Table 6 Ongoing RCTs with PSK

Title of the study	Organizations/sponsors	Tumor	Stage	Treatment regimen
Randomized controlled study of postoperative adjuvant therapy for gastric cancer using TS-1 or TS-1 + PSK	Hokuriku-Kinki Immunochemotherapy Study Group Gastric Cancer (HKIT-GC)	Gastric cancer	II, IIIA	TS-1(1 year) TS-1+PSK (1 year)
Study of TS-1 or TS-1 + PSK for gastric cancer patients	Tokyo Metropolitan Oncology Group (TMOG)	Gastric cancer	II, III	TS-1 (1 year) TS-1+PSK (1 year)
Randomized phase III adjuvant study for stage III colorectal cancer	Hokkaido Gastrointestinal Cancer Study Group, Colorectal Adjuvant Chemotherapy Division (HGCSG-CAD)	Colorectal cancer	III	UFT + LV (5 courses) UFT + LV (5 courses)/UFT (1 year) UFT + LV + PSK (5 courses)/UFT + PSK (1 year)
Uracil and tegafur/leucovorin (UFT/LV) versus UFT/LV+PSK for stage IIIa/IIIb colorectal cancer	Iwate Clinical Oncology Group, Colorectal Cancer (ICOG-CC)	Colorectal cancer	IIIa, IIIb	UFT + LV UFT + LV + PSK
Phase III trial comparing UFT + PSK to UFT + LV in stage IIB, III colorectal cancer	Multicenter Clinical Study Group of Osaka, Colorectal Cancer Treatment Group (MCSGO-CCTG)	Colorectal cancer	IIB, III	UFT+PSK (1 year) UFT+LV (6 months)
Phase III trial comparing surgery alone to UFT + PSK in stage II rectal cancer	Japanese Foundation for Multidisciplinary Treatment of Cancer	Rectal cancer	II	Surgery alone UFT + PSK (1 year)

TS-1 tegafur–gimeracil–oteracil potassium, *UFT* tegafur-uracil, *LV* leucovorin

stage II or III colorectal cancer. Two weeks after intravenous MMC (given on the day of surgery and the following day), one group received oral UFT and PSK 3 g/day for 2 years (chemotherapy + PSK group), and the other group received oral UFT alone (chemotherapy group). Ohwada et al. [92] have reported that the 5-year DFS rate was significantly ($P = 0.016$) higher in the chemotherapy + PSK group (73.0%) compared with the chemotherapy group (58.8%). Combined therapy with PSK reduced the risk of recurrence by 43.6%. The mean DFS period was significantly ($P = 0.031$) prolonged in the chemotherapy + PSK group (50.3 months) compared with the chemotherapy group (40.0 months). The 5-year OS rate was higher in the chemotherapy + PSK group (81.8%) than in the chemotherapy group (72.1%), although there was no significant difference ($P = 0.056$). Furthermore, they reported an adverse event rate of 15.1% for both groups, with no grade 3 or 4 events. They concluded that, compared with combined intravenous 5-FU and leucovorin (LV) treatment, for which many grade 3 or higher adverse events have been reported, UFT + PSK therapy was a useful adjuvant therapy that did not require frequent hospital visits and had few adverse reactions.

Sakamoto et al. [93] have performed a meta-analysis of three RCTs that were conducted and published between 1980 and 2004 on curatively resected colorectal cancer patients and compared chemotherapy + PSK with chemotherapy alone. The overall survival risk ratio was 0.71 (95% CI 0.55–0.90, $P = 0.006$) and the DFS risk ratio was 0.72 (95% CI 0.58–0.90, $P = 0.003$), which showed a significant survival benefit of combined therapy with PSK (Fig. 7). Their study confirms the significance of using PSK in postoperative adjuvant therapy for colorectal cancer and opens the possibility of developing improved therapy for colorectal cancer.

Several ongoing studies on PSK have been examining various combination therapy regimens used as postoperative adjuvant therapy. The Hokkaido Gastrointestinal Cancer Study Group, Colorectal Adjuvant Chemotherapy Division (HGCSG-CAD) has been comparing 6 months UFT + LV therapy (UFT + LV group), 6-month UFT + LV with UFT extended for 1 year (UFT + LV/UFT

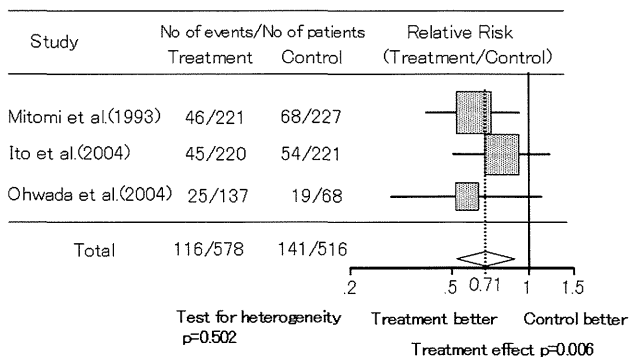

Fig. 7 Meta-analysis of the effect of adjuvant immunochemotherapy with PSK on OS in patients with colorectal cancer after curative resection. Adapted from Sakamoto et al. [93]

group), and PSK added on to the latter regimen (UFT + LV + PSK/UFT + PSK group) in patients with curatively resected stage III colorectal cancer (http://clinicaltrials.gov/ct2/home). The Iwate Clinical Oncology Group, Colorectal Cancer (ICOG-CC) trial has been comparing UFT + LV with UFT + LV + PSK in patients with curatively resected stage IIIa and IIIb colorectal cancer (http://clinicaltrials.gov/ct2/home). The Multicenter Clinical Study Group of Osaka, Colorectal Cancer Treatment Group (MCSGO-CCTG) has been comparing UFT + PSK (1 year) with UFT + LV (6 months) in patients with curatively resected stage IIB and III colorectal cancer (http://clinicaltrials.gov/ct2/home). In the JFMC38-0901 trial, the effect of 12 months UFT + PSK therapy compared with surgery alone is being evaluated in patients with curatively resected stage II rectal cancer (http://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=search&action=list&language=J).

Lung cancer (Table 7)

Konno et al. [94] have compared the combination of intravenous vincristine (VCR), cyclophosphamide (CPA), and MMC once weekly for 8 weeks with or without 8–10 Gy radiotherapy (chemotherapy/radiotherapy group) with the combination of PSK 3 g/day added to the above regimen (chemotherapy/radiotherapy + PSK group) in 97 patients with small-cell lung carcinoma. Although the response rates did not differ between the two groups, the median response duration was significantly ($P = 0.042$) longer in the chemotherapy/radiotherapy + PSK group (25 weeks) than in the chemotherapy/radiotherapy group (13 weeks). Evidence for combined use of PSK and currently used chemotherapy regimen for extensive-stage small-cell lung cancer is anticipated; therefore, the Research Network for Chemotherapy of Lung Cancer (RNCLC) has been conducting a phase II trial to examine the effect of cisplatin + irinotecan + PSK compared with historical controls (http://clinicaltrials.gov/ct2/home).

To examine the usefulness of PSK as postoperative adjuvant therapy for lung cancer, Ikeda et al. [95] have studied 113 patients with non-small cell lung cancer randomized after surgery into three groups: chemotherapy with VCR, MMC, methotrexate, CPA or 5-FU combined with PSK 3 g/day (chemotherapy + PSK group); chemotherapy combined with OK-432 (chemotherapy + OK-432 group); and chemotherapy alone (chemotherapy group). The three-group comparison detected a significant difference ($P < 0.05$) in the 4-year survival, and the two-group comparisons found a significant difference ($P < 0.05$) between the chemotherapy + PSK and chemotherapy groups.

Hayakawa et al. [96] have investigated PSK therapy in 188 patients with non-small cell lung cancer, mainly stages I–III squamous cell cancer, who had achieved complete or partial response after radiotherapy. The patients were randomized to receive adjuvant treatment with PSK intermittent administration of 3 g/day for 2 weeks followed by 2 weeks off, or no adjuvant treatment. The 5-year survival rate was significantly ($P < 0.001$) higher in the group given PSK. As demonstrated in these studies, PSK is effective also for non-small cell lung cancer.

