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Safety Verification Trials of mFOLFIRI and Sequential Irinotecan + Bevacizumab as First- or Second-Line Therapies for Metastatic Colorectal Cancer in Japanese Patients

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Key Words
Advanced colorectal cancer · Irinotecan · Bevacizumab · S-1 · Randomized trial

Abstract
Objective: S-1 is effective in sequential combination with irinotecan (IRIS) in treating metastatic colorectal cancer. We conducted a randomized phase II trial of modified leucovorin, fluorouracil and irinotecan (mFOLFIRI) + bevacizumab and sequential IRIS + bevacizumab as first- or second-line therapies. ***Methods:*** Sixty metastatic colorectal cancer patients were randomly assigned to receive mFOLFIRI + bevacizumab or sequential IRIS + bevacizumab (7.5 mg/kg of bevacizumab and 150 mg/m^2 of irinitecan, and 80 mg/m^2/day of S-1 orally from day 3 until day 16 as a 3-week course). The primary endpoint was the safety of each method until week 12, with the secondary endpoint being the comparison of the safety and efficacy of the two methods. ***Results:*** The safety of the two treatments was comparable, except that G3 anorexia and diarrhoea were less frequent with sequential IRIS + bevacizumab. The overall response rate was 62% [95% confidence interval (CI) 40.1–79.8] versus 72% (95% CI 50.6–86.2), and progression-free survival was 324 days (95% CI 247–475) versus 345 days (95% CI 312–594) with mFOLFIRI + bevacizumab versus IRIS + bevacizumab, respectively. ***Conclusion:*** Sequential IRIS + bevacizumab is a safe and effective method of systemic chemotherapy against metastatic colorectal cancer and is compatible with mFOLFIRI + bevacizumab.

Introduction

Over the past 10 years, as a result of multidisciplinary therapies including systemic chemotherapy, there has been a dramatic improvement in the success of treat-

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ments against unresectable and/or recurrent colorectal cancer [1]. Particularly, based on the results of several clinical trials, bevacizumab was shown to extend progression-free survival (PFS) when used in combination with other chemotherapies including irinotecan, fluorouracil and leucovorin [2], leucovorin, fluorouracil and oxaliplatin (FOLFOX) [3], leucovorin, fluorouracil and irinotecan (FOLFIRI) [4], and 5-fluorouracil and leucovorin (5-FU/LV) [5]. These results are further supported by large-scale observational studies [6, 7]; however, in standard chemotherapy treatments, as often represented by either FOLFOX or FOLFIRI, placement of a peripherally inserted central venous port (CV port) is required for continuous 5-FU infusion. The usage of CV ports can cause complications, including infections and thrombosis, resulting in decreasing the patient's quality of life [8, 9].

In consideration of these factors, chemotherapy regimens using oral fluoropyrimidines rather than continuous 5-FU infusion must be developed. The CapeOX regimen, which uses capecitabine, an oral fluoropyrimidine pro-drug of 5-FU rather than 5-FU/LV, plus oxaliplatin, has identical therapeutic effects to FOLFOX. Favourable results were also observed when used in combination with bevacizumