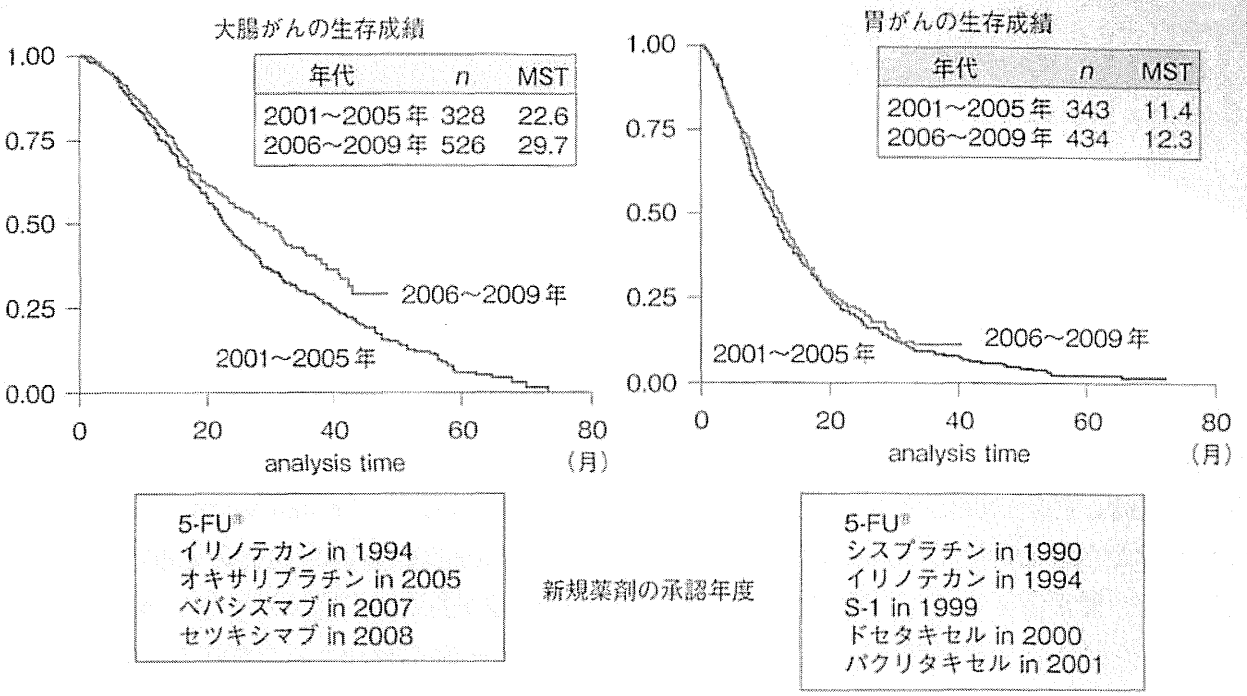

図2 大腸がんと胃がんにおける薬物療法の進歩（2000年以降）

（愛知県がんセンター中央病院のデータより）

イマチニブは，*c-kit*遺伝子のexon 11に変異があれば約80％で奏効が期待できるが，exon 9に変異があれば約50％である．イマチニブ耐性例ではイマチニブ増量投与のほかに，スニチニブの投与が推奨されている．スニチニブはKITを介して作用するだけでなく，血管内皮細胞成長因子受容体（vascular endothelial growth factor receptor：VEGFR）を遮断するマルチターゲットのチロシンキナーゼ阻害薬であり，exon 9および血小板由来成長因子受容体（platelet-derived growth factor receptor：PDGFR）に変異がある場合と野生型に有効性が高く，これらの変異がある場合と比較してexon 11に変異がある場合には有効性は低くなる．

留意すべき副作用として，イマチニブでは嘔気・嘔吐，下痢，浮腫，倦怠感，貧血・好中球減少などが挙げられ，スニチニブでは血小板減少などの骨髄抑制，皮膚変色（黄変），下痢，倦怠感，手足症候群など多岐にわたる．

肝細胞がんにおける分子標的治療薬

肝細胞がんに対する薬物療法は，切除，ラジオ波焼灼術，肝動脈化学塞栓術が適応とならない高度進行例や，肝動脈化学塞栓術での治療に抵抗性を示す多発例などが対象である．ソラフェニブは，プラセボと比較した第Ⅲ相試験において有意に良好な無増悪生存期間と全生存期間を示し，現在，進行肝細胞がんに対する標準治療として位置づけられている．ソラフェニブは，セリン/スレオニンキナーゼであるRafファミリーに対する阻害作用，MAPキナーゼシグナル伝達経路の阻害作用を介した腫瘍増殖抑制作用，EGFR-2/PDGFR-βシグナル伝達系の阻害作用を介した血管新生抑制作用などのマルチキナーゼ阻害薬であり，これら複数の機序を介して腫瘍の進行を抑制することが知られている．

留意すべき副作用として，手足症候群，肝機能障害，高血圧などが挙げられる．

● 原 著 ●
ORIGINAL ARTICLE

Efficacy of Docetaxel in Patients with Paclitaxel-Resistant Advanced Gastric Cancer

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Summary

Background: Although there appears to be incomplete cross-resistance between docetaxel and paclitaxel in several types of malignancies, to our best knowledge there have been no available data on this for advanced gastric cancer. Methods: We retrospectively evaluated the efficacy and safety of docetaxel in patients with paclitaxel-resistant advanced gastric cancer. Docetaxel was administered at 50-60 mg/m^2 every 3 weeks. Results: Twenty-one patients were evaluated. All patients had received 2 or more previous chemotherapy regimens. Among the 12 patients with measurable lesions, apparent tumor shrinkage was seen in 1 patient for an overall response rate of 8.3% and a disease control rate of 33.3%. Median progression free survival and overall survival of all patients were 2.6 months and 6.7 months, respectively. There were no correlations between the progression free survival of docetaxel and the progression free survival of previous paclitaxel and between the progression free survival of docetaxel and taxane-free interval (Spearman's correlation coefficients of $\rho=-0.14$ and $\rho=-0.02$, respectively). Grade 3/4 neutropenia developed in 8 patients (38%) and Grade 3 febrile neutropenia in 1 patient (4.8%). Conclusions: Docetaxel showed modest activity in paclitaxel-resistant advanced gastric cancer patients, and no correlations between previous efficacy of paclitaxel or taxane-free interval were seen. Key words: Gastric cancer, Paclitaxel, Docetaxel, Taxane-free interval (*Received Nov. 22, 2011/Accepted Mar. 13, 2012*)

要旨 他複数の癌腫においてパクリタキセルとドセタキセルの交叉耐性は不完全といわれているが，胃癌においての検討はない。われわれは，パクリタキセル不応の進行再発胃癌におけるドセタキセル単剤療法（50～60 mg/m^2，3週毎）の有効性と安全性をレトロスペクティブに調査した。対象となった21例は，全例で2レジメン以上の前治療を受けていた。測定可能病変を有する12例において，奏効率は8.3%（1例），病勢安定率は33.3%であった。無再発生存期間（PFS）は中央値2.6か月，全生存期間は中央値6.7か月であった。ドセタキセルのPFSと前治療のパクリタキセルのPFSとの関連は認めず，また，ドセタキセルのPFSとタキサン無治療期間（TFI）の関連も認めなかった（スピアマンの相関係数$\rho=-0.14$および$\rho=-0.02$）。副作用としてGrade 3/4の好中球減少症8例（38%），Grade 3の発熱性好中球減少症1例（4.8%）を認めた。パクリタキセル不応の進行再発胃癌におけるドセタキセル療法は，少数ながら効果の認められる症例が存在したものの，前治療のパクリタキセルの効果やTFIとの関連は認められなかった。

Introduction

The prognosis of patients with advanced gastric cancer (AGC) remains poor; commonly used combination chemotherapy regimens, consisting of a fluoropyrimidine plus a platinum agent with or without docetaxel or anthracyclines, provide a median survival of only 1 year[1-4]. Based on the results of the phase 3 SPIRITS trial[3], S-1 plus cisplatin is considered to be the standard first-line chemotherapy regimen for most Japanese AGC patients. However, the median progression-free survivals of first-line regimens have been approximately 4 to 6 months[1-4], and therefore many patients need second-line chemotherapy.

The taxanes, including docetaxel and paclitaxel, have been reported to be effective for gastric cancer. The reported response rate for monotherapy was approximately 20% in previous phase II studies[5-7]. Although docetaxel in combination therapy showed a survival benefit for AGC[1], paclitaxel, espe-

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cially administered weekly, has been commonly used in Japan as second-line or higher chemotherapy because of its feasibility[3,8-11]. Currently, there is an ongoing phase Ⅲ study comparing weekly paclitaxel to irinotecan for second-line AGC chemotherapy.

The principal mechanism of action of taxanes, including docetaxel and paclitaxel, is the induction of stable microtubule polymerization by inhibiting microtubule disassembly[12]. Because microtubules are essential for cell division, cells exposed to taxanes are arrested in the premitotic G_2 phase and fail to divide. Although these mechanisms are similar in paclitaxel and docetaxel, *in vivo* data have indicated that there are several differences between these 2 agents[13-15]. Not only did docetaxel show greater antitumor activity than paclitaxel against several cell lines[13,14], but also docetaxel was reported to induce Bcl-2 phosphorylation and apoptotic cell death at 100-fold lower concentrations than paclitaxel[15]. Supporting these preclinical results, there have been several clinical studies indicating the existence of incomplete cross-resistance between paclitaxel and docetaxel. In a phase Ⅱ study of paclitaxel-resistant patients with breast cancer, the overall response rate to docetaxel was reported to be 18.1%[16]. In 2 prospective studies using docetaxel monotherapy for ovarian cancer patients refractory to a first-line regimen containing paclitaxel, the reported response rates were 22.4% to 23%[17,18]. Finally, second-line docetaxel has shown a survival benefit for patients with non-small cell lung cancer regardless of previous paclitaxel exposure[19]. These results indicate incomplete cross-resistance between docetaxel and paclitaxel, although to our best knowledge, there have been no studies evaluating this in AGC. In this study therefore, we evaluated the efficacy and safety of docetaxel therapy for patients with paclitaxel-resistant AGC.

Ⅰ. Patients and methods

1. Patients

This was a retrospective cohort study of AGC patients who received docetaxel every 3 weeks after their disease had progressed when they were receiving weekly paclitaxel. To be included in the study, disease progression in subjects had to have been radiologically or clinically confirmed during the time they were receiving weekly paclitaxel or within 3 months after the last dose of paclitaxel. Other principal inclusion criteria included the following: histologically proven inoperable gastric cancer, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2, sufficient bone marrow function, and adequate liver and renal function.

A total of 132 patients with AGC were treated with docetaxel from January 2005 to March 2010 in our institution. Of these, 29 patients had received prior weekly paclitaxel therapy before docetaxel, and of these, 21 patients met the inclusion criteria and were included in the analysis. Written informed consent was collected from all patients before treatment.

2. Treatment delivery

After premedication using intravenous dexamethasone (8-16 mg), docetaxel was infused over a 1-hour period every 3 weeks, at a dose of 60 mg/m^2 in 17 patients and 50 mg/m^2 in 4 patients. In general, chemotherapy was delayed until recovery for a neutrophil count $<1.5\times10^9$/L, platelet count $<75\times10^9$/L, or any significant persisting nonhematologic toxicity. The docetaxel dose was reduced by 20% for the occurrence of Grade 4 neutropenia, febrile neutropenia, or Grade 3/4 thrombocytopenia. Other dose adjustments were made on an individual basis. Treatment was repeated until there was evidence of disease progression, unacceptable toxicity, or at the patient's request.

3. Evaluation of treatment and statistical analysis

Objective responses were evaluated every 8 weeks or earlier if there were indications of treatment failure due to disease progression or toxicity. Responses were graded according to response evaluation criteria in solid tumors (RECIST) as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Toxicity of docetaxel was evaluated according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) ver. 4.0.

Progression free survival (PFS) was measured from the first day of docetaxel administration until disease progression, or the date of death from any cause. PFS of previous paclitaxel was also calculated. Overall survival (OS) was measured from the first day of treatment to death from any cause. Median PFS and median OS were estimated by the Kaplan-Meier method. The interval between the final infusion of weekly paclitaxel and the first administration of docetaxel was defined as the taxane-free interval (TFI). The correlations between the PFS of docetaxel and the PFS of previous paclitaxel and the PFS of docetaxel and the TFI were evaluated using the nonparametric Spearman's rank correlation coefficient (ρ). Statistical analysis was performed using Graph-Pad Prism ver. 5.0 software (Graph-Pad software, San Diego, CA), and the significance level of the results was set at 0.05 (2-sided).

Ⅱ. Results

1. Patient characteristics

Patient characteristics are listed in Table 1. The median follow-up time at the time of analysis was 34.5 months (range, 7.3 to 60.9 months). The median age was 70 years. The dominant histology was poorly differentiated adenocarcinoma, and 38% of patients had peritoneal dissemination. All patients had previously received at least 2 chemotherapy regimens prior to docetaxel. Fourteen of 21 patients (67%) had been treated with irinotecan, and three of 7 patients did not receive irinotecan because of symptomatic peritoneal dissemination leading to intestinal stenosis. The median number of previous weekly paclitaxel administrations was 8 times (range, 4 to 48). The median TFI was 2.6 months (range, 0.3 to 17.0 months), and the median PFS of patients receiving paclitaxel before docetaxel was 3.7 months (range, 0.2 to 21.6

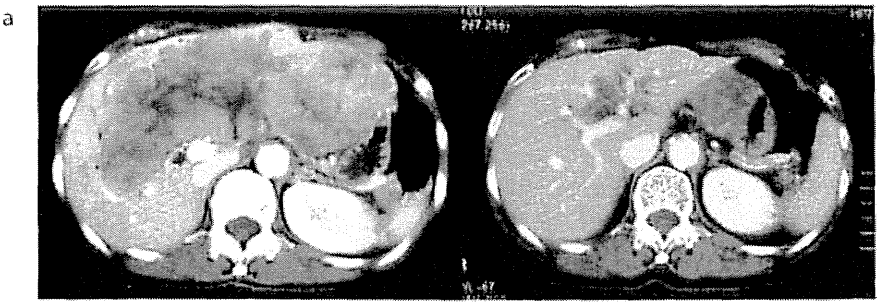

Fig. 1 A 71-year-old female with liver metastases from AGC refractory to S-1, paclitaxel, and irinotecan chemotherapy
a: CT scan acquired prior to docetaxel monotherapy showed large liver metastases.
b: CT scan acquired after 8 months of docetaxel chemotherapy. Apparent reductions in the size of multiple liver metastases are seen. Tumor responses were maintained for more than 1 year.

Table 1 Patient characteristics

Characteristics		n	%
Age (yr)	Median	70	—
	Range	44-77	—
Gender	Male	15	71
	Female	6	29
ECOG PS	0	8	38
	1	11	52
	2	2	10
Histological type*	Wel	3	14
	Mod	5	24
	Por	13	62
Metastatic sites	Liver	9	43
	Lymph nodes	8	38
	Peritoneum	8	38
Prior chemotherapeutic regimens	2	7	33
	3	10	48
	4	4	19
Prior irinotecan	Yes	14	67
Chemotherapy	No	7**	33
Prior paclitaxel	Median	8	—
Administration (times)	Range	4-48	—

ECOG PS: Eastern Cooperative Oncology Group performance status, wel/mod/por: well/moderately/poorly differentiated adenocarcinoma
*: According to the Japanese classification
**: 3 of the 7 patients were unable to use irinotecan because of intestinal obstruction

months).

2. Treatment results and objective response

The median number of docetaxel administrations was 4 times (range, 1 to 19). The dosage was reduced in 7 patients because of the following toxicities: Grade 4 neutropenia in 3, Grade 3 anorexia in 2, and Grade 3 anemia and febrile neutropenia each in 1. All patients stopped docetaxel due to progression except 1 patient lost of follow up during stable disease.

Among the 12 patients with measurable lesions evaluated using the RECIST, no patient achieved CR, 1 patient experienced PR (Fig. 1), and 3 had SD. Eight patients had PD. The

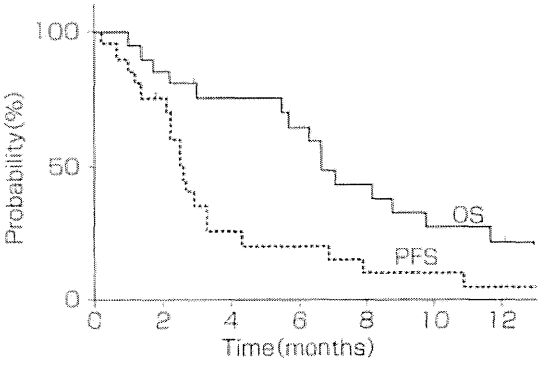

Fig. 2 Kaplan-Meier survival curve of progression-free survival and overall survival
The median progression free survival was 2.6 months (95% CI, 2.1-3.3 months) and the median overall survival was 6.7 months (95% CI, 2.2-9.8 months).

overall response rate was 8.3% [95% confidence interval (CI), 2.0-48.4%] and the disease control rate was 33.3% (95% CI, 10-65%). The median progression free survival of all patients was 2.6 months (95% CI, 2.1-3.3 months; Fig. 2), with 5 patients (23.8%) free from progression for more than 4 months. The median overall survival was 6.7 months (95% CI, 2.2-9.8 months; Fig. 2).

3. Toxicity

A total of 21 patients were assessable for toxicity. The toxicity profiles are listed in Table 2. Although Grade 3 or 4 neutropenia occurred in 8 patients (38%), febrile neutropenia was observed in only 1 patient. Peripheral neuropathy of Grade 1 or 2 was observed in 4 patients (19%), which did not necessitate stopping or reducing the dosage. Two patients were admitted to the hospital because of pneumonia without neutropenia, and they improved after antibiotics. Grade 3 pneumonitis and rash each occurred in 1 patient, and both conditions improved after steroid administration.

4. PFS of docetaxel and PFS of previous paclitaxel and TFI

Almost no correlations were observed between the PFS of docetaxel and the PFS of previous paclitaxel ($\rho = -0.14$; Fig.

Table 2 Toxicities

Toxicities	Grade				Grade
	1	2	3	4	3/4 (%)
Leukopenia	7	1	3	2	5 (24)
Neutropenia	3	1	3	5	8 (38)
Anemia	4	3	2	2	4 (19)
Thrombocytopenia	0	1	1	0	1 (5)
Anorexia	5	2	2	0	2 (10)
Fatigue	6	4	0	0	0
Nausea	6	0	0	0	0
Vomiting	1	0	0	0	0
Diarrhea	5	0	0	0	0
Mucositis	2	0	0	0	0
Neuropathy	3	1	0	0	0
Rash	1	0	1	0	1 (5)
Febrile neutropenia	—	—	1	0	1 (5)
Pneumonitis	0	0	1	0	1 (5)
Infection*	0	0	3	0	3 (15)

*: pneumonia

3) and between the PFS of docetaxel and TFI ($\rho=-0.02$; Fig. 4). With the 20 patients who stopped docetaxel due to disease progression, there were no correlations as well between the PFS of docetaxel and the PFS of previous paclitaxel ($\rho=-0.19$) and between the PFS of docetaxel and TFI ($\rho=-0.04$).

Ⅲ. Discussion

To our knowledge, this is the first report to evaluate the efficacy and safety of docetaxel monotherapy for patients with paclitaxel-resistant AGC. Although the low response rate may indicate that the activity of docetaxel against paclitaxel-resistant AGC was modest, the median PFS of 2.6 months and median OS of 6.7 months may not be inferior to previous reports of docetaxel monotherapy for patients with paclitaxel-naïve AGC[5,6] or to results of a newer agent in a similar setting[20].

There may be several reasons for the low response rate in our study of AGC patients compared with the rates seen in past studies of other cancers such as breast or ovarian cancer[16-18]. The dose of docetaxel used in those studies ranged from 80-100 mg/m^2 [16-18]. In our study, the dose was 50-60 mg/m^2, which is the approved dose for AGC in Japan, based on previous phase Ⅱ studies[5,6]. AGC is also relatively refractory to chemotherapy, including docetaxel, compared with ovarian and breast cancer[5,6,21,22]. In addition, since approximately half the patients in this study did not have measurable lesions, the response rate did not include these patients. Therefore, the small sample used for response evaluation may not accurately reflect the efficacy of docetaxel. We had 1 patient who achieved a PR for more than 1 year, despite apparent tumor progression after 8 weekly paclitaxel infusions without response. Additionally, 4 other patients were progression free for more than 4 months, which suggests that docetaxel may have had

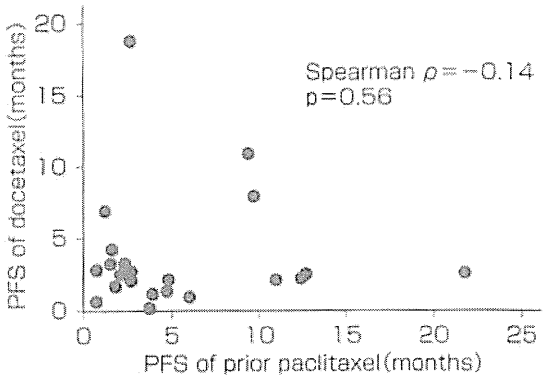

Fig. 3 PFS of docetaxel and prior paclitaxel
No correlation was observed between the PFS of docetaxel and the PFS of prior paclitaxel ($\rho=-0.14$, $p=0.56$).

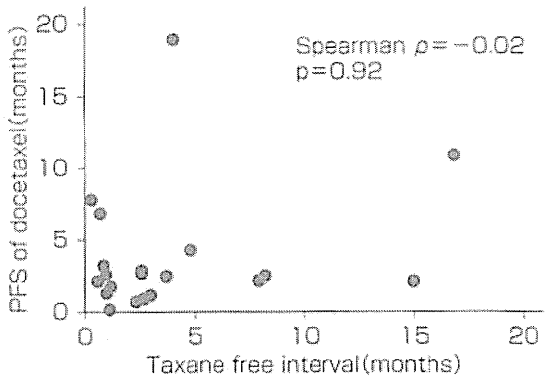

Fig. 4 TFI and PFS of docetaxel
No correlation was observed between TFI and the PFS of docetaxel ($\rho=-0.02$, $p=0.92$).

effects on disease stabilization. These cases demonstrate incomplete cross-resistance between docetaxel and paclitaxel in AGC. Therefore, identifying the patients with paclitaxel-resistant AGC who might achieve benefit from docetaxel may be extremely important.

Results of 2 previous studies of other cancers suggest that patients with a long TFI more often respond to a second taxane therapy[17,23]. However, in our study, the correlation between the PFS of docetaxel and TFI was quite low, as was the correlation between the PFS of docetaxel and the PFS of previous paclitaxel. Therefore additional study is needed to identify a predictive marker for docetaxel efficacy.

In the present study, there were no treatment-related deaths, and the frequencies of Grade 3 or 4 adverse events during treatment were similar to results of previous phase Ⅱ studies of docetaxel for AGC[5,6]. Gastrointestinal toxicity was quite low and no patient experienced Grade 3 or higher nausea and diarrhea, even though there were 3 patients with symptomatic peritoneal dissemination and intestinal stenosis. Although irinotecan is an effective agent for AGC treatment, it is associated with relatively high rates of gastrointestinal toxicity, especially in patients with severe peritoneal metastatic disease. Our results suggest that docetaxel may be a treatment option for these patients.