Table 7 RCTs of chemotherapy and/or radiotherapy with PSK for lung cancer

References	Tumor characteristics	No. of patients	Treatment	Response rate (%) or percentage survival/year	*P* value	Suggestive data
						Duration of tumor response
Konno [94]	Small-cell lung cancer	48	A: VCR+CPA+MMC (radiation)+PSK	45	NS	A: 25 weeks
		49		46		B: 13 weeks
			B: VCR+CPA+MMC (radiation)			$P = 0.042$
Ikeda [95]	Non-small cell lung cancer stage I–IV	27	A: VCR+MMC+MTX (CPA, 5-FU)+PSK	55.9/4	3 groups	
		39		36.7/4	<0.05	
		47	B: VCR+MMC+MTX (CPA, 5-FU)+OK-432	34.7/4	A versus C	
			C: VCR+MMC+MTX (CPA, 5-FU)		<0.05	
Hayakawa [96]	Non-small cell lung cancer	77	A: Radiation+PSK	30/5	<0.001	
	Stage I–III	111	B: Radiation	9/5		

VCR vincristine, *CPA* cyclophosphamide, *MMC* mitomycin C, *NS* not significant, *MTX* methotrexate, *5-FU* 5-fluorouracil, *OK-432* picibanil

Other clinical uses (Tables 8, 9)

A number of reports on the effects of PSK on cancers not included in the approved indications have been published. In one report, nasopharyngeal carcinoma patients who had undergone radiotherapy or radiotherapy + chemotherapy were given PSK or no further treatment. The 5-year survival rate was significantly ($P = 0.043$) improved in the PSK-treated group compared to the non-PSK-treated group [97]. Patients with primary or relapsed superficial bladder cancer were randomized after surgery to receive PSK, chemotherapy with carboquone, or chemotherapy + PSK, and were compared with surgery alone. The 3-year DFS rate was significantly better in the PSK-treated group compared with surgery alone ($P = 0.008$) or the chemotherapy-treated group ($P = 0.006$) [98]. In esophageal cancer patients treated postoperatively with radiotherapy, or radiotherapy combined with PSK or radiotherapy + chemotherapy (bleomycin, or pepleomycin + tegafur), or radiotherapy + chemotherapy combined with PSK, the 5-year survival tended to be prolonged in the radiotherapy + chemotherapy + PSK group compared with the radiotherapy + chemotherapy group, although the difference was not significant ($P = 0.1034$) [99]. Breast cancer patients were treated with postoperative chemotherapy (5-FU + CPA + MMC + prednisolone) with or without PSK. The 10-year OS rate tended to be higher ($P = 0.0706$) in the PSK-treated group compared with the group given chemotherapy alone [100]. Although BRMs such as PSK have a direct effect on tumors, their major action is to enhance and modulate the immune response, which can account for a reasonable degree of effectiveness against various tumor types.

Few adverse reactions from the use of PSK have been reported, and most of them are gastrointestinal symptoms with no report of serious toxicity such as bone marrow suppression, or liver or renal function impairment [76, 88, 101]. PSK is relatively non-toxic and it has been reported to attenuate the adverse reactions or immunosuppression induced by chemotherapy or radiotherapy [102, 103]. Furthermore, Yoshimura et al. [104] have examined the quality of life (QOL) of 20 patients with unresectable stage III and IV lung adenocarcinoma treated with chemotherapy (cisplatin + vindesine) + PSK or chemotherapy alone, and found that good QOL was maintained in the patients treated with chemotherapy + PSK. Motai et al. [105] have investigated the frequency of prescription of analgesics for cancer pain in head and neck cancer, by comparing those treated and not treated with PSK. They reported significantly ($P < 0.05$) reduced frequency of analgesic use in

Table 8 RCTs of chemotherapy and/or radiotherapy with PSK for various cancers

References	Tumor characteristics	No. of patiens	Treatment	Results	*P* value
				5-year survival rates	
Go [97]	Nasopharyngeal carcinoma	17	A: RT(±CT[a]) + PSK	28%	0.043
		17	B: RT(±CT)	15%	
				3-year DFS rates	4 groups
Matsumoto [98]	Superficial bladder tumor	65	A: Resection+PSK	56.3%	0.026
	pTa, pT1	67	B: Resection only	32.6%	A versus B
	G1, G2	65	C: Resection+CQ+PSK	43.1%	0.008
		66	D: Resection+CQ	35.6%	A versus D
					0.006
				5-year survival rates	
Ogoshi [99]	Esophageal cancer	38	A: Resection+RT+PSK	42.3%	C versus D
	stage I–IV	31	B: Resection+RT	40.0%	0.1930
		56	C: Resection+RT+CT[b]+PSK	37.2%	
		49	D: Resection+RT+CT	29.1%	
				10-year survival rates	3 groups
Iino [100]	Breast cancer	74	A: Resection+FEMP[c]+PSK	81.8%	0.1686
		76	B: Resection+FEMP+Levamisole	76.9%	A versus C
		77	C: Resection+FEMP	64.6%	0.0706

RT radiotherapy, *CT* chemotherapy, *DFS* disease-free survival, *pT* pathologic tumor, *G* grade, *CQ* carboquone

[a] Cisplatin or 5-FU or methotrexate or vincristine

[b] Bleomycin or pepleomycin+tegafur

[c] 5-FU+CPA+MMC+prednisolone

Table 9 Other effects of PSK in cancer therapy

References	Evaluation	Tumor characteristics	No. of patients	Treatment	Results
Kohara [102]	Toxicity of chemotherapy	Solid tumors	20 49	A: 5-FU (dry syrup) + PSK B: 5-FU (dry syrup)	Frequency of chemotherapy toxicity A: 7 cases (35.0%) B: 26 cases (53.1%)
Sadahiro [103]	Immune cells	Rectal cancer	15 15	A: RT+S-1+PSK (preoperative) B: RT+S-1 (preoperative)	Increases of the proportion of NK cells in the peripheral blood ($P = 0.003$) and cytotoxic T-cell counts in the peri-tumoral and normal mucosa (P=0.005, 0.003)
Yoshimura [104]	QOL	Stage III, IV adenocarcinoma of the lung, inoperable	10 10	A: CDDP+VDS+PSK B: CDDP+VDS	Good score of QOL A > B
Motai [105]	Cancerous pain	Nasopharyngeal carcinoma	31 31	A: PSK B: Non-PSK	Frequency of analgesic use A: 72.9 ± 16.2 B: 146.9 ± 43.6 $P < 0.05$

5-FU 5-fluorouracil, *RT* radiation therapy, *S-1* tegafur–gimeracil–oteracil potassium, *CDDP* cisplatin, *VDS* vindesine, *QOL* quality of life

patients treated with PSK, which suggested that PSK had some effect on cancer pain relief. Apart from its anticancer effects, PSK is a useful agent in cancer treatment as shown by the above studies.

Concluding remarks and future perspectives

Recent developments in the investigations of the mechanisms of action of PSK and its main clinical effects have been reviewed. Regarding the action of PSK against immunosuppression, PSK has been reported to restore or attenuate immunosuppression due to various factors. With regard to the actions on immune cells, the induction of DC maturation, the correction of Th1/Th2 imbalance, etc. have been reported. Furthermore, the involvement of PSK in intracellular signal transduction pathways also begins to unfold. With regard to the direct action on tumors, considerable knowledge about apoptosis induction by PSK has been accumulating, and the anti-metastatic effect and chemotherapy potentiating effect due to direct action on tumors have been reported. Future studies of the actions of PSK on immune cells and tumor cells at the molecular level under various conditions, and identification of the target molecules of PSK, are necessary to clearly define the whole mechanisms of action of PSK. Furthermore, it is essential to investigate the actions of PSK along with recent advances in molecular biology and tumor immunology. Although many research results on the mechanisms of action of PSK have been reported, it is undeniable that the main mechanism of action is unclear. It seems that PSK is an immunomodulator rather than a purely immunopotentiator [106]. PSK probably does not exert the same actions in all patients. The effects of PSK under different local (tumor site) or systemic immune conditions and tumor cell properties, and the mechanism of action of PSK in each circumstance should be studied.

The beneficial effect of PSK as postoperative adjuvant therapy for gastric and colorectal cancer has been shown in multiple RCTs. In addition, the effects of PSK in gastric and colorectal cancer have been verified in multiple meta-analyses. Prolongation of the remission period has also been found in small-cell lung cancer. The combined effect or comparison of combined formulation and biochemical modulation of fluoropyrimidine anticancer agents is being examined by RCTs, and the results will be available in the near future. Besides gastric, colorectal and small-cell lung cancer, PSK also exhibits reasonable effects on other cancers. These results are expected, because, unlike chemotherapeutic agents, PSK exerts anticancer effects through acting on host immunity. Also, PSK causes few adverse reactions and has been reported to reduce those associated with chemotherapy, improve QOL, and mitigate cancer pain. The next step of PSK research is to define which type of patient and disease conditions will allow PSK to exert its optimal effect, irrespective of cancer type. In this regard, there is an urgent need to elucidate the mechanisms of action of PSK at the molecular level so as to identify the biomarkers. Achievement of these goals will benefit patients from the personalized medicine point of view.

Several reports have already suggested that the patient's immune function, as indicated by blood IAP level, peripheral granulocyte/lymphocyte ratio, and DC infiltration of

Table 10 Potential biomarkers of PSK

Subjects	Potential biomarker	References
Human colon cancer cell line (in vitro)	Expression of ECA39 protein in tumor cells	Yoshikawa [111]
Colon cancer patients	Diffuse nuclear accumulation of β-catenin activation in primary tumor	Yamashita [112]
Colon cancer patients	Preoperative peripheral blood CEA level: ≥3.0 ng/ml Preoperative PPD skin reaction level: <19.0 nm	Takahashi [113]
Colorectal cancer patients	Increase of NK cell population in peripheral blood after PSK administration	Ohwada [114]
Colorectal cancer patients	Ratio of $CD4^+$ $IL\text{-}10^+$ T-cell percentage in peripheral blood before and after PSK treatment: <0.8	Yoshino [46]
Gastric or colorectal cancer patients	In vitro activation level of peripheral blood lymphocytes by PSK	Yoshinaga [116]

CEA carcinoembryonic antigen, *PPD* purified protein derivative of tuberculin, *NK* natural killer

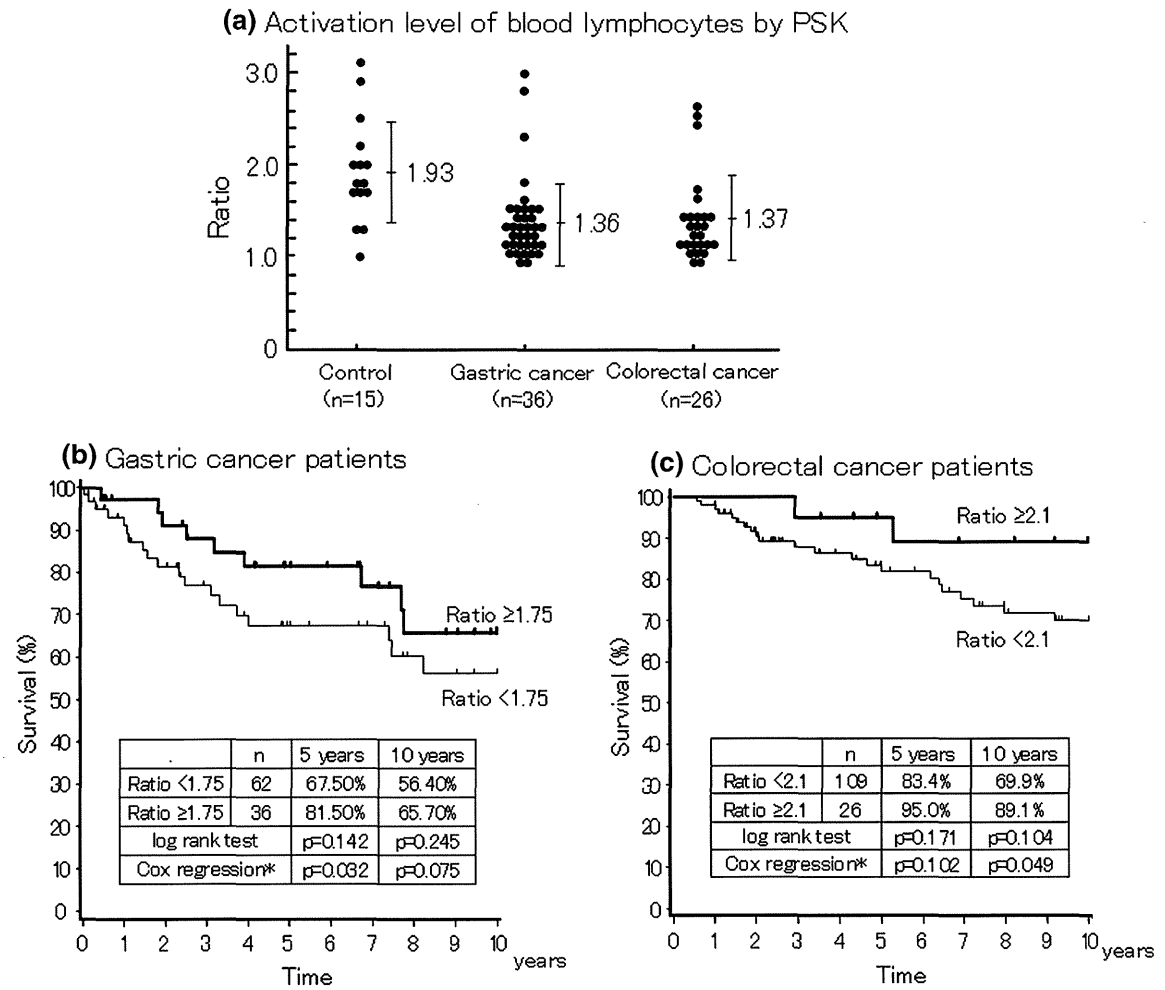

Fig. 8 PSK-stimulated activation of blood lymphocytes in healthy volunteers and cancer patients (**a**). Effects of adjuvant immunochemotherapy with PSK on 10-year OS in gastric cancer (**b**) and colorectal cancer (**c**) patients with low or high PSK-induced lymphocyte activation level. The increase in DNA synthesis of lymphocytes was defined as ratio of the level of PSK-treated lymphocytes versus PSK-non-treated lymphocytes. *Asterisk* adjusted by gender, age, Dukes' stage, tumor size, lymphatic vessel invasion, and venous invasion. Adapted from Sugimachi et al. [115] and Yoshinaga et al. [116]

tumor tissue, as well as HLA type, is a potential biomarker of response to PSK therapy [107–110]. The recent advances in biomarker research are summarized in Table 10. Yoshikawa et al. [111] have examined the action of PSK on human colorectal cancer cell line, using protein microarray with antibodies against 500 human proteins and found that expression of ECA39 protein was reduced. ECA39 expression in resected tumors is associated with poor DFS and OS; therefore, these findings suggest that ECA expression is a marker of response to PSK therapy. Yamashita et al. [112] have examined nuclear translocation of β-catenin in cancer tissues of colorectal cancer patients and reported that OS was improved with PSK immunochemotherapy in patients showing diffuse β-catenin nuclear accumulation in tumor tissues. Takahashi et al. [113] have reported that, in colon cancer patients with preoperative peripheral blood carcinoembryonic antigen level: $\geq$3.0 ng/ml or PPD skin reaction level: <19.0 mm, 7-year DFS and OS were significantly better with postoperative adjuvant immunochemotherapy using PSK than in patients treated with chemotherapy alone. Ohwada et al. [114] have reported that colorectal cancer patients with an increase in NK cell population at 3 months after surgery had more favorable DFS when treated with PSK immunochemotherapy than chemotherapy alone. Yoshino et al. [46] have found that relapse (3 years) did not occur in colorectal cancer patients with peripheral blood $CD4^+$ $IL\text{-}10^+$ T-cell ratios (post-/pre-PSK treatment): <0.8 when PSK was administered 1 week before surgery, and reported that these patients might be candidate PSK responders. We have examined the outcome in gastric and colorectal cancer patients using the PSK-induced peripheral blood lymphocyte blastogenesis reaction as an indicator for response to PSK therapy and gained an impression that patients with high reactivity had better survival outcome (Fig. 8) [115, 116]. We have also investigated the in vitro effect of PSK on PBMC gene expression in healthy individuals using DNA microarray analysis and observed changes in expression of six genes in four of five individuals. Using real-time RT-PCR, we found increased expression of IL-18BP, CCL2, IL-8, and vesicle amine transport 1 homolog and reduced expression of chondroitin sulfate proteoglycan in all five individuals [117]. The relationship between expression of these genes and relapse suppression needs to be examined further. We speculate that more than one biomarker might indicate response to PSK therapy. Identification of these biomarkers one by one will pave the way for the future use of PSK in cancer treatment.

Conflict of interest Y.M. has received honoraria and research funding from Daiichi Sankyo Co. Ltd. and Kureha Corp. H.B. has received research funding from Daiichi Sankyo Co. Ltd. All other authors declare no conflicts of interest.

