initially subsequently received S-1 at progression (H. Isayama and Y. Nakai, personal communication, July 2011). The use of S-1 in the second-line setting may therefore mask an OS advantage.

These results are similar to a prior meta-analysis of gemcitabine/capecitabine (another 5-FU prodrug) vs. gemcitabine, although none of those individual trials actually demonstrated an actual OS benefit for the doublet.(Cunningham et al, 2009) In a phase III evaluation that was part of this meta-analysis, Cunningham and colleagues randomized 533 patients with locally advanced or metastatic disease and an ECOG PS of ≤2. While there were statistically significant improvements in RR (12.4 vs. 19.1%) and PFS (3.8 vs. 5.3 months), there was only a trend toward improved OS (6.2 vs. 7.1 months, p=0.08), with the magnitude of the difference in OS (0.9 months) being relatively small

While comparisons between phase III studies are always undertaken with caution, it is potentially hypothesis-generating to compare the gemcitabine/capecitabine trials with the current gemcitabine/S-1 trials. Of course, one obvious explanation for the OS benefit of the small JACCRO study and the overall trend of this meta-analysis is that S-1 is superior to capecitabine. S-1 was specifically developed to enhance the anti-neoplastic activity of 5-FU by combining tegafur, another oral 5-FU prodrug, with a DPD inhibitor, which prevents the breakdown of 5-FU. Capecitabine has never been compared directly with S-1 but randomized evaluations of infusional 5-FU and S-1 in advanced gastric and colon cancers have suggested comparable efficacy. (Ajani et al; Boku et al, 2009; Muro et al) Another possibility is the difference in baseline prognostic factors of patients enrolled on these trials. While most factors (e.g. age, locally advanced vs. metastatic disease,

metastatic sites) appear balanced, the patients enrolled on the gemcitabine/S-1 studies appear to have better PS compared to those enrolled in the study by Cunningham et al. (65% with ECOG PS 0 vs. 23%). This difference in the proportion of patients with good PS is potentially important, since the other negative phase III evaluation of gemcitabine/capecitabine by Hermann et al. suggested that patients with a Karnofsky performance status (KPS) ≥90% had superior OS when capecitabine was added. (Herrmann et al, 2007)

The other notable meta-analysis that has demonstrated a benefit for a gemcitabine doublet was performed by Heinemann et al.(Heinemann et al, 2008) They combined five trials that evaluated combinations of gemcitabine with either cisplatin or oxaliplatin. None of these five trials revealed an OS benefit for doublet chemotherapy, while only two of the five trials revealed statistically significant improvements in RR and PFS. When the results of the trials were combined, there was an improvement in OS (HR=0.85, p=0.01). This meta-analysis of 15 trials overall also suggested that only patients with good PS (ECOG ≤1 or KPS ≥90%) appear to benefit from combination chemotherapy.

It is important to note that the results of this meta-analysis are applicable only to East Asian patients because of ethnic variations in the pharmacokinetics and maximum-tolerated dose (MTD) of S-1. CYP2A6 of the cytochrome P450 enzyme family in the liver has been identified as the principal enzyme responsible for the conversion of tegafur to 5-FU. Different polymorphisms of the CYP2A6 gene exist amongst Asians and Caucasians, which are hypothesized to lead to more rapid conversion of tegafur to 5-FU in Caucasians, resulting in a higher area-under-the-curve and more drug toxicity.(Ajani et al, 2005) As a result, the MTDs of S-1 in combination chemotherapy or monotherapy for advanced gastric cancer are lower in American and European patients than in Japanese patients.(Ajani et al, 2005; Chollet et al, 2003) Determination of the MTD of the gemcitabine/S-1 doublet and assessment of its efficacy in a non-East Asian population are therefore required before these findings can be generalized.

Finally, it is appropriate to comment on the recent phase III study of FOLFIRINOX vs. gemcitabine for patients with metastatic disease and an ECOG PS of ≤1.(Conroy et al) This important French study reported an improvement in RR (31.8% vs. 11.3%) and median PFS (6.4 vs. 3.3 months) and OS (11.1 vs. 6.8 months) for the FOLFIRINOX group. As would be expected, toxicity was significantly greater in the FOLFIRINOX arm even in this highly selected population. Grade 3/4 neutropenia was reported in 46% of patients, while neutropenic fever occurred in 5.4% of patients. Other common grade 3/4 toxicities included fatigue (24%), vomiting (15%) and diarrhea (13%). Unfortunately, an indirect comparison with the studies in this meta-analysis is difficult as approximately one-fourth of these patients had locally advanced disease. At a minimum, it does seem likely that FOLFIRINOX is associated with more toxicity than gemcitabine/S-1. Furthermore, a recent presentation at the 2013 Gastrointestinal Cancers Symposium and 2013 ASCO annual meeting showed that the combination of nab-paclitaxel and gemcitabine also improves outcomes when compared to gemcitabine alone.

Clearly, a major limitation of this meta-analysis is that it was performed on abstracted data rather than individual patient data. The limitations of such a meta-analysis are well-known and include an inability to verify and update patient data as well as a limited ability to calculate overall PFS and OS.(Piedbois & Buyse, 2004). Finally, both the GEMSAP and JACCRO studies are relatively small (with only approximately 100 patients each) and even small imbalances in unmeasured prognostic factors could have affected the outcomes. In this respect, the lack of inter-trial heterogeneity and the consistent overall trend of all three studies should provide some reassurance.

Based on the results of this meta-analysis and on the significant improvement in QoL with the doublet over gemcitabine, gemcitabine/S-1 should be considered a first-line option for the treatment of advanced PC in Asian patients, especially those who are not good candidates for FOLFIRINOX. Because of its acceptable toxicity profile, future trials should use gemcitabine/S-1 as a chemotherapy backbone to which novel targeted therapies may be added. A randomized comparison of gemcitabine/S-1 to FOLFIRINOX and/or to gemcitabine/nab-paclitaxel in patients with good PS is also warranted to establish the superior regimen.

Running head: Gemcitabine/S-1 in pancreatic cancer

Conflicts of interest

Dr Ioka reports receiving research support from Taiho, Chugai-Roche and Yakult.

Dr Lopes reports receiving honoraria from Taiho and Eli Lilly.

Drs Ku, Haaland, Isayama, Nakai, Cheng and Okusaka do not have any relevant disclosures.

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