In conclusion, although the small sample size and retrospective single-institution study design were major limitations of this study, the results suggest that docetaxel may have modest efficacy in patients with paclitaxel-resistant advanced gastric cancer. Additional investigations to identify AGC patients most likely to benefit from taxane rechallenge appear to be necessary.

Conflict of interest statement: None of the authors have financial or personal conflicts of interest to disclose.

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References

1) Van Cutsem E, Moiseyenko VM, Tjulandin S, *et al*: Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* **24**(31): 4991-4997, 2006.
2) Cunningham D, Starling N, Rao S, *et al*: Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* **358**(1): 36-46, 2008.
3) Koizumi W, Narahara H, Hara T, *et al*: S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* **9**(3): 215-221, 2008.
4) Kang YK, Kang WK, Shin DB, *et al*: Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* **20**(4): 666-673, 2009.
5) Taguchi T, Sakata Y, Kanamaru R, *et al*: Late phase II clinical study of RP56976 (docetaxel) in patients with advanced/recurrent gastric cancer: a Japanese Cooperative Study Group trial (group A). *Gan To Kagaku Ryoho* **25**(12): 1915-1924, 1998.
6) Mai M, Sakata Y, Kanamaru R, *et al*: A late phase II clinical study of RP56976 (docetaxel) in patients with advanced or recurrent gastric cancer: a cooperative study group trial (group B). *Gan To Kagaku Ryoho* **26**(4): 487-496, 1998.
7) Yamada Y, Shirao K, Ohtsu A, *et al*: Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. *Ann Oncol* **12**(8): 1133-1137, 2001.
8) Hironaka S, Zenda S, Boku N, *et al*: Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. *Gastric Cancer* **9**(1): 14-18, 2006.
9) Kodera Y, Ito S, Mochizuki Y, *et al*: A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric Cancer (CCOG0302 study). *Anticancer Res* **27**(4C): 2667-2671, 2007.
10) Takiuchi H, Fukuda H, Boku N, *et al*: Randomized phase II study of best-available 5-fluorouracil (5-FU) versus weekly paclitaxel in gastric cancer (GC) with peritoneal metastasis (PM) refractory to 5-FU-containing regimens (JCOG0407). *J Clin Oncol* **28**(15S): abstr 4052, 2010.
11) Takashima A, Boku N, Kato K, *et al*: Survival prolongation after treatment failure in patients with advanced gastric cancer (AGC): Results from combined analysis of JCOG9205 and JCOG9912. *J Clin Oncol* **28**(15S): abstr 4061, 2010.
12) Donehower RC and Rowinsky EK: An overview of the experience with TAXOL (paclitaxel) in the U. S. A. *Cancer Treat Rev* **19**(*Suppl* C): 63-78, 1993.
13) Hanauske AR, Degen D, Hilsenbeck SG, *et al*: Effects of Taxotere and Taxol on in vitro colony formation of freshly explanted human tumor cells. *Anticancer Drugs* **3**(2): 121-124, 1992.
14) Kelland LR and Abel G: Comparative in vitro cytotoxicity of taxol and Taxotere against cisplatin-sensitive and -resistant human ovarian carcinoma cell lines. *Cancer Chemother Pharmacol* **30**(6): 444-450, 1992.
15) Haldar S, Basu A and Croce CM: Bcl2 is the guardian of microtubule integrity. *Cancer Res* **57**(2): 229-233, 1997.
16) Valero V, Jones SE, Von Hoff DD, *et al*: A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. *J Clin Oncol* **16**(10): 3362-3368, 1998.
17) Verschraegen CF, Sittisomwong T, Kudelka AP, *et al*: Docetaxel for patients with paclitaxel-resistant Müllerian carcinoma. *J Clin Oncol* **18**(14): 2733-2739, 2000.
18) Rose PG, Blessing JA, Ball HG, *et al*: A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* **88**(2): 130-135, 2003.
19) Fossella FV, DeVore R, Kerr RN, *et al*: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* **18**(12): 2354-2362, 2000.
20) Doi T, Muro K, Boku N, *et al*: Multicenter phase II study of everolimus in patients with previously treated metastatic gastric cancer. *J Clin Oncol* **28**(11): 1904-1910, 2010.
21) Nabholtz JM and Gligorov J: Docetaxel in the treatment of breast cancer: current experience and future prospects. *Expert Rev Anticancer Ther* **5**(4): 613-633, 2005.
22) Katsumata N: Docetaxel: an alternative taxane in ovarian cancer. *Br J Cancer* **89**(*Suppl* 3): S9-S15, 2003.
23) Yonemori K, Katsumata N, Uno H, *et al*: Efficacy of weekly paclitaxel in patients with docetaxel-resistant metastatic breast cancer. *Breast Cancer Res Treat* **89**(3): 237-241, 2005.

TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial

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Summary

Background Treatments that confer survival benefit are needed in patients with heavily pretreated metastatic colorectal cancer. The aim of this trial was to investigate the efficacy and safety of TAS-102—a novel oral nucleoside antitumour agent.

Methods Between August 25, 2009, and April 12, 2010, we undertook a multicentre, double-blind, randomised, placebo-controlled phase 2 trial in Japan. Eligible patients were 20 years or older; had confirmed colorectal adenocarcinoma; had a treatment history of two or more regimens of standard chemotherapy; and were refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin. Patients had to be able to take oral drugs; have measurable lesions; have an Eastern Cooperative Oncology Group performance status of between 0 and 2; and have adequate bone-marrow, hepatic, and renal functions within 7 days of enrolment. Patients were randomly assigned (2:1) to either TAS-102 (35 mg/m² given orally twice a day in a 28-day cycle [2-week cycle of 5 days of treatment followed by a 2-day rest period, and then a 14-day rest period]) or placebo; all patients received best supportive care. Randomisation was done with minimisation methods, with performance status as the allocation factor. The randomisation sequence was generated with a validated computer system by an independent team from the trial sponsor. Investigators, patients, data analysts, and the trial sponsor were masked to treatment assignment. The primary endpoint was overall survival in the intention-to-treat population. Safety analyses were done in the per-protocol population. The study is in progress and is registered with Japan Pharmaceutical Information Center, number JapicCTI-090880.

Findings 112 patients allocated to TAS-102 and 57 allocated to placebo made up the intention-to-treat population. Median follow-up was 11·3 months (IQR 10·7–14·0). Median overall survival was 9·0 months (95% CI 7·3–11·3) in the TAS-102 group and 6·6 months (4·9–8·0) in the placebo group (hazard ratio for death 0·56, 80% CI 0·44–0·71, 95% CI 0·39–0·81; p=0·0011). 57 (50%) of 113 patients given TAS-102 in the safety population had neutropenia of grade 3 or 4, 32 (28%) leucopenia, and 19 (17%) anaemia. No patient given placebo had grade 3 or worse neutropenia or leucopenia; three (5%) of 57 had grade 3 or worse anaemia. Serious adverse events occurred in 21 (19%) patients in the TAS-102 group and in five (9%) in the placebo group. No treatment-related deaths occurred.

Interpretation TAS-102 has promising efficacy and a manageable safety profile in patients with metastatic colorectal cancer who are refractory or intolerant to standard chemotherapies.

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Introduction

Colorectal cancer accounts for about 10% of all cancer cases and is the fourth leading cause of cancer-related deaths worldwide.[1] Cytotoxic agents such as a fluoropyrimidine, irinotecan, and oxaliplatin, and antibodies such as bevacizumab (an anti-VEGF monoclonal antibody) and cetuximab and panitumumab (anti-EGFR monoclonal antibodies) significantly improve the survival of patients with unresectable metastatic colorectal cancer.[2–5] Although many patients have a good long-term performance status, a standard treatment for those who are refractory to or unable to tolerate these agents does not exist.

TAS-102 (Taiho Pharmaceutical, Tokyo, Japan) is a novel oral nucleoside antitumour agent consisting of α,α,α-trifluorothymidine (FTD) and 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl-2,4 (1*H*,3*H*)-pyrimidinedione hydrochloride (TPI) at a molar ratio of 1:0·5. FTD is the active antitumour component of TAS-102: its monophosphate form inhibits thymidylate synthase and its triphosphate form is incorporated into DNA in tumour cells. The incorporation into DNA is known to have antitumour effects, because inhibition of thymidylate synthase caused by oral FTD rapidly disappears after the drug's elimination.[6] TPI is a potent inhibitor of thymidine phosphorylase, which is the enzyme that degrades FTD. After intravenous injection of FTD alone, sufficient concentrations have been recorded in plasma.[7] However, when monkeys are given oral FTD alone, it is rapidly degraded to its inactive

form in the intestines and liver (first-pass effect). Therefore, TPI is necessary to maintain adequate plasma concentrations of FTD that has been taken orally.[8]

Preclinical studies[9,10] have shown that TAS-102 exerts an antitumour effect against cancer cells irrespective of their sensitivity to fluoropyrimidines. TAS-102 has a mechanism of action different from that of other antitumour agents such as a fluoropyrimidine, irinotecan, and oxaliplatin. As a result, TAS-102 is expected to be effective against tumours refractory to the various antitumour agents available.

The results of several independent phase 1 clinical trials[11–13] of patients with solid tumours in the USA showed that the optimum dosage of TAS-102 was a 28-day cycle: a 2-week cycle of 5 days of treatment followed by a 2-day rest period, and then a 14-day rest period. The maximum tolerated dose was 25 mg/m² given orally twice daily to patients with heavily pretreated breast cancer.[14]

Subsequently, a phase 1 clinical trial[15] was done in Japan; the recommended dose was 35 mg/m² twice daily given orally, with the same treatment cycle. 21 patients were enrolled in the Japanese phase 1 study,[15] 18 of whom had colorectal cancer. Clinical benefit was achieved in 11 patients, including one with a partial response; eight were able to continue treatment for 12 weeks. These results suggested that TAS-102 could further improve the outcomes of patients with unresectable metastatic colorectal cancer who have already received conventional chemotherapy with a fluoropyrimidine, irinotecan, and oxaliplatin. Thus, we further investigated the efficacy and safety of TAS-102.

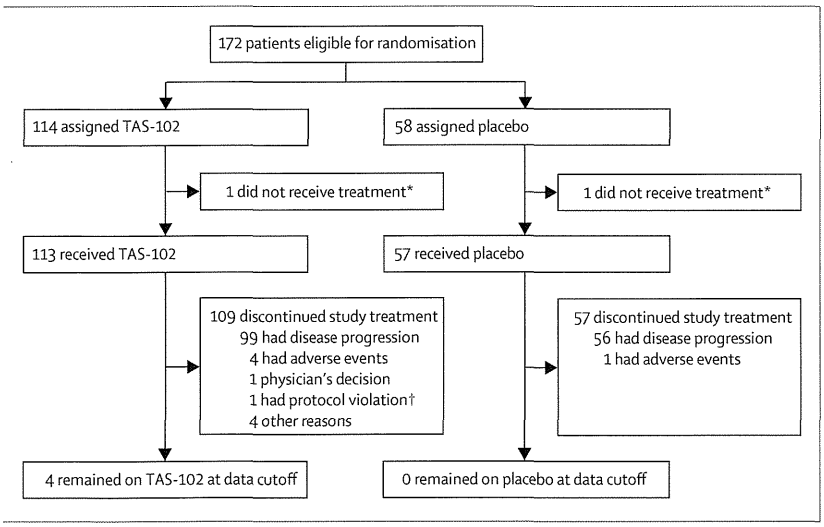

Figure 1: **Trial profile**
*One patient was randomly allocated to TAS-102 did not receive treatment because of aggravation of a rash related to previous chemotherapy and one patient allocated to placebo did not receive treatment because of occurrence of pulmonary thromboembolism; these patients were excluded from the efficacy and safety populations. †One patient received TAS-102 but was concomitantly taking a prohibited treatment, so was excluded from the efficacy population, but included in the safety population.