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First-line sunitinib plus FOLFIRI in Japanese patients with unresectable/metastatic colorectal cancer: A phase II study

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This phase II, open-label, single-arm study investigated sunitinib + FOLFIRI in Japanese patients with treatment-naïve unresectable/metastatic colorectal cancer. Patients received i.v. FOLFIRI (levo-leucovorin 200 mg/m^2 + irinotecan 180 mg/m^2, followed by 5-fluorouracil 400 mg/m^2 bolus then 2400 mg/m^2 46-h infusion) every 2 weeks, and oral sunitinib 37.5 mg/day on Schedule 4/2 (4 weeks on, 2 weeks off), until disease progression or treatment withdrawal. Progression-free survival (PFS) was the primary endpoint, with a target median of 10.8 months (35% improvement over FOLFIRI alone). Seventy-one patients started a median of 3 (range 1–11) sunitinib cycles (median relative dose intensity, <60%). The median PFS was 6.7 months (95% confidence interval, 4.7–9.2) by independent review, 7.2 months (95% confidence interval, 5.4–9.5) by investigator assessment. Objective response rate (complete responses + partial responses) was 36.6% (independent review) and 42.3% (investigator assessment). Clinical benefit rate (complete responses + partial responses + stable disease) was 83.1% (independent review) and 88.7% (investigator assessment). Common all-causality, any-grade, adverse events were: neutropenia and leukopenia (both 97.2%); thrombocytopenia (84.5%); diarrhea and nausea (both 78.9%); decreased appetite (74.6%); and fatigue (66.2%). Neutropenia (96%) was the most frequent grade 3/4 adverse event. This study was closed early due to findings from a concurrent phase III study of sunitinib + FOLFIRI in non-Japanese patients with metastatic colorectal cancer. In conclusion, the median PFS for sunitinib + FOLFIRI in Japanese patients was shorter than the 10.8 month target, indicating that sunitinib did not add to the antitumor activity of FOLFIRI. This study was registered with ClinicalTrials.gov (NCT00668863). (*Cancer Sci* 2012; 103: 1502–1507)

The median survival of patients with metastatic CRC has improved over the past decade, from approximately 1 year with 5-FU-based monotherapy to approximately 2 years with combination systemic therapy.[1] FOLFIRI is now a standard first-line treatment for metastatic CRC.[1] The addition of other agents (typically the anti-VEGF mAb, bevacizumab) to FOLFIRI has improved patient outcomes.

Sunitinib malate (SUTENT; Pfizer, New York, NY, USA) is an oral, multitargeted tyrosine kinase inhibitor of VEGFR-1, -2, and -3, platelet-derived growth factor receptors (-α and -β), stem cell factor receptor, FMS-like tyrosine kinase 3, colony-stimulating factor 1 receptor, and glial cell line-derived neurotrophic receptor.[2–7] Sunitinib is currently approved multinationally for the treatment of advanced renal cell carcinoma and imatinib-resistant/-intolerant gastrointestinal stromal tumor.[8] It is also now approved for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors.[9]

Sunitinib has shown antitumor activity in non-clinical CRC models, both as a single agent[4] and in combination with chemotherapy (Pfizer, unpublished data, 2002). In a phase II study of patients with previously treated metastatic CRC, single-agent sunitinib showed some evidence of efficacy (median OS, 10.2 months in patients with bevacizumab-naïve tumors; 7.1 months in patients with bevacizumab-pretreated tumors) and the study investigators concluded that sunitinib warranted further evaluation in combination with standard regimens used to treat metastatic CRC.[10]

Subsequently, a phase I study investigated sunitinib combined with FOLFIRI in patients with chemotherapy-naïve metastatic CRC, and identified the maximum tolerated dose of sunitinib as 37.5 mg/day given on Schedule 4/2.[11] This regimen was evaluated further in two concurrent first-line metastatic CRC studies: a phase II, open-label, single-arm study in Japanese patients (ClinicalTrials.gov identifier: NCT00668863); and a phase III, double-blind, randomized study in non-Japanese patients (ClinicalTrials.gov identifier: NCT00457691).[12] Results of the single-arm phase II study are presented here.

Materials and Methods

Patients. Patients aged $\geq$20 years with histologically- or cytologically-confirmed adenocarcinoma of the colon or rectum, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function were included in the study. All patients had unresectable or metastatic disease by diagnostic imaging and were candidates for FOLFIRI therapy. No prior systemic chemotherapy for unresectable or metastatic CRC was permitted (prior adjuvant therapy was allowed providing there was longer than 6 months between the end of therapy and documentation of recurrent disease). Patients had measurable disease based on RECIST version 1.0.[13]

Patients were excluded if they had had full-field radiotherapy $\leq$4 weeks prior to study treatment or limited-field radiotherapy $\leq$2 weeks prior to study treatment, or previous radiation treatment to >30% of bone marrow. Additional exclusion

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criteria comprised: recent surgery or major bleeding; history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess $\leq$6 months prior to study treatment (unless the affected tissue had been removed surgically); unresolved bowel obstruction or chronic diarrhea; arrhythmia grade 2 or higher (CTCAE version 3.0); clinically significant cardiovascular disease, cardiac dysrhythmias, or prolonged QTc interval; or central nervous system involvement.

Study design and treatment plan. This open-label, single-arm, phase II study was carried out in multiple centers and investigated the efficacy and safety/tolerability of sunitinib combined with FOLFIRI in a Japanese population. The study protocol was approved by the institutional review board or independent ethics committee of each participating center, and conformed to the provisions of the Declaration of Helsinki (1996). All patients provided written informed consent.

Patients received sunitinib plus FOLFIRI as first-line therapy for unresectable or metastatic CRC. Oral sunitinib 37.5 mg/day was given on Schedule 4/2. Intravenous FOLFIRI was given using standard procedures every 2 weeks: levoleucovorin 200 mg/m^2; irinotecan 180 mg/m^2; immediately followed by 5-FU 400 mg/m^2 bolus then 5-FU 2400 mg/m^2 as a 46-h infusion. Treatment cycles were 6 weeks in duration (each 6-week sunitinib cycle included three cycles of FOLFIRI).

Treatment was continued until disease progression or withdrawal of treatment for another reason. Dose delays or reductions were permitted to manage treatment-related AEs. For sunitinib and FOLFIRI, dose delays >4 weeks were generally not permitted. Sunitinib doses could be reduced to 12.5 mg/day; FOLFIRI doses could be reduced according to institutional practices or guidelines provided in the study protocol. The use of hematopoietic growth factors was permitted.

Study assessments. The primary study endpoint was PFS, defined as time from the date of enrolment to first documentation of objective tumor progression or death due to any cause, whichever occurred first. Secondary endpoints included OS, RECIST-defined ORR and CBR,[13] and safety.

Tumors were imaged at baseline, every 6 weeks, when disease progression was suspected, to confirm an objective response (partial response or complete response) $\geq$4 weeks after initial documentation of response, and at the end of treatment/study withdrawal (if not carried out in the previous 6 weeks). Tumor assessments were subjected to review by study investigators and members of an Independent Radiological Committee.

Safety was evaluated based on AEs, laboratory results, physical examinations, vital signs, performance status, and electrocardiograms. Severity of AEs was graded using the National Cancer Institute CTCAE (version 3.0).

A Steering Committee reviewed efficacy and safety data periodically throughout the study and made recommendations regarding study amendment, continuation, and discontinuation.

Statistical methods. As this was a single-arm, exploratory, phase II study, there were no formal hypotheses for statistical testing. The planned sample size of 70 patients was determined based on assumptions that median PFS would be 8.0 months for patients receiving FOLFIRI alone (historical data)[14] and 10.8 months for patients receiving sunitinib plus FOLFIRI (a 35% improvement). Seventy patients would permit construction of a two-sided 95% CI with a width of approximately 7.2 months, if patient accrual was accomplished in 2 years and follow-up continued for 2 years.

The efficacy and safety analysis population included all enrolled patients with adenocarcinoma of the colon or rectum and unresectable or metastatic disease who had received

Table 1. Baseline characteristics of Japanese patients with unresectable/metastatic colorectal cancer treated with sunitinib and FOLFIRI (*n* = 71)

	Sunitinib 37.5 mg/day (Schedule 4/2) plus FOLFIRI
Gender, *n* (%)	
Male	42 (59.2)
Female	29 (40.8)
Median age, years (range)	60 (26–78)
ECOG performance status, *n* (%)	
0	55 (77.5)
1	16 (22.5)
No. of organ sites with disease, *n* (%)	
1	47 (66.2)
>1	24 (33.8)
Primary tumor site, *n* (%)	
Colon	37 (52.1)
Rectum	34 (47.9)
Prior adjuvant treatment, *n* (%)	8 (11.3)
Prior surgery, *n* (%)	53 (74.6)
Prior radiation therapy, *n* (%)	3 (4.2)
Prior systemic therapy, *n* (%)†	
1 regimen‡	6 (8.5)
2 regimens‡	2 (2.8)
None	60 (84.5)

†*n* = 3 unknown. ‡Patients received prior adjuvant therapy which was allowed providing there was >6 months between the end of therapy and documentation of recurrent disease. ECOG, Eastern Cooperative Oncology Group; FOLFORI, leucovorin, 5-fluorouracil, and irinotecan; Schedule 4/2, 4 weeks on treatment followed by 2 weeks off.