Methods

Study design and participants

Between Aug 25, 2009, and April 12, 2010, we undertook a multicentre, double-blind, randomised, placebo-controlled phase 2 trial of TAS-102 in Japan. Eligible patients were 20 years or older; had histologically or cytologically confirmed unresectable metastatic colorectal adenocarcinoma; had a previous treatment history of two or more regimens of standard chemotherapy; and were refractory or intolerant to a fluoropyrimidine, irinotecan, and oxaliplatin. Patients had to be able to take oral drugs; and to have measurable lesions as per the Response Evaluation Criteria In Solid Tumors (RECIST; version 1.0)[16] and an Eastern Cooperative Oncology Group (ECOG) performance status of between 0 and 2. Adequate bone-marrow, hepatic, and renal functions were established by tests within the 7 days before enrolment. Patients could have no serious comorbidities.

Previous treatments were discussed by the investigators in charge and study monitors before enrolment to confirm eligibility—ie, whether progression of disease as documented in medical records could be reasonably interpreted as refractory, and whether discontinuation due to unacceptable toxic effects could be reasonably interpreted as intolerance. Whether patients of doubtful eligibility could be enrolled was assessed by the steering committee (AO, TD, IH, and HB) at a central review meeting.

The study was done in accordance with the Declaration of Helsinki and the Japanese Good Clinical Practice guideline. The protocol was approved by the institutional review boards of participating hospitals. Written informed consent was obtained from all patients.

Randomisation and masking

Patients were randomly assigned in a 2:1 ratio to either TAS-102 plus best supportive care or placebo plus best supportive care through central registration. Randomisation was done with minimisation methods, with baseline ECOG performance status (0 *vs* 1 or 2) as the allocation factor. The randomisation sequence was generated by an independent team from the trial sponsor who used a validated computer system. Assignment of patients was initiated via fax. The investigators, patients, data analysts, and the trial sponsor were masked to the randomisation sequence and treatment assignment.

Procedures

A dose of 35 mg/m² TAS-102 was taken orally twice a day after meals (ie, 70 mg/m² per day). Two tablets (15 mg and 20 mg) were used to achieve the correct dose. TAS-102 or placebo was taken in a 28-day cycle: a 2-week cycle of 5 days of treatment followed by a 2-day rest period, and then a 14-day rest period. Placebo was matched to TAS-102 tablets for taste, colour, and size, and contained lactose, partly pregelatinised starch, stearic acid, hydroxypropyl methyl cellulose, polyethylene glycol, and

titanium oxide. In patients who had adverse events, the dose could be reduced by 10 mg/day as judged necessary on a course basis. Treatment continued until tumour progression, unacceptable toxic effects, or withdrawal of consent. Patients were not allowed to crossover between groups after progression or toxic effects.

All patients were examined and tested every 2 weeks. Diagnostic imaging was undertaken 4, 8, and 12 weeks after treatment initiation, and every 8 weeks thereafter. When treatment was discontinued for any reason other than progressive disease, diagnostic imaging was done according to the planned schedule until disease progression.

The primary endpoint of this study was overall survival, defined as the time between randomisation and death from any cause or the date of last follow-up. Secondary endpoints were progression-free survival (time between randomisation and disease progression or death from any cause), objective response, disease control (a complete or partial response plus stable disease more than 6 weeks from the initiation of study treatment), duration of response (time between point when patient first achieved complete or partial response and disease progression), time to treatment failure (time between randomisation and treatment discontinuation, disease progression, or death from any cause), efficacy of TAS-102 in patients with or without *KRAS* mutations, and adverse events. Progression-free survival, type and duration of response, and time to treatment failure were assessed by an external independent radiological review committee. *KRAS* mutational status was tested by the ARMS-Scorpion method in a central laboratory.[17] Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).[18] Adverse events were deemed to be serious when they led to death, were life-threatening, led to admission or extension of hospital stay, turned into permanent or noticeable disabilities or dysfunctions, triggered congenital abnormalities, or caused other medically important disorders.

We measured dose intensity and relative dose intensity at the cutoff date. Dose intensity was defined as cumulative dose (mg/m²) divided by the number of weeks from initial treatment to discontinuation. Relative dose intensity was defined as dose intensity (mg/m² per week) divided by initial dose (mg/m² per week).

Statistical analysis

A sample size of 162 patients with a one-sided significance level of 10% was necessary to verify superiority in overall survival with a power of 80%, with an expected hazard ratio (HR) of 0·67. Median overall survival was anticipated to be 9·0 months in the TAS-102 group and 6·0 months in the placebo group.[15] We judged a clinically relevant HR to be about 0·70. Patients continued to receive the study treatment (with group assignments remaining concealed) until the primary analysis of overall survival was done when the number of deaths reached 121 in both groups. The Kaplan-Meier method was used to estimate survival distribution. We used a stratified log-rank test, adjusted by the allocation factor, for comparisons between the two groups, and a Cox proportional hazards model to estimate HRs, the two-tailed 80% CIs corresponding to the significance level, and 95% CIs. Additionally, we did interaction tests to assess the treatment effects by the

	TAS-102 (n=112)	Placebo (n=57)
Men	64 (57%)	28 (49%)
Women	48 (43%)	29 (51%)
Age (years)	63 (28–80)	62 (39–79)
Eastern Cooperative Oncology Group performance status		
0	72 (64%)	35 (61%)
1	37 (33%)	21 (37%)
2	3 (3%)	1 (2%)
Diagnosis		
Colon cancer	63 (56%)	36 (63%)
Rectal cancer	49 (44%)	21 (37%)
Number of metastatic organs		
1	25 (22%)	11 (19%)
2	43 (38%)	20 (35%)
3	27 (24%)	12 (21%)
≥4	17 (15%)	14 (25%)
Metastatic organ		
Liver	65 (58%)	38 (67%)
Lung	87 (78%)	44 (77%)
Lymph nodes	48 (43%)	23 (40%)
Peritoneum	11 (10%)	17 (30%)
Previous treatment and reason for discontinuation		
Surgical history	103 (92%)	50 (88%)
Adjuvant chemotherapy	54 (48%)	15 (26%)
Number of palliative chemotherapies		
2	17 (15%)	13 (23%)
≥3	95 (85%)	44 (77%)
Fluoropyrimidine-based treatment	112 (100%)	57 (100%)
Refractory	109 (97%)	55 (96%)
Intolerant	3 (3%)	2 (4%)
Oxaliplatin-based treatment	112 (100%)	57 (100%)
Refractory	95 (85%)	45 (79%)
Intolerant	17 (15%)	12 (21%)
Irinotecan-based treatment	112 (100%)	57 (100%)
Refractory	106 (95%)	56 (98%)
Intolerant	6 (5%)	1 (2%)
Bevacizumab	87 (78%)	47 (82%)
Cetuximab	71 (63%)	36 (63%)
KRAS mutational status*		
Wild-type	54 (55%)	24 (48%)
Mutant	45 (45%)	26 (52%)

Data are n (%) or median (range). *KRAS mutational status assessed for 99 (88%) patients in the TAS-102 group and for 50 (88%) patients in the placebo group.

***Table 1:* Demographics and baseline characteristics of the efficacy population**

allocation factor as well as baseline characteristics, including *KRAS* mutational status.

We compared progression-free survival and time to treatment failure with the log-rank test. We compared objective response, disease control, and toxic effects with Fisher's exact test. We also did interaction tests for progression-free survival and disease control to assess the differences between treatment effects by the allocation factor as well as baseline characteristics, including *KRAS* mutational status. Relative dose intensity was calculated as the ratio of the actual dose taken to the planned dose.

The efficacy analysis was done in the intention-to-treat population, and the safety analysis in the per-protocol population. We used SAS (version 8.2) for statistical analyses.

See Online for appendix

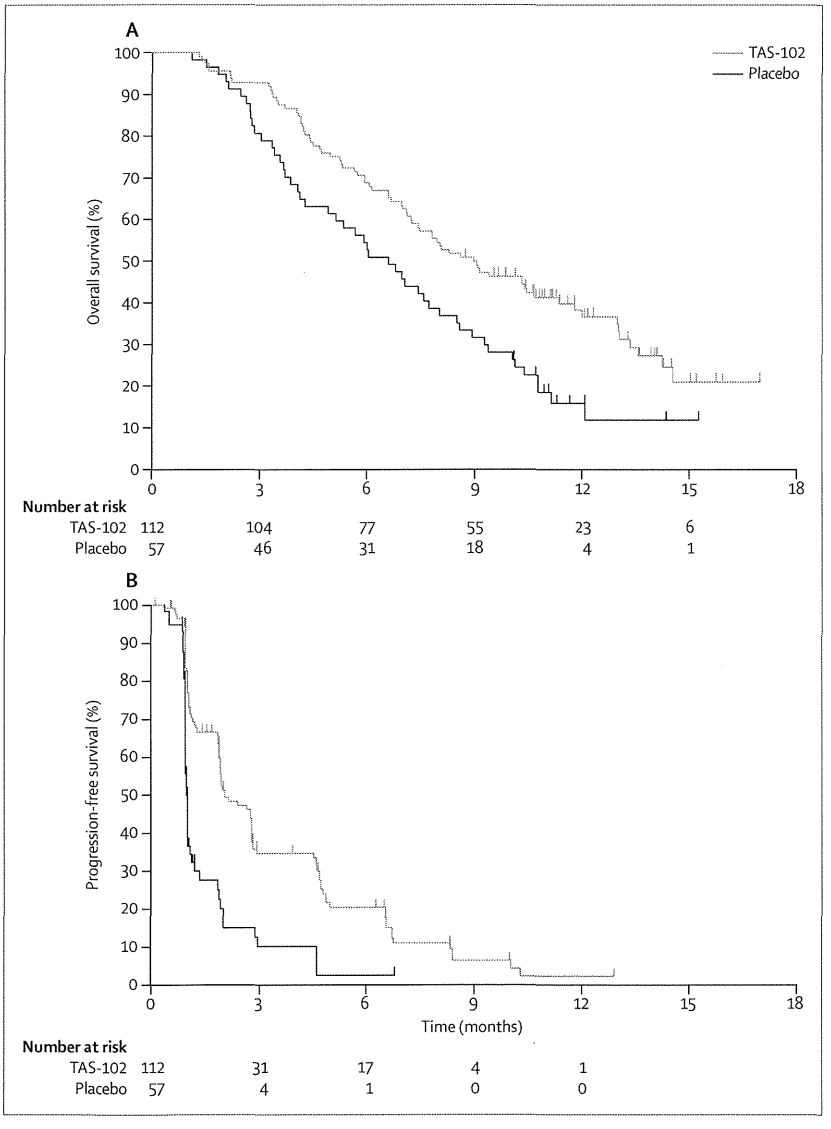

Figure 2: Kaplan-Meier curves of overall survival (A) and progression-free survival (B) as assessed by independent review committee

This study is registered with Japan Pharmaceutical Information Center, number JapicCTI-090880.

Role of the funding source

The study sponsor contributed to study design, data collection, and data analysis, but not to data interpretation. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Table 1 shows baseline characteristics of patients in the efficacy analysis. Most patients were judged to be refractory to all agents available for colorectal cancer treatment. Tumour tissues for central assessment of *KRAS* mutational status were available from 149 patients (88%; table 1). Baseline characteristics were much the same in the two groups, with the exception that more patients in the TAS-102 group received adjuvant chemotherapy than did those in the placebo group. Baseline characteristics in the *KRAS* population were similar to those in the efficacy population (data not shown). 49 (91%) patients with wild-type *KRAS* in the TAS-102 group and 23 (96%) in the placebo group had been given an anti-EGFR monoclonal antibody. Median follow-up was 11·3 months (IQR 10·7–14·0).