Table 2. Study treatment exposure in Japanese patients with unresectable/metastatic colorectal cancer treated with sunitinib and FOLFIRI (*n* = 71)

	Sunitinib 37.5 mg/day (Schedule 4/2) plus FOLFIRI				
	Sunitinib	Irinotecan	Leucovorin	5-FU bolus	5-FU infusion
Median no. of cycles started (range)	3 (1–11)	3 (1–11)	3 (1–11)	3 (1–11)	3 (1–11)
Patients with $\geq$1 dose delay, *n* (%)	47 (66.2)	61 (85.9)	61 (85.9)	58 (81.7)	61 (85.9)
Patients with $\geq$1 dose interruption, *n* (%)	70 (98.6)	6 (8.5)	4 (5.6)	–	4 (5.6)
Patients with dose reductions, *n* (%)					
1 reduction	36 (50.7)	40 (56.3)	14 (19.7)	38 (53.5)	35 (49.3)
$\geq$2 reductions	6 (8.5)	10 (14.1)	2 (2.8)	4 (5.6)	6 (8.5)
Median relative dose intensity, % (range)	53 (11–92)	49 (27–80)†	58 (27–80)†	–	52 (27–77)†

†*n* = 70. –, not available; FOLFORI, leucovorin, 5-fluorouracil (5-FU), and irinotecan; Schedule 4/2, 4 weeks on treatment followed by 2 weeks off.

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at least one dose of study medication. Time-to-event endpoints were analyzed using Kaplan–Meier methods. Other efficacy and safety data were summarized using descriptive statistics.

Results

Study conduct, patients, and treatments. Enrolment began in April 2008, with 71 patients enrolled by May 2009. In June 2009, the study was closed early when the concurrent phase III study of the same treatment regimen in non-Japanese patients with metastatic CRC (ClinicalTrials.gov identifier: NCT00457691) was halted due to futility.[12] Sunitinib discontinuation was recommended, or left to investigator discretion in patients with clinical benefit. The efficacy and safety analysis population comprised all 71 patients.

Patient baseline characteristics are summarized in Table 1. Patients started a median of three treatment cycles (range, 1–11; Table 2). Overall, the sunitinib dose was delayed in 66% of patients, was interrupted in 99% of patients, and was reduced in 59% of patients (Table 2). The resulting median sunitinib RDI was <53%. The median RDI for irinotecan, leucovorin, and 5-FU was <58% (Table 2). Most patients withdrew from study treatment/the study due to disease progression (59%, n = 42) or AEs (18%, n = 13).

Efficacy. At the time of data analysis, 44 patients (62.0%) had progressed (by independent review); median PFS was 6.7 months (95% CI, 4.7–9.2; Fig. 1). By investigator assessment, 45 patients (63.4%) had progressed; median PFS was 7.2 months (95% CI, 5.4–9.5). *Post-hoc* analyses of PFS by baseline characteristics are shown in Table 3.

At the time of data analysis, eight patients (11.3%) had died (7 [9.9%] due to the disease under study and 1 [1.4%] due to other causes) and median OS had not yet been reached (due to early study closure).

The ORR by independent assessment was 36.6% (one complete and 25 partial responses; Fig. 2, Table 4), and the CBR was 83.1% (Table 4). The investigator-assessed ORR was

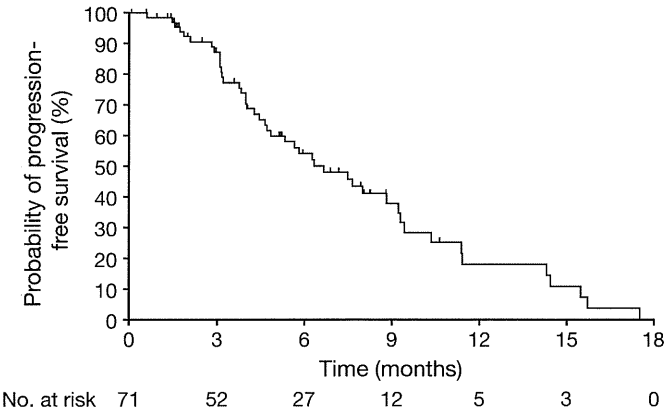

Fig. 1. Kaplan–Meier curve of progression-free survival (independent assessment) in Japanese patients with unresectable/metastatic colorectal cancer who were treated with sunitinib and FOLFIRI.

Table 3. *Post-hoc* analysis of progression-free survival according to baseline variables in Japanese patients with unresectable/metastatic colorectal cancer were treated with sunitinib and FOLFIRI (n = 71)

Variable	n	Median PFS (months)	HR (95% CI)
Age			
<65	50	6.7	1.2 (0.6–2.3)
≥65	21	6.3	
Gender			
Male	42	7.6	1.4 (0.8–2.5)
Female	29	5.3	
Primary disease site			
Colon	37	6.3	1.2 (0.7–2.2)
Rectum	34	7.5	
Time since diagnosis			
<7 weeks	47	5.6	1.0 (1.0–1.0)
≥7 weeks	24	7.5	
ECOG PS			
0	54	7.5	0.5 (0.3–1.1)
1	17	4.7	
Disease stage			
<IV	18	15.5	0.5 (0.2–1.2)
IV	53	6.7	
No. of disease sites			
1	47	7.5	0.61 (0.3–1.1)
>1	24	4.7	

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PFS, progression-free survival.

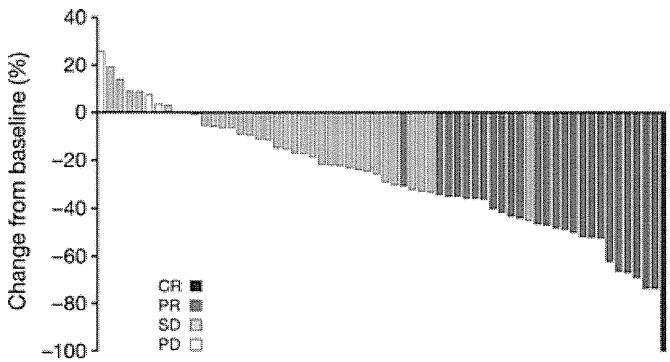

Fig. 2. Change from baseline in target lesion size per evaluable patient (independent assessment). Seventy-one Japanese patients with unresectable/metastatic colorectal cancer were treated with sunitinib and FOLFIRI. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Table 4. Best overall objective response (independent assessment) in Japanese patients with unresectable/metastatic colorectal cancer treated with sunitinib and FOLFIRI (n = 71)

	Sunitinib 37.5 mg/day (Schedule 4/2) plus FOLFIRI
Best overall objective response, n (%)	
Complete response	1 (1.4)
Partial response	25 (35.2)
Stable disease/no response	33 (46.5)
Objective progression	6 (8.5)
Early death†	1 (1.4)
Indeterminate	5 (7.0)
Objective response rate, % (95% exact confidence interval‡)	36.6 (25.5–48.9)

†Patient died prior to having sufficient evaluations for overall response. ‡Calculated using exact method based on binomial distribution. FOLFORI, leucovorin, 5-fluorouracil, and irinotecan; Schedule 4/2, 4 weeks on treatment followed by 2 weeks off.

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Table 5. Adverse events, regardless of causality, reported in ≥20% of patients with unresectable/metastatic colorectal cancer treated with sunitinib and FOLFIRI (*n* = 71)

Adverse event, *n* (%)	Sunitinib 37.5 mg/day (Schedule 4/2) plus FOLFIRI				
	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Neutropenia†	0 (0.0)	1 (1.4)	29 (40.8)	39 (54.9)	69 (97.2)
Leukopenia†	0 (0.0)	21 (29.6)	41 (57.7)	7 (9.9)	69 (97.2)
Thrombocytopenia†	23 (32.4)	16 (22.5)	16 (22.5)	5 (7.0)	60 (84.5)
Diarrhea	31 (43.7)	18 (25.4)	7 (9.9)	0 (0.0)	56 (78.9)
Nausea	37 (52.1)	13 (18.3)	6 (8.5)	0 (0.0)	56 (78.9)
Decreased appetite	30 (42.3)	11 (15.5)	12 (16.9)	0 (0.0)	53 (74.6)
Fatigue	30 (42.3)	11 (15.5)	6 (8.5)	0 (0.0)	47 (66.2)
Alopecia	40 (56.3)	4 (5.6)	0 (0.0)	0 (0.0)	44 (62.0)
Vomiting	21 (29.6)	11 (15.5)	8 (11.3)	0 (0.0)	40 (56.3)
Stomatitis	25 (35.2)	9 (12.7)	2 (2.8)	0 (0.0)	36 (50.7)
Dysgeusia	33 (46.5)	2 (2.8)	0 (0.0)	0 (0.0)	35 (49.3)
Hand–foot syndrome	23 (32.4)	5 (7.0)	5 (7.0)	0 (0.0)	33 (46.5)
Anemia†	11 (15.5)	14 (19.7)	5 (7.0)	2 (2.8)	32 (45.1)
Constipation	24 (33.8)	5 (7.0)	0 (0.0)	0 (0.0)	29 (40.8)
Pyrexia	20 (28.2)	7 (9.9)	0 (0.0)	0 (0.0)	27 (38.0)
Hypertension	9 (12.7)	9 (12.7)	7 (9.9)	0 (0.0)	25 (35.2)
Lymphocyte count decreased†	0 (0.0)	11 (15.5)	12 (16.9)	1 (1.4)	24 (33.8)
Blood albumin decreased†	13 (18.3)	6 (8.5)	3 (4.2)	0 (0.0)	22 (31.0)
Skin discoloration	22 (31.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (31.0)
ALT increased†	11 (15.5)	4 (5.6)	3 (4.2)	0 (0.0)	18 (25.4)
Febrile neutropenia†	0 (0.0)	0 (0.0)	17 (23.9)	0 (0.0)	17 (23.9)
AST increased†	12 (16.9)	2 (2.8)	2 (2.8)	0 (0.0)	16 (22.5)
Blood phosphorous decreased†	3 (4.2)	4 (5.6)	8 (11.3)	0 (0.0)	15 (21.1)

†Based on adverse event reports. There was one grade 5 adverse event of myocardial infarction. ALT, alanine transaminase; AST, aspartate transaminase; FOLFORI, leucovorin, 5-fluorouracil, and irinotecan; Schedule 4/2, 4 weeks on treatment followed by 2 weeks off.

42.3% (30 partial responses), and the CBR was 88.7%. Median duration of response was 28.3 weeks (95% CI, 25.1–44.3 weeks; independent review).

Safety. Non-hematological, all-causality, any-grade, AEs are summarized in Table 5. Decreased appetite (16.9%), vomiting (11.3%), and hypertension (9.9%) were the most common grade 3 or 4 AEs judged related to treatment. One patient, a 65-year-old woman who had smoked for 45 years, died due to a grade 5 AE, myocardial infarction, which was considered to be related to all study medications.

Thirty-two patients (45.1%) experienced serious AEs, considered by the investigator to be related to study treatment in 29 patients (40.8%). The most common treatment-related serious AEs were febrile neutropenia and decreased appetite (8.5% each; Table 6).

Sixty-seven patients (94.4%) required sunitinib dose interruptions and 69 patients (97.2%) required FOLFIRI dose interruption due to AEs. Seven patients (9.9%) required sunitinib dose reduction and 10 patients (14.1%) required FOLFIRI dose reduction due to AEs. Study treatment (sunitinib and FOLFIRI) was discontinued permanently due to AEs in 13 patients (18.3%).

Discussion

This phase II study investigated sunitinib combined with FOLFIRI for the first-line treatment of Japanese patients with unresectable or metastatic CRC. The study was closed early when the concurrent phase III study of first-line sunitinib plus FOLFIRI in non-Japanese patients with metastatic CRC was stopped due to futility; median PFS was 7.8 months in the sunitinib plus FOLFIRI arm, and 8.4 months in the placebo plus FOLFIRI arm.[12] In the present study, median PFS (6.7 months by independent review; 7.2 months by investigator assessment), as well as ORR (36.6% by independent review; 42.3% by investigator assessment) and CBR (83.1% by independent review; 88.7% by investigator assessment), were similar to previous studies of 5-FU and irinotecan-containing chemotherapy regimens in Japanese patients.[15–21] Median PFS in our trial was less than the target of 10.8 months (35% improvement compared with FOLFIRI alone), indicating that the addition of sunitinib did not result in enhanced efficacy. The survival data were not mature at the time of analysis, due to early study termination.

In a retrospective analysis of 48 Japanese patients with unresectable, metastatic CRC who received FOLFIRI (*n* = 38 first-line), median PFS was 8.4 months and the ORR was 37%.[15] In 42 Japanese patients with advanced CRC (*UGT1A1*1/*1*, and **1/*6* or **1/*28* genotypes) who received first-line FOLFIRI, median PFS was 8.5–8.6 months (approximately 36.9–37.4 weeks) and ORR was 48–56%.[17] In other studies of Japanese patients with advanced or recurrent CRC, ORR ranged between 38% and 50%.[16,18,19]

Regrettably, the design of the present study did not include molecular profiling or biomarker investigations, therefore precluding the identification of specific patient populations who may benefit from the sunitinib plus FOLFIRI regimen. It is possible that the low RDIs of 53% for sunitinib and <58% for FOLFIRI in the present study might have led to suboptimal treatment benefit. It is known, for example, that increased exposure to sunitinib is associated with improved clinical outcome.[22] The low RDIs in the present study likely resulted from the increased toxicity (e.g. the high incidence of severe hematologic AEs) associated with combination treatment that resulted in dose interruption and/or dose reduction. The RDI on Schedule 4/2 was lower than on Schedule

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Table 6. Treatment-related serious adverse events in Japanese patients with unresectable/metastatic colorectal cancer treated with sunitinib and FOLFIRI (n = 71)

System organ class	Sunitinib 37.5 mg/day (Schedule 4/2) plus FOLFIRI	
	Preferred term	n (%)
Blood and lymphatic system disorders	Febrile neutropenia	6 (8.5)
	Leukopenia	2 (2.8)
	Thrombocytopenia	2 (2.8)
	Lymphadenitis	1 (1.4)
	Neutropenia	1 (1.4)
Cardiac disorders	Myocardial infarction	1 (1.4)
Gastrointestinal disorders	Vomiting	5 (7.0)
	Nausea	4 (5.6)
	Intestinal obstruction	2 (2.8)
	Diarrhea	1 (1.4)
	Gastric dilation	1 (1.4)
	Gastrointestinal perforation	1 (1.4)
	Hemorrhoids	1 (1.4)
	Ileus	1 (1.4)
	Pneumonitis intestinalis	1 (1.4)
General disorders and administration site conditions	Fatigue	2 (2.8)
	Pyrexia	1 (1.4)
Infections and infestations	Abdominal abscess	1 (1.4)
	Infection	1 (1.4)
	Influenza	1 (1.4)
	Localized infection	1 (1.4)
	Pneumonia	1 (1.4)
	Septic shock	1 (1.4)
Injury, poisoning, and procedural complications	Wound complication	1 (1.4)
	Wound dehiscence	1 (1.4)
Investigations	Neutrophil count decreased	3 (4.2)
	White blood cell count decreased	1 (1.4)
Metabolism and nutrition disorders	Decreased appetite	6 (8.5)
	Dehydration	1 (1.4)
Nervous system disorders	Cerebral infarction	1 (1.4)
Renal and urinary disorders	Hydronephrosis	1 (1.4)
Vascular disorders	Hypertension	1 (1.4)
	Thrombosis	1 (1.4)

FOLFORI, leucovorin, 5-fluorouracil, and irinotecan; Schedule 4/2, 4 weeks on treatment followed by 2 weeks off.

2/2 in a study of sunitinib combined with mFOLFOX6 in Japanese patients, although the small patient population limited the availability of dose-intensity data.[23] Maintaining the dose of sunitinib, particularly when combined with intensive chemotherapy, may be important in order to prolong median PFS. Therefore, Schedule 2/2 may be the optimal schedule to use when combining sunitinib with FOLFIRI or FOLFOX. Early study termination might also have contributed to the observed efficacy outcomes, and/or metastatic CRC cells may not be particularly dependent upon the signaling pathways inhibited by sunitinib. Further analyses would be necessary to confirm these hypotheses.

As mentioned above, there was a high incidence of severe (CTCAE grade 3/4) hematologic AEs when these Japanese patients with treatment-naïve unresectable or metastatic CRC received combination sunitinib plus FOLFIRI (neutropenia, 95.8%; leukopenia, 67.6%; thrombocytopenia, 29.6%; and febrile neutropenia, 23.9%). Additionally, almost 20% of patients discontinued study treatment permanently due to AEs, and over 90% required temporary interruptions of study treatment in order to manage treatment-related toxicities. The combination of sunitinib and FOLFIRI was associated with a higher incidence of grade $\geq$ 3 hematologic laboratory abnormalities compared with placebo plus FOLFIRI in the concurrent phase III study in non-Japanese patients (neutropenia, 68% *vs* 30%, respectively; thrombocytopenia, 11% *vs* <1%; and febrile neutropenia, 7% *vs* 3%).[12] Moreover, recent studies in Japanese metastatic CRC patients have reported that patients with certain *UGT1A1*28* or *UGT1A1*6* polymorphisms are more susceptible to irinotecan-related neutropenia when treated with FOLFIRI.[16,24] *UGT1A1* genotype was not evaluated in the present study and all patients received the full irinotecan starting dose (180 mg/m^2). This might, in part, have contributed to the high incidence of severe hematologic AEs reported here. Further, findings from the present study suggest that prophylactic use of oral antibacterial agents may be useful in patients receiving this regimen.