The cutoff date for overall survival was Feb 4, 2011. 123 deaths (75 in the TAS-102 group, 48 in the placebo group) had occurred by this point. Median overall survival was 9·0 months (95% CI 7·3–11·3) in the TAS-102 group and 6·6 months (4·9–8·0) in the placebo group (hazard ratio [HR] for death 0·56, 80% CI 0·44–0·71, 95% CI 0·39–0·81; p=0·0011; figure 2). In the prespecified subgroup analyses for overall survival, the effect of TAS-102 was similar in all categories, although not all improvements were significant (figure 3).

Median progression-free survival assessed by the independent review committee was 2·0 months (95% CI 1·9–2·8) in the TAS-102 group and 1·0 months (1·0–1·0) in the placebo group (HR 0·41, 95% CI 0·28–0·59; p<0·0001; figure 2). Median progression-free survival assessed by the investigators was 2·7 months (1·9–3·2) in the TAS-102 group and 1·0 months (1·0–1·0; HR 0·35, 95% CI 0·25–0·50; p<0·0001; appendix).

In both the assessment by the independent review committee and by investigators, one patient (1%) in the TAS-102 group achieved a partial response, with a duration of more than 225 days (ie, response continuing). No patients achieved an objective response in the placebo group. In the assessment by the independent review committee, 49 (43%) patients given TAS-102 achieved disease control (one [1%] patient had a partial response and 48 [43%] patients had stable disease), as did six (11%) given placebo (all six had stable disease; p<0·0001). In the investigator assessment,

61 (54%) patients given TAS-102 achieved disease control (one [1%] had a partial response and 60 [54%] had stable disease), as did eight (14%) given placebo (all eight had stable disease; p<0·0001). In the subgroup analyses and interaction tests for progression-free survival and disease control, the effect of TAS-102 was largely consistent across all categories (although not always significant; appendix).

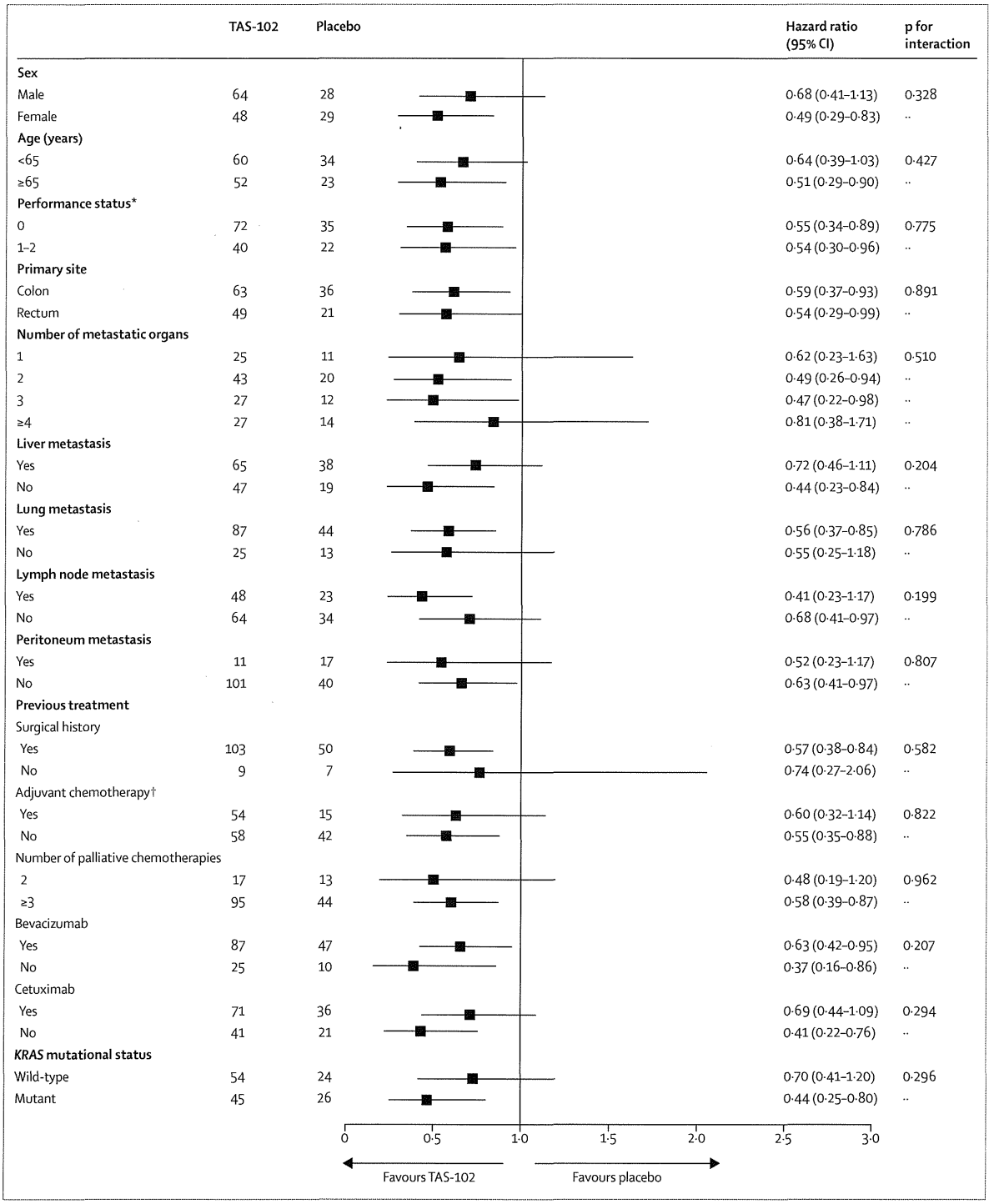

Figure 3: **Overall survival in prespecified subgroups**
*Eastern Cooperative Oncology Group criteria. †More patients received adjuvant chemotherapy in the TAS-102 group than in the placebo group, but this difference had no effect on the assessment of overall survival with the Cox proportional hazards model with one variable (p=0·605); there was no interaction (p=0·822).

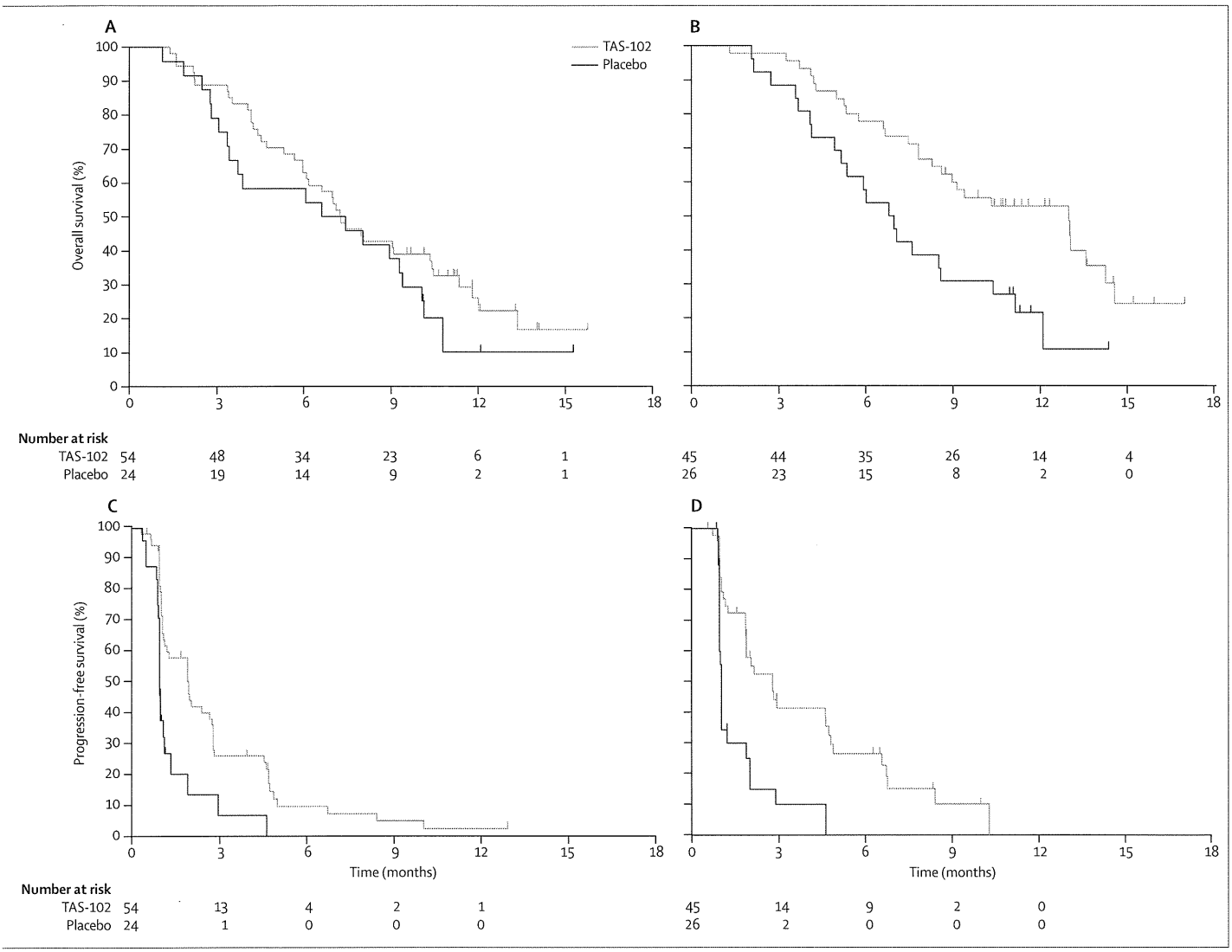

Figure 4: **Kaplan-Meier curves of overall survival and progression-free survival in patients with wild-type and mutant *KRAS***
(A) Overall survival of patients with wild-type *KRAS*. (B) Overall survival of patients with mutant *KRAS*. (C) Progression-free survival of patients with wild-type *KRAS*, as assessed by independent review committee. (D) Progression-free survival of patients with mutant *KRAS*, as assessed by independent review committee.

Median time to treatment failure assessed by the independent review committee was 1·9 months (95% CI 1·3–2·1) in the TAS-102 group and 1·0 months (1·0–1·0) in the placebo group (HR 0·40, 95% CI 0·28–0·56; p<0·0001). Median time to treatment failure assessed by the investigators was 2·7 months (95% CI 1·9–3·2) in the TAS-102 group and 1·0 months (1·0–1·0) in the placebo group (HR 0·34, 95% CI 0·24–0·49; p<0·0001).

In the TAS-102 group, 22 (20%) patients required at least one dose reduction, mainly because of neutropenia or thrombocytopenia, or both. 35 (31%) patients given TAS-102 required a treatment interruption, predominantly due to neutropenia. The median length of treatment interruption was 7 days (IQR 3·0–8·5). Toxic effects resolved sufficient to reinitiate treatment in all cases. The dose intensity of TAS-102 after the initial dose was 147 mg/m² per week and its relative dose intensity was 85·7%. At the time of data cutoff, 165 patients had discontinued treatment, 155 (94%; 99 TAS-102, 56 placebo) of whom did so because of disease progression. Four patients continued to receive TAS-102 treatment at data cutoff.

TAS-102 could be effective irrespective of *KRAS* mutational status (figure 3), although the drug seemed to have more of an effect on overall survival in patients with *KRAS* mutations. In patients with wild-type *KRAS*, median overall survival was 7·2 months (95% CI 6·1–10·3) in those given TAS-102 and 7·0 months (3·4–9·4) in those given placebo (p=0·191; figure 3). In patients with mutant *KRAS*, median overall survival was 13·0 months (8·6–14·3) in TAS-102 group and 6·9 months (5·2–8·6) in the placebo group (p=0·0056; figures 3, 4).