In conclusion, sunitinib 37.5 mg/day on Schedule 4/2 combined with FOLFIRI in Japanese patients with unresectable or metastatic CRC showed similar clinical activity (median PFS, ORR) compared with historical findings for 5-FU and irinotecan-containing regimens. The median PFS achieved in this trial did not meet the target of a 35% improvement compared with FOLFIRI alone, indicating that sunitinib did not add to the antitumor activity of FOLFIRI. Additionally, combination treatment was associated with a high incidence of grade 3/4 hematologic AEs that may have impacted the RDIs. We anticipate that further investigation of sunitinib in combination with chemotherapy on Schedule 2/2, together with the identification of biomarkers of response, may be required.

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Disclosure Statement

Naoko Mizutani and Maria Jose Lechuga are Pfizer employees and hold Pfizer stock. Satoshi Hashigaki is a Pfizer employee. Yasushi Tsuji, Taroh Satoh, Akihito Tsuji, Kei Muro, Motoki Yoshida, Tomohiro Nishina, Michitaka Nagase, Yoshito Komatsu, Takeshi Kato, Yoshinori Miyata, and Tadamichi Denda have no conflicts of interest to disclose.

Abbreviations

5-FU	5-fluorouracil
AE	adverse event
CBR	clinical benefit rate
CI	confidence interval
CRC	colorectal cancer
CTCAE	Common Terminology Criteria for Adverse Events
FOLFIRI	leucovorin, 5-fluorouracil, and irinotecan
FOLFOX	5-fluorouracil, leucovorin, and oxaliplatin
mFOLFOX	modified FOLFOX regimen
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
Schedule 2/2	2 weeks on treatment followed by 2 weeks off
Schedule 4/2	4 weeks on treatment followed by 2 weeks off
VEGFR	vascular endothelial growth factor receptor

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Original Article

Multicenter Feasibility Study of Combination Therapy with Fluorouracil, Leucovorin and Paclitaxel (FLTAX) for Peritoneal Disseminated Gastric Cancer with Massive Ascites or Inadequate Oral Intake

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Objective: Oral fluoropyrimidine plus cisplatin is a standard treatment for advanced gastric cancer, but patients with severe peritoneal metastasis often cannot tolerate this regimen. The aim of this study was to assess the feasibility of fluorouracil, *l*-leucovorin and paclitaxel therapy in such patients.

Methods: In the first phase of the study, we investigated the maximum tolerated dose and recommended dose in Cycle 1 of fluorouracil, *l*-leucovorin and paclitaxel, at two dose levels [Level 1 ($n = 6$): 5-fluorouracil/*l*-leucovorin/paclitaxel = 500/250/60 mg/m^2; Level 2 ($n = 6$): 600/250/80 mg/m^2 on Days 1, 8 and 15, every 28 days]. Nineteen additional patients at the recommended dose level were enrolled in the second phase to investigate the feasibility of fluorouracil, *l*-leucovorin and paclitaxel therapy. The primary endpoint in the second phase was the completion rate of two cycles.

Results: Dose-limiting toxicities were observed in a patient at Level 1 with Grade 4 gastrointestinal perforation (the site of primary tumor), and in two patients at Level 2 with Grade 3 febrile neutropenia and Grade 3 infection, respectively. In Cycle 2, treatment-related death occurred at Level 2 in one patient who had Grade 4 febrile neutropenia with pneumonia. The maximum tolerated dose was set at Level 2, and the recommended dose was determined as Level 1. In the second phase, the completion rate of two cycles was 92% and the ascites response was 44%. Median progression-free survival was 4.2 months and overall survival was 8.0 months. Grade 3/4 neutropenia was observed in 12% of patients.

Conclusions: Fluorouracil, *l*-leucovorin and paclitaxel at Level 1 is feasible as first-line treatment for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake.

Key words: gastric cancer – peritoneal metastasis – ascites – fluorouracil – paclitaxel

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INTRODUCTION

Gastric cancer remains a major cause of death in Asian countries, and this tumor type is the second leading mortality cause in Japan. The majority of gastric cancer cases are diagnosed at an unresectable stage at which the prognosis is extremely poor. Current treatment for unresectable gastric cancer is based on systemic chemotherapy with an oral fluoropyrimidine (i.e. S-1 or capecitabine) plus cisplatin. S-1 plus cisplatin is a standard treatment in Japan based on the SPIRITS trial, which demonstrated the superiority of S-1 plus cisplatin compared with S-1 alone, while capecitabine plus cisplatin has also been recognized as a standard therapy around the world (1,2).

Patients exhibit peritoneal metastasis in approximately half of all cases of unresectable gastric cancer. Peritoneal metastasis causes many serious complications, such as malignant ascites, intestinal obstruction, hydronephrosis and obstructive jaundice. Gastric cancer patients with severe peritoneal metastasis, and particularly those with massive ascites, have been excluded from clinical trials of cisplatin-containing regimens, and patients with inadequate oral intake have been excluded from trials with oral fluoropyrimidine. For such patients, continuous infusion of fluorouracil (5-FU ci) had been used in Japan based on the results of a Japan Clinical Oncology Group (JCOG) 0106 trial, which demonstrated that methotrexate (MTX) and 5-FU sequential therapy (MTX/5-FU) were not superior to 5-FU ci in chemotherapy-naïve patients with peritoneal metastasis, except in those with massive ascites (3). In a recent a Phase III trial (ISO-5FU study), a weekly bolus regimen of 5-FU/*l*-leucovorin (*l*-LV) for unresectable gastric cancer was shown to be non-inferior to S-1, which had been also proved to be non-inferior to 5-FU ci in the previous JCOG9912 trial (4,5). Therefore, bolus 5-FU/*l*-LV has been used as one of the treatment options for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake in the clinical setting.

Many patients with severe peritoneal metastasis suffer from acute clinical symptoms, such as abdominal fullness, vomiting, nausea, anorexia and abdominal pain, and show rapid progression of the disease. Chemotherapy with greater therapeutic efficacy than that of 5-FU/*l*-LV is needed as first-line treatment to promptly improve the symptoms and quality of life of patients. 5-FU/*l*-LV and paclitaxel (FLTAX) are both appropriate regimens for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake, because this regimen does not require that patients be hydrated and includes no oral agents. Weekly administration of FLTAX was demonstrated to be an effective regimen in Phase I/II studies for general unresectable gastric cancer patients, except those with peritoneal disseminated gastric cancer and massive ascites or inadequate oral intake (6,7). We conducted a multicenter feasibility study of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. The study consisted of two phases: in the first phase, we assessed the dose-limiting toxicity (DLT) and determined the maximum tolerated dose (MTD) and recommended dose (RD), and in the second phase, the feasibility of the FLTAX regimen at the RD level was assessed in an additional group of patients.

PATIENTS AND METHODS

Eligibility Criteria

Eligibility criteria included: histologically proven gastric adenocarcinoma; unresectable advanced or recurrent disease; age range of 20–80 years; Eastern Cooperative Oncology Group performance status of 0–2; peritoneal metastasis with bowel stenosis confirmed by barium enema, ascites and/or peritoneal nodule detected by computed tomography scan; massive ascites extending throughout the entire abdominal cavity, or inadequate oral intake which is defined as receiving an intravenous drip infusion because of nutritional support or proper hydration; previously untreated disease or the disease after one prior systemic chemotherapy as follows: recurrence during adjuvant chemotherapy or within 6 months after its completion, or failure of 5-FU ci or oral fluoropyrimidine as the first-line chemotherapy; preserved organ function, including leukocyte counts $\geq$3000/mm^3, platelet counts $\geq$100 000/mm^3, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 100 U/l, total bilirubin $\leq$1.5 mg/dl and serum creatinine $\leq$2.0 mg/dl and provision of written informed consent.

The levels of ascites were classified as follows: massive ascites was defined as extending throughout the entire abdominal cavity; moderate ascites was defined as inconsistent with either mild or massive ascites; mild ascites was defined as localized only in the upper or lower part of the abdominal cavity; no ascites was defined as undetectable by computed tomography scanning.

Exclusion criteria included active infection, uncontrolled heart disease, uncontrolled diabetes, pulmonary fibrosis or active pneumonitis, history of hypersensitivity to alcohol, prior taxane-containing chemotherapy, massive pleural effusion, symptomatic brain metastasis, watery diarrhea, active concomitant malignancy and pregnancy or lactation.

This study was approved by the independent ethics committee for each trial center and was conducted in accordance with the Declaration of Helsinki, and local laws and regulations. This study was registered with UMIN-CTR, number 000002093.

Study Design and Treatment

This was a multicenter feasibility study conducted in 2 phases, carried out across 12 sites in Japan. The first phase consisted of a dose-escalation study to determine DLT, MTD and RD of FLTAX. The predefined dose escalation scheme in the first phase consisted of two levels as follows: Level 1, 500 mg/m^2 of 5-FU, 250 mg/m^2 of *l*-LV and

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60 mg/m^2 of paclitaxel; Level 2, 600 mg/m^2 of 5-FU, 250 mg/m^2 of *l*-LV and 80 mg/m^2 of paclitaxel.