Median progression-free survival was 1·9 months (95% CI 1·1–2·8) in patients with wild-type *KRAS* given TAS-102 and 1·0 months (1·0–1·1) in those given placebo (HR 0·40, 95% CI 0·23–0·69; p=0·0004) as assessed by the independent review committee. It was 2·8 months (95% CI 1·9–4·7) in patients with mutant *KRAS* given TAS-102 and 1·0 month (1·0–1·2) in those given placebo (HR 0·34, 95% CI 0·19–0·61; p<0·0001; p for interaction=0·772; figure 4; appendix). 22 (41%) patients with wild-type *KRAS* in the TAS-102 group achieved disease control (one [2%] had a partial response, 21 [39%] had stable disease), as did two (8%) in the placebo group (both had stable disease; p=0·0038) as assessed by the independent review committee. 21 (47%) patients with mutant *KRAS* given TAS-102 achieved disease control (all had stable disease), as did three (12%) given placebo (all had stable disease; p=0·0037; p for interaction=0·835; appendix).

Grade 3–4 neutropenia, leucopenia, anaemia, fatigue, and diarrhoea were frequently recorded in the TAS-102 group (table 2). By contrast, grade 3 or worse adverse events were uncommon in the placebo group (table 2). No patients had hand-foot syndrome or peripheral neuropathy of grade 3 or more. Serious adverse events occurred in 21 (19%) patients in the TAS-102 group and five (9%) in the placebo group. Febrile neutropenia was the most common serious adverse event in the TAS-102 group, occurring in four (4%) patients. Eight (7%) patients in the TAS-102 group and nine (16%) in the placebo group died within 12 weeks of the start of treatment; all deaths were caused by progressive disease. Four (4%) patients in the TAS-102 group and one (2%) in the placebo group discontinued the study because of drug-related adverse events and one (1%) patient in the TAS-102 group discontinued treatment because of a non-related adverse event. No treatment-related deaths were reported during this study. The proportion of patients who received subsequent treatments in both groups was similar (table 3).

	TAS-102 (n=113)		Placebo (n=57)		p value*
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	
Haematological					
Neutropenia	81 (72%)	57 (50%)	1 (2%)	0	<0·0001
Leucopenia	86 (76%)	32 (28%)	2 (4%)	0	<0·0001
Anaemia	82 (73%)	19 (17%)	9 (16%)	3 (5%)	<0·0001
Lymphopenia	39 (35%)	11 (10%)	7 (12%)	2 (4%)	0·0019
Thrombocytopenia	44 (39%)	5 (4%)	1 (2%)	0	<0·0001
Non-haematological					
Fatigue	66 (58%)	7 (6%)	24 (42%)	2 (4%)	0·052
Diarrhoea	43 (38%)	7 (6%)	12 (21%)	0	0·037
Nausea	73 (65%)	5 (4%)	16 (28%)	0	<0·0001
Anorexia	70 (62%)	5 (4%)	19 (33%)	2 (4%)	0·0006
Febrile neutropenia	5 (4%)	5 (4%)	0	0	0·170
Vomiting	38 (34%)	4 (4%)	14 (25%)	0	0·290

Data are n (%). The safety population included all patients who received at least one dose of the study treatment. *p values were calculated with Fisher's exact test for the difference in the incidence of adverse events of any grade.

***Table 2:* Adverse events with a frequency of at least 3% in the safety population**

	TAS-102 (n=108)*	Placebo (n=57)*
Subsequent cancer treatment	46 (43%)	26 (46%)
Fluoropyrimidine-based treatment	30 (28%)	21 (37%)
Irinotecan-based treatment†	8 (7%)	12 (21%)
Oxaliplatin-based treatment	13 (12%)	10 (18%)
Bevacizumab	13 (12%)	12 (21%)
Anti-EGFR monoclonal antibody	12 (11%)	5 (9%)

Data are n (%). *Number of patients who discontinued the study treatment. †More patients in the placebo group received irinotecan-based treatment than in the TAS-102 group (p=0·022 by Fisher's exact test).

***Table 3:* Cancer treatment after discontinuation of study treatment**

Discussion

Compared with placebo, TAS-102 reduces the risk of death in patients refractory or intolerant to two or more regimens of standard chemotherapy containing a fluoropyrimidine, irinotecan, and oxaliplatin. Additionally, TAS-102 significantly improves progression-free survival and increases the proportion of patients who achieve disease control, relative to placebo. Although only one patient achieved a partial response in the TAS-102 group, the proportion who achieved disease control in this group was significantly higher than in the placebo group. The increase in disease control in the TAS-102 group could have contributed to the improved progression-free survival and overall survival in patients treated with this agent.

KRAS mutations are generally thought to be a negative predictive marker for the treatment effect of an anti-EGFR monoclonal antibody.[19,20] Because the mechanism of action of TAS-102 involves direct incorporation of FTD into DNA, it seems likely that *KRAS* will not directly affect the activity of TAS-102. In an in-vivo study with COL-1 cells harbouring wild-type *KRAS* and HCT-116 cells harbouring mutant *KRAS*, TAS-102 had an antitumour effect on both types of tumour cell (unpublished data). We recorded no significant interaction between *KRAS* mutational status and activity of TAS-102. Moreover, when we did an adjusted analysis for overall survival, progression-free survival, and disease control as assessed by independent review committee, including the interaction between *KRAS* mutational status and effect of TAS-102, we obtained results similar to those of the primary analysis (data not shown). However, TAS-102 had greater efficacy in the patients with mutant *KRAS* than in those with the wild-type allele. Because this subgroup analysis was based on a small number of patients, further investigation in future clinical studies with large sample sizes are necessary. The results of our pharmacogenomic study to assess the

Panel: Research in context

Systematic review

In April, 2008, we searched PubMed, the database of the American Society of Clinical Oncology, and National Comprehensive Cancer Network clinical practice guidelines in oncology (both colon and rectal cancers) for reports published in English. We used the keywords "colorectal cancer", "standard chemotherapy and colorectal cancer", "fluoropyrimidine, irinotecan, oxaliplatin, and colorectal cancer", "cetuximab and colorectal cancer", "panitumumab and colorectal cancer", "bevacizumab and colorectal cancer", "*KRAS* and colorectal cancer", "*KRAS* and cetuximab", "*KRAS* and panitumumab", and "salvage therapy". Established standard treatments for patients with metastatic colorectal cancer are chemotherapy based on fluoropyrimidine, oxaliplatin, and irinotecan (in combination and sequentially), and monoclonal antibodies targeting VEGF (bevacizumab) and EGFR (cetuximab and panitumumab in patients with *KRAS* wild-type tumours only). For patients who have disease progression despite all available standard treatment, additional options are needed; many could maintain good performance status and be candidates for new treatment options.

Interpretation

TAS-102 has promising efficacy with an easily manageable safety profile in patients with metastatic colorectal cancer who are refractory or intolerant to standard chemotherapies with fluoropyrimidine, irinotecan, and oxaliplatin. The results of our study could further improve the outcomes of patients with unresectable colorectal cancer who have already received standard chemotherapy regimens.

value of expression of thymidine kinase 1 and thymidine phosphorylase as predictive factors of the treatment effect of TAS-102 will be reported elsewhere.

The toxic effects of TAS-102 were generally mild and the agent was well tolerated. Myelosuppression was the main adverse event caused by TAS-102, but was manageable with dose reductions or temporary interruptions in treatment. Non-haematological adverse events such as peripheral neuropathy, hand-foot syndrome, fatigue, and diarrhoea—often recorded with other cytotoxic agents[21,22]—were uncommon. Subsequent treatments that could be potential confounders of an overall survival endpoint, such as cytotoxic and molecular targeting agents, were given to similar or greater proportions of patients in the placebo group than in the TAS-102 group.

No clear definitions of refractory disease or intolerance were specified in the protocol, except that recurrence during or within 6 months after completion of adjuvant chemotherapy was defined as refractory. However, previous treatments were discussed before enrolment to ensure that all participants were eligible. Additionally, the initial imaging diagnosis was done 4 weeks after randomisation, which is earlier than is usual in similar studies (normally 8 weeks).[4,5] Because disease progression had been identified in 38 (67%) patients in the placebo group at initial imaging, median progression-free survival in the placebo group was 1 month in assessments by the independent review and the investigators, and thus is unlikely to be excessively biased.

Our double-blind, randomised, placebo-controlled phase 2 trial had a small sample size and only Japanese patients were enrolled. In view of the differences in haematological toxic effects, we believe that the investigators in charge might have been aware of the assignment for some patients, but that each patient was not aware of his or her assignment, because no patient's withdrawal because of their assignment was recorded. However, all secondary efficacy endpoints were assessed by independent review.

The issue of the different recommended doses in Japan and the USA (35 mg/m² *vs* 25 mg/m²), despite similar pharmacokinetic profiles in the two populations, needs to be resolved. The recommended dose in patients from the USA is low on the basis of the high incidence of neutropenia of grade 3 or worse—one of the dose-limiting toxic effects of TAS-102—in patients with heavily pretreated metastatic breast cancer who had received several lines of previous aggressive chemotherapies and might have been particularly sensitive to TAS-102 because of poor bone-marrow reserves.[14] US investigators have done an additional trial to investigate the tolerability of the Japanese recommended dose of TAS-102 in US patients for pretreated metastatic colorectal cancer, which has been suggested to be tolerable and to have a safety profile consistent with that in Japanese patients.[23]

In conclusion, TAS-102 has promising efficacy with a manageable safety profile in patients with metastatic colorectal cancer who are refractory or intolerant to standard chemotherapy (panel). An international phase 3 trial to confirm the clinical benefits of TAS-102 in all populations is in progress (RECOURSE; NCT01607957), comparing TAS-102 monotherapy (with the same dosage and dose schedule as in our study) plus best supportive care with placebo plus best supportive care in patients with metastatic colorectal cancer who are refractory or intolerant to all approved agents including fluoropyrimidine, irinotecan, oxaliplatin, bevacizumab, and anti-EGFR monoclonal antibodies.

Contributors

All authors wrote the report and approved the final draft. TY, NM, KYamaz, TN, YK, HB, AT, KYamag, KM, NS, YT, TM, and TE collected data. TY advised on the content of the study protocol related to *KRAS* research, on doubts that arose during the study, and on measurement methods and data interpretation. HB and AO coordinated trial implementation in all sites, including coordination of the study protocol and resolution of doubts in its interpretation. CH and TT interpreted data. TT analysed data.

Conflicts of interest

TY has received consulting fees from Takeda; honoraria from Chugai, Takeda, Yakult, Bristol-Myers Squibb, and MerckSerono; and research funding from Daiichi Sankyo, Taiho, Bayer, and ImClone. YK has received consulting fees, honoraria, and research funding from Taiho.

HB owns Taiho stock, and has received honoraria, research funding, and travel grants from Taiho. AT and TE have received honoraria from Taiho. KYamag has received honoraria from Chugai, Bristol-Myers Squibb, and MerckSerono. KM has received consulting fees from Ono and Novartis; honoraria from Taiho, Chugai, Yakult, Bristol-Myers Squibb, and Takeda; and research funding from Taiho, Yakult, Daiichi Sankyo, Pfizer, AstraZeneca, Kyowa Hakko Kirin, Eizai, and MerckSerono. TM and TE have received research funding from Taiho. CH has received consulting fees from Taiho. TT is employed by Taiho, and owns Taiho stock. AO is employed by Bayer; has received consulting fees from Takeda, Daiichi Sankyo, Novartis, Chugai, and Taiho; and has received honoraria from Takeda, Daiichi Sankyo, Taiho, GlaxoSmithKline, Pfizer, Yakult, MerckSerono, and Bristol-Myers Squibb. The other authors declare that they have no conflicts of interest.

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References

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61:** 69–90.

2 Van Cutsem E, Nordlinger B, Cervantes A. Advanced colorectal cancer: ESMO clinical practice guidelines for treatment. *Ann Oncol* 2010; **21** (suppl 2): v93–97.

3 National Comprehensive Cancer Network. NCCN guidelines for: colon cancer (version 3.2012). 2012. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed April 26, 2012).

4 Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med* 2007; **357:** 2040–48.

5 Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007; **25:** 1658–64.

6 Tanaka N, Oguchi K, Fujita R, et al. Trifluorothymidine incorporation into DNA strongly enforces the potential of TAS-102 and leads to remarkably prolonged survival of cancer patients. American Association for Cancer Research; Chicago, IL, USA; April 15, 2012. 1783.

7 Dexter DL, Wolberg WH, Ansfield FJ, et al. The clinical pharmacology of 5-trifluoromethyl-2'-deoxyuridine. *Cancer Res* 1972; **32:** 247–53.

8 Fukushima M, Suzuki N, Emura T, et al. Structure and activity of specific inhibitors of thymidine phosphorylase to potentiate the function of antitumor 2'-deoxyribonucleosides. *Biochem Pharmacol* 2000; **59:** 1227–36.

9 Murakami Y, Kazuno H, Emura T, Tsujimoto H, Suzuki N, Fukushima M. Different mechanisms of acquired resistance to fluorinated pyrimidines in human colorectal cancer cells. *Int J Oncol* 2000; **17:** 277–83.

10 Emura T, Murakami Y, Nakagawa F, Fukushima M, Kitazato K. A novel antimetabolite, TAS-102 retains its effect on FU-related resistant cancer cells. *Int J Mol Med* 2004; **13:** 545–49.

11 Hong DS, Abbruzzese JL, Bogaard K, et al. Phase I study to determine the safety and pharmacokinetics of oral administration of TAS-102 in patients with solid tumors. *Cancer* 2006; **107:** 1383–90.

12 Overman MJ, Varadhachary G, Kopetz S, et al. Phase 1 study of TAS-102 administered once daily on a 5-day-per-week schedule in patients with solid tumors. *Invest New Drugs* 2008; **26:** 445–54.

13 Overman MJ, Kopetz S, Varadhachary G, et al. Phase I clinical study of three times a day oral administration of TAS-102 in patients with solid tumors. *Cancer Invest* 2008; **26:** 794–99.

14 Green MC, Pusztai L, Theriault LR, et al. Phase I study to determine the safety of oral administration of TAS-102 on a twice daily (BID) schedule for five days a week (wk) followed by two days rest for two wks, every (Q) four wks in patients (pts) with metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 2006; **24:** abstr 10576.

15 Doi T, Ohtsu A, Yoshino T, et al. Phase I study of TAS-102 treatment in Japanese patients with advanced solid tumours. *Br J Cancer* 2012; **107:** 429–34.

16 Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; **92:** 205–16.

17 Sheridan C. EGFR inhibitors embrace *KRAS*. *Nat Biotechnol* 2008; **26:** 839–40.

18 Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v3.0. Aug 9, 2006. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf (accessed April 20, 2009).

19 Lievre A, Bachet JB, Boige V, et al. *KRAS* mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol* 2008; **26:** 374–79.

20 Karapetis CS, Khambata-Ford S, Jonker DJ, et al. *K-ras* mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008; **359:** 1757–65.

21 Cassidy J, Clarke S, Díaz-Rubio E, et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. *Br J Cancer* 2011; **105:** 58–64.

22 Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; **22:** 229–37.

23 Patel M, Bendell J, Mayer RJ, et al. A phase 1 dose-escalation study of TAS-102 in patients (pts) with refractory metastatic colorectal cancer (mCRC). *Proc Am Soc Clin Oncol* 2012; **30:** abstr 3631.

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ORIGINAL ARTICLE

A phase II trial of ixabepilone in Asian patients with advanced gastric cancer previously treated with fluoropyrimidine-based chemotherapy

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Abstract
Purpose The highest rates of gastric cancer occur in Eastern Asia. Fluoropyrimidine-based therapy is used initially in unresectable and metastatic disease, but no single standard of care exists following disease progression. Ixabepilone, an epothilone B analog, is a non-taxane microtubule-stabilizing agent with clinical activity across multiple tumor types approved by the United States Food and Drug Administration for treatment of metastatic breast cancer.
Methods Asian patients with unresectable or metastatic gastric adenocarcinoma who had failed fluoropyrimidine-based chemotherapy received ixabepilone 40 mg/m^2 by 3-h intravenous infusion every 3 weeks. The primary endpoint was objective response rate (ORR).
Results Fifty-two patients were treated (65.4 % men; median age: 56.5 years). The ORR was 15.4 % (95 % confidence interval [CI] 6.9–28.1); 8 patients achieved partial responses for a median duration of 3.1 months (95 % CI 2.6–4.1 months) and 26 patients (50.0 %) had stable disease. Median progression-free survival was 2.8 months (95 % CI 2.1–3.5 months). The most common grade 3 non-hematological toxicities were fatigue (9.6 %), decreased appetite (7.7 %), sensory neuropathy (5.8 %),

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and diarrhea (5.8 %). Grade 3/4 neutropenia occurred in 46.2 % of patients.

Conclusions Ixabepilone is active in Asian patients with advanced gastric cancer and shows a toxicity profile similar to those previously reported in other tumor types.

Keywords Gastric cancer · Second-line therapy · Asian patients · Ixabepilone

Introduction

Gastric cancer was newly diagnosed in an estimated 989,600 people and caused an estimated 738,000 deaths worldwide in 2008 [1]; it was the third leading cause of cancer deaths in men and fifth leading cause in women. The highest rates of gastric cancer occur in Eastern Asia, where the age-standardized incidence is 42.4 per 100,000 among men and 18.3 per 100,000 among women [1]. Surgery with curative intent is the mainstay of treatment in localized disease, with perioperative chemotherapy or adjuvant chemoradiation or chemotherapy for patients with stage II or III disease depending on national standards [2–4]. However, more than two-thirds of patients have unresectable disease at the time of diagnosis and 60 % of resectable cases eventually relapse [5, 6]. Non-curative gastrectomy may be used in palliation, but it is associated with high rates of procedure-related morbidity and mortality as well as poor 1-year survival [7].

In the metastatic disease setting, combination chemotherapy with regimens containing a fluoropyrimidine and a platinum agent is widely used initially, with a third cytotoxic agent often included for medically fit patients [2, 3]. Nevertheless, even with the most active regimens, progression-free survival (PFS) remains in the range of 5–7 months and median survival is only 9–11 months [8–11]. In Japan, cisplatin plus the oral fluoropyrimidine S-1 has emerged as a preferred first-line regimen producing median survival of 13 months [12]. Following progression, 20–40 % of patients in Western countries subsequently receive second-line chemotherapy [13], but the number is higher (60–70 %) in Asian countries, particularly Japan and Korea. There is no established second-line regimen; options include paclitaxel, docetaxel, or irinotecan given alone or in doublet regimens, which produced median survival of 4–8 months in prospective clinical trials [14–18]. These survival data underscore the need for more effective therapy in metastatic gastric cancer.

Ixabepilone is the first member of the epothilone class of microtubule-stabilizing drugs to be approved for use in cancer therapy, specifically monotherapy or in combination with capecitabine for treatment of recurrent breast cancer [19, 20]. Ixabepilone is structurally distinct from the taxanes because it binds to a different site on β-tubulin and has reduced susceptibility to common mechanisms that confer resistance to taxanes and other anti-cancer drugs [21, 22]. Phase II clinical studies have demonstrated that ixabepilone has activity against a wide range of tumor types besides breast cancer, including hormone-refractory prostate cancer [23, 24], pancreatic cancer [25], non-small cell lung cancer [26], endometrial carcinoma [27], ovarian cancer [28], and renal cell carcinoma [29].

Ixabepilone administered every 3 weeks produced an objective response rate (ORR) of 5 or 9 % in Western patients with metastatic gastric cancer previously treated with a fluoropyrimidine and/or a platinum [30] or a taxane [31], respectively. Despite this modest activity in Western patients, further evaluation of ixabepilone in Asian patients with gastric cancer is warranted based on growing evidence highlighting epidemiological and genetic differences between Asian and Western populations [32]; gene expression profiling revealed differential expression of multiple genes in Eastern versus Western gastric tumor libraries [33]. Moreover, several retrospective analyses have shown that Asian patients are more likely to be diagnosed with localized tumors and have tumors located in the gastric antrum, whereas Western patients are more likely to have distant metastases and a prognostically less favorable tumor location in the cardia [34–36]. In these retrospective cohorts, median survival was longer in Asian patients than in Western patients, likely reflecting the differences in disease characteristics at presentation.

The present phase II study was designed to evaluate the efficacy and safety of single-agent ixabepilone in Asian patients with advanced gastric adenocarcinomas in which prior fluoropyrimidine-based therapy had failed. The primary objective was to determine the ORR; secondary objectives were to assess time to response, duration of response, disease control rate (DCR), PFS, and safety and tolerability.

Methods

Patients

Men and women of Asian ethnicity aged ≥18 years with histologically confirmed unresectable or metastatic gastric adenocarcinoma originating in the stomach or gastroesophageal junction were eligible if a fluoropyrimidine-based chemotherapy regimen had failed in an adjuvant, locally advanced, or metastatic setting. Failure of fluoropyrimidine-based chemotherapy was defined by disease progression while receiving such therapy or by disease recurrence within 12 months of the last dose. Eligibility also required measurable disease by response evaluation criteria in solid tumors (RECIST) guidelines (version 1.1)

[37], Eastern Cooperative Oncology Group performance status 0–1, adequate hematologic, hepatic, and renal function, and life expectancy >12 weeks. Women of childbearing potential required a negative pregnancy test within 72 h before starting ixabepilone and agreed to use an adequate method of contraception to avoid pregnancy for up to 4 weeks after the last dose. All patients provided written informed consent before participating in this study.

Patients were excluded if they had known central nervous system metastasis or neurological signs and symptoms suggestive of such metastasis, prior taxane or ixabepilone therapy, peripheral neuropathy (≥grade 2), or any significant medical illness precluding systemic anticancer therapy. Patients who had received >1 prior chemotherapy regimen for metastatic disease or >2 prior chemotherapy regimens overall were ineligible. Concurrent anti-cancer treatment including investigational agents was not permitted during this study. Strong CYP3A4 inhibitors (e.g., ketoconazole) were discontinued within 1 week prior to starting study treatment.

Study design

This phase II, single-arm, open-label study was conducted at 9 sites in Asia including 2 sites in Japan, 3 sites in Korea, 2 sites in Taiwan, and 1 site each in Hong Kong and Singapore from November of 2009 to June of 2011. The study was run in accordance with ethical principles originating in the 1964 Declaration of Helsinki and in compliance with Good Clinical Practice and national regulatory guidelines. The study protocol and informed consent form were approved by the Institutional Review Board or Independent Ethics Committee at each study site before patient enrollment.

Ixabepilone was administered at a dose of 40 mg/m^2 as a 3-h infusion every 21 days. Premedication with H_1 and H_2 antagonists was given to prevent hypersensitivity reactions. Patients who experienced a hypersensitivity reaction were required to receive additional premedication with intravenous corticosteroids before subsequent ixabepilone doses.

Subsequent cycles of ixabepilone were administered after all treatment-related toxicities had resolved to baseline or grade 1 (or ≤grade 2 for alopecia and fatigue), absolute neutrophil counts were ≥1,500 cells/μL, and platelet counts were ≥100,000 cells/μL. Patients who did not meet these criteria were re-evaluated weekly; those who failed to recover within 3 weeks of a scheduled re-treatment were discontinued from protocol treatment. The duration of treatment was based on a tumor assessment done every other cycle starting from the first dose of the study treatment. Patients achieving a complete response (CR) were treated for a maximum of 4 cycles after documentation of CR or up to a maximum of 8 cycles, whichever came first. Patients with stable disease (SD) or a partial response (PR) were treated until disease progression, unacceptable toxicity, or a maximum of 8 cycles.

Patients experiencing certain toxicities had the dose of ixabepilone reduced in subsequent cycles to 32 mg/m^2, and if toxicity recurred, to 25 mg/m^2. Toxicities mandating dose reduction were grade 4 neutropenia lasting ≥7 days, febrile neutropenia, grade 4 thrombocytopenia, grade 3 thrombocytopenia with bleeding, grade 2 neuropathy lasting ≥7 days, or grade 3 neuropathy lasting <7 days. The reduced dose was then administered in all subsequent cycles. Ixabepilone was discontinued for toxicity requiring more than 2 dose reductions or in the event of grade 3 neuropathy lasting ≥7 days, disabling neuropathy, or any grade 4 nonhematologic toxicity. Palliative and supportive care for disease-related symptoms was allowed during the study.

Assessments

Clinical and radiological evaluation (abdominal and chest computed tomography) of treatment response was conducted every other cycle until disease progression was documented. Treatment response was evaluated according to modified RECIST guidelines (version 1.1) [37]. Patients with CRs or PRs were to have repeat tumor assessments within 4–6 weeks to confirm the response. The ORR was the proportion of patients who achieved either a CR or PR; the DCR was the proportion of patients whose best response was CR, PR, or SD. The time to response was defined as the time interval from the first dose of ixabepilone until measurement criteria for PR or CR were first met, whereas the duration of response was defined as the time interval from when measurement criteria for PR or CR were first met until documented progressive disease or death. PFS was defined as the time interval from the first day of treatment until documented progressive disease or death.

A focused physical examination, including neuropathy assessment, was performed within 2 weeks before the first dose of ixabepilone and then prior to each subsequent dose. Serum chemistry and hematology were measured at the same time, whereas blood counts and differentials were ordered weekly during the first 3 cycles and then as clinically indicated to monitor recovery from hematological toxicity. Adverse events were monitored continuously and graded according to the National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0.

Statistics

This study used Simon's 2-stage optimal design to determine whether ixabepilone produces an ORR of clinical interest (>8 %); an ORR ≤8 % was not of clinical interest and an ORR ≥20 % was of strong clinical interest. The first stage required 25 response-evaluable patients. Study termination

Table 1 Patient characteristics

Characteristic	$N = 52$
Age, years	
Median (range)	56.5 (29.0–77.0)
≥65 years, *n* (%)	12 (23.1)
Gender, *n* (%)	
Male	34 (65.4)
Female	18 (34.6)
Ethnicity, *n* (%)	
Chinese	23 (44.2)
Japanese	15 (28.9)
Korean	13 (25.0)
Asian other	1 (1.9)
ECOG performance status, *n* (%)	
0	20 (38.5)
1	32 (61.5)
Number of disease sites, *n* (%)	
1	11 (21.2)
2	13 (25.0)
≥3	28 (53.8)
Disease sites, *n* (%)	
Lymph node	37 (71.2)
Gastric	29 (55.8)
Peritoneum (including ascites)	23 (44.2)
Liver	19 (36.5)
Lung	8 (15.4)
Other	30 (57.7)

ECOG Eastern Cooperative Oncology Group

was planned if ≤2 of the 25 patients responded to treatment; otherwise, an additional 27 response-evaluable patients would be treated. The study required at least 8 responders among the 52 evaluable patients at the end of the second stage to reject the null hypothesis of ORR ≤8 %. The test had 80 % power to reject the null hypothesis at a significance level of 5 % if the true ORR is 20 %.

The ORR and DCR were calculated for all treated patients. For each, a 2-sided 95 % exact confidence interval (CI) was computed using the Clopper–Pearson method. Duration of response and PFS were analyzed by Kaplan–Meier methodology, with computation of median values and their 2-sided 95 % CIs. All other parameters, including time to response, demographic and baseline characteristics, and safety variables, were analyzed with descriptive statistics.

Results

Patient disposition and characteristics

Fifty-eight patients were screened, 6 (10.3 %) were not treated because of screening failure, and the remaining 52 patients (89.7 %) were enrolled and received ixabepilone. Of those treated, 4 patients (7.7 %) completed ixabepilone therapy according to the study protocol, 38 patients (73.1 %) discontinued because of disease progression, 5 patients (9.6 %) withdrew consent or requested study drug discontinuation, 4 patients (7.7 %) discontinued because of adverse events, and 1 patient (1.9 %) died.

The median age of the study cohort was 56.5 years (range: 29.0–77.0 years); most were men (65.4 %) and all were of Asian ethnicity (Table 1). The majority of patients had 3 or more disease sites (53.8 %), most frequently in the lymph nodes (71.2 %), stomach (55.8 %), and liver (36.5 %).

Table 2 Best overall response

Parameter	$N = 52$
Best response, *n* (%)	
CR	0 (0)
PR	8 (15.4)
SD	26 (50.0)
Progressive disease	15 (28.8)
Unable to determine	3 (5.8)
ORR (95 % CI)	15.4 (6.9–28.1)
DCR (95 % CI)	65.4 (50.9–78.0)

Exposure

Ixabepilone was administered for a median of 3.5 courses (range: 1–10). Of the 45 patients who received at least 2 courses, 18 (40 %) required at least 1 dose reduction of ixabepilone. The reasons for the first dose reduction included hematologic toxicity in 6 patients (13.3 %), neuropathy in 4 patients (8.9 %), and other non-hematologic toxicity in 8 patients (17.8 %).

Efficacy

The ORR with ixabepilone therapy was 15.4 % (95 % CI 6.9–28.1); all objective responses were PR (Table 2). Twenty-six additional patients (50.0 %) had SD and, therefore, the DCR was 65.4 % (95 % CI 50.9–78.0). For patients achieving PR, the median time to response was 8.9 weeks (range: 5.1–12.1 weeks) and the median duration of response was 3.1 months (95 % CI 2.6–4.1 months). Median PFS was 2.8 months (95 % CI 2.1–3.5 months) (Fig. 1).

Safety

The adverse events reported were consistent with the known safety profile of ixabepilone. Fifty patients (96.2 %) had at least 1 adverse event, most commonly alopecia,

decreased appetite, neutropenia, peripheral sensory neuropathy, and fatigue (Table 3). Most non-hematologic toxicity was grade 1 or 2; the most common grade 3 events were fatigue (9.6 %), decreased appetite (7.7 %), peripheral sensory neuropathy (5.8 %), and diarrhea (5.8 %). Overall, peripheral neuropathies were reported by 33 patients (63.5 %), with the most common forms being peripheral sensory neuropathy (48.1 %) and hypoesthesia (11.5 %). Peripheral motor neuropathy occurred in 1 patient (1.9 %; grade 2). In terms of hematological toxicity, grade 3/4 neutropenia and leukopenia occurred in 24 (46.2 %) and 11 (21.1 %) patients, respectively, with febrile neutropenia in 4 patients (7.7 %). Grade 3 anemia and thrombocytopenia occurred in 3 (5.8 %) and 2 (3.8 %) patients, respectively.

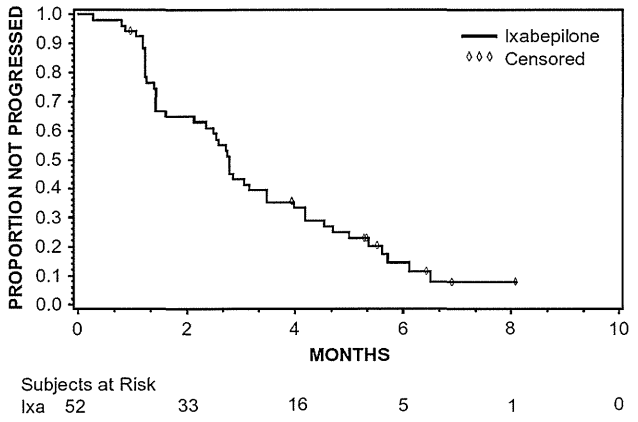

Fig. 1 Kaplan–Meier plot of progression-free survival

Four patients (7.7 %) discontinued treatment because of drug-related adverse events, including 3 patients with peripheral neuropathy and 1 patient with febrile neutropenia. There was 1 death because of drug-related toxicity: a 69-year-old male patient died of pneumonia and neutropenic sepsis during course 6 of ixabepilone therapy. The patient started course 6 with a reduced dose of 32 mg/m^2 because the investigator had considered the patient too weak to continue at the initial dose. The death occurred 18 days after the last treatment. Three other patients died within 30 days of their last dose of ixabepilone, all of which were assessed by the investigator as due to disease progression.

Discussion

The results of this phase II study demonstrate that ixabepilone has activity of clinical interest when administered

Table 3 Treatment-related adverse events (AEs) reported at an incidence ≥10 %

AE	Grade 1	Grade 2	Grade 3	Grade 4	Total
Any AE	7 (13.5)	11 (21.2)	12 (23.1)	19 (36.5)	50 (96.2)[a]
Hematologic AEs					
Neutropenia	0 (0)	2 (3.8)	8 (15.4)	16 (30.8)	26 (50.0)
Leukopenia	0 (0)	1 (1.9)	9 (17.3)	2 (3.8)	12 (23.1)
Non-hematologic AEs					
Alopecia	26 (50.0)	9 (17.3)	0 (0)	0 (0)	35 (67.3)
Decreased appetite	14 (26.9)	11 (21.2)	4 (7.7)	0 (0)	29 (55.8)
Peripheral sensory neuropathy	12 (23.1)	10 (19.2)	3 (5.8)	0 (0)	25 (48.1)
Fatigue	5 (9.6)	12 (23.1)	5 (9.6)	0 (0)	22 (42.3)
Rash	11 (21.2)	5 (9.6)	1 (1.9)	0 (0)	17 (32.7)
Diarrhea	10 (19.2)	1 (1.9)	3 (5.8)	0 (0)	14 (26.9)
Constipation	9 (17.3)	4 (7.7)	0 (0)	0 (0)	13 (25.0)
Nausea	8 (15.4)	4 (7.7)	1 (1.9)	0 (0)	13 (25.0)
Myalgia	9 (17.3)	2 (3.8)	1 (1.9)	0 (0)	12 (23.1)
Arthralgia	7 (13.5)	4 (7.7)	0 (0)	0 (0)	11 (21.2)
Weight decreased	2 (3.8)	9 (17.3)	0 (0)	0 (0)	11 (21.2)
Pruritus	6 (11.5)	3 (5.8)	0 (0)	0 (0)	9 (17.3)
Pyrexia	8 (15.4)	0 (0)	0 (0)	0 (0)	8 (15.4)
Vomiting	5 (9.6)	3 (5.8)	0 (0)	0 (0)	8 (15.4)
Stomatitis	2 (3.8)	3 (5.8)	2 (3.8)	0 (0)	7 (13.5)
Asthenia	1 (1.9)	5 (9.6)	0 (0)	0 (0)	6 (11.5)
Dysgeusia	5 (9.6)	1 (1.9)	0 (0)	0 (0)	6 (11.5)
Hypoesthesia	2 (3.8)	3 (5.8)	1 (1.9)	0 (0)	6 (11.5)
Nail disorder	5 (9.6)	0 (0)	1 (1.9)	0 (0)	6 (11.5)

[a] Includes 1 patient with grade 5 pneumonia and neutropenic sepsis