In the first phase, six patients were enrolled per dose level. If 0–2 DLT occurred in six patients, the next six patients were enrolled at the next dose level. If three or more DLT were observed at dose level 1, the FLTAX regimen would be deemed unfeasible for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. In the second phase, additional patients were enrolled and were assessed together with the patients at the RD level in the first phase.

Paclitaxel was administered as a 60 min intravenous infusion followed by 5-FU as a bolus intravenous infusion. A 120 min intravenous infusion of *l*-LV was started at the same time as the paclitaxel infusion; all agents were administered on Days 1, 8 and 15 every 28 days. As prophylaxis for potential paclitaxel hypersensitivity reactions, 8 mg of dexamethasone, 50 mg of ranitidine and 10 mg of chlorpheniramine were administered before the infusion of paclitaxel. Protocol treatment was defined as two cycles of FLTAX. Completion of two cycles was defined as the successful administration of FLTAX in at least four out of a total of six doses during two cycles. Post-protocol treatment was not defined, but continuation of FLTAX was recommended until disease progression or unacceptable toxicity occurred.

Dose-limiting Toxicity and RD

A DLT was defined as any of following events observed in Cycle 1: febrile neutropenia; neutrophil counts $<500/mm^3$ for 5 days or longer without use of granulocyte colony-stimulating factor; platelet counts $<25\,000/mm^3$ or requiring platelet transfusion; Grade 3 non-hematological toxicity except for glucose, electrolyte, nausea, vomiting, anorexia, constipation and fatigue; treatment delay of Cycle 2 longer than 14 days and skipping of chemotherapy on Days 8 and 15 in Cycle 1 and treatment delay of Cycle 2 due to prolonged toxicities.

Dose Modification of FLTAX

When adverse events, described as follows, developed in Cycle 1, the dosage at Cycle 2 was reduced by one level: neutrophil counts $<500/mm^3$; febrile neutropenia; infection with Grade 3 or 4 neutropenia; platelet counts $<25\,000/mm^3$; Grade 3 or higher non-hematological toxicity except for glucose, electrolyte, nausea, vomiting, anorexia, constipation and fatigue; delay of Day 1 in Cycle 2 longer than 8 days or skipping of chemotherapy on both Days 8 and 15. Dose reduction was performed level-by-level from Level 2 to Level 0: the lowest dosage (Level 0) of 400 mg/m^2 of 5-FU, 200 mg/m^2 of *l*-LV and 50 mg/m^2 of paclitaxel, dosage of Level 1 and Level 2 is shown in *Study design and treatment*. Once the dosage of each drug was reduced, a regain in dosage was not permitted. If Grade 3 sensory neuropathy did not recover by the start of a subsequent cycle, treatment could be continued with 5-FU/*l*-LV alone. Dose adjustment was done on a per cycle basis but not within a cycle.

Criteria for Administration on Day 8 and 15

When adverse events, described as follows, developed on Day 8 and 15 in each cycle, administration of FLTAX was skipped: neutrophil counts $<1000/mm^3$, platelet counts $<75000/mm^3$, AST or ALT >150 IU/l, total bilirubin >2.0 mg/dl, serum creatinine >2.0 mg/dl, fever (38.0°C or higher), and physician's decision due to Grade 2 or higher non-hematological toxicities.

Criteria for Starting Cycle 2

After confirming that the following criteria were met, Cycle 2 was started: leukocyte counts $\geq 3000/mm^3$, neutrophil counts $\geq 1500/mm^3$, platelet counts $\geq 100\,000/mm^3$, serum creatinine ≤ 2.0 mg/dl, total bilirubin ≤ 2.0 mg/dl, without fever (38.0°C or higher) and recovery of non-hematological toxicities appearing in Cycle 1 to Grade 1 or lower at initiation of Cycle 2. If initiation of Cycle 2 was delayed more than 4 weeks from the scheduled initiation date, the patient was withdrawn from the study.

Study Assessments

Physical examination and laboratory tests were checked every week during the protocol treatment, and adverse events were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). Tumor response was evaluated for patients with measurable lesions after each cycle during protocol treatment with the Response Evaluation Criteria in Solid Tumors guidelines, version 1.0 using computed tomography of the chest, abdomen and pelvis (8). The ascites response was evaluated as follows: complete response (CR) was defined as disappearance of ascites; partial response (PR) was defined as decreasing by one or more levels, as described above; incomplete response/stable disease was defined as other than CR, PR or progressive disease (PD) and PD was defined as an increase by one or more level, or need for more frequent drainage.

Overall survival was defined from the date of registration to the date of death or to the last contact date. Progression-free survival was defined from the date of registration to the date of disease progression or death from any cause. If there was no documented disease progression and if the patient had not died, data on progression-free survival were censored on the date that the absence of progression was confirmed.

Study Endpoints

The primary endpoints were the RD of FLTAX based on the assessment of DLT and MTD in the first phase of the study,

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and the feasibility of FLTAX in peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake based on the completion rate of two cycles in the second phase. The secondary endpoints were safety, ascites response rate, progression-free survival and overall survival.

Statistical Analysis

The completion rate of two cycles of FLTAX as the primary endpoint was expected to be 60% based on data from clinical trials of advanced gastric cancer patients with ascites indicating a median treatment duration of 8–10 weeks (9–11). The threshold rate of completion of two cycles was set at 30%, with an α of 0.1 (one-sided) and power of 80%, and the required number of patients was 19. The target number of patients was set at 20 to allow for a sufficiently large study cohort after dropouts and exclusions. Progression-free survival and overall survival were estimated using the Kaplan–Meier method.

RESULTS

Patients

From June 2009 to July 2010, 32 patients were registered in this study: 13 patients were enrolled in the first phase—6 at Level 1, and 7 at Level 2. One patient at Level 2 was registered but never received protocol treatment and failed to meet the administration criteria over 7 days. Twenty-five patients who received the RD (including six patients at Level 1 in the first phase) were evaluated in the second phase. By the time of registration of 15 patients in the second phase, death within 30 days after the last administration of FLTAX including post-protocol treatment occurred in six patients (three second-line patients at Level 1, two second-line patients at Level 2 and one first-line patient at Level 2). All these patients died from disease progression, except one second-line patient at Level 2 who died due to a treatment-related cause. The continuation of this study was approved by the Date and Safety Monitoring Committee after protocol amendment to limit the patients in first-line setting. Table 1 shows the baseline demographics of the patients in the first and second phases.

Table 1. Patient characteristics

Category	First phase		Second phase
	Level 1 ($n = 6$)	Level 2 ($n = 6$)	RD ($n = 25$)[a]
Age, median (range)	63 (57–69)	49 (32–69)	65 (55–75)
Gender, male/female	5/1	3/3	15/10
ECOG PS, 0/1/2	0/4/2	0/5/1	1/19/5
Severe peritoneal metastasis			
Massive ascites	2	1	13
Inadequate oral intake	3	2	9
Massive ascites and inadequate oral intake	1	3	3
Drip infusion			
Peripheral infusion	2	0	3
IVH	2	5	9
Primary lesion			
Absent/present	1/5	1/5	5/20
Prior chemotherapy			
Absent	3	4	18
Present	3	2	7
S-1	1	0	1
S-1/CDDP	2	2	6
Histology			
Intestinal type	0	1	3
Diffuse type	5	4	21
Adenocarcinoma (only cytology)	1	1	1
Ascites			
None	0	0	1
Mild	3	2	6
Moderate	0	0	2
Massive	3	4	16

RD, recommended dose; ECOG, Eastern Cooperative Oncology Group; PS, performance status; IVH, intravenous hyperalimentation; CDDP, cisplatin.
[a]The RD group ($n = 25$ patients) included six patients at Level 1 dose in the first phase.

MTD and RD Determination

In the first phase, one of six patients at Level 1 had DLT of Grade 4 gastrointestinal perforation (a good response to chemotherapy resulted in perforated gastric cancer). Two of six patients at Level 2 had DLT (one had Grade 3 febrile neutropenia and another had Grade 3 infection of the central venous device without neutropenia), and there was one treatment-related death; a patient who developed pneumonia with Grade 4 neutropenia at 17 days after protocol treatment out of the DLT assessment period. Therefore, Level 2 was considered as the MTD and Level 1 was determined as the RD for the second phase of the study.

Feasibility and Safety

The completion rate of two cycles in the second phase was 92% [90% confidence interval (CI): 76.9–98.5]: 21 of 25 patients continued further FLTAX treatment after protocol treatment of two cycles, and the median number of cycles was 4 (range 1–11). The reasons for treatment discontinuation in the second phase were disease progression ($n = 21$)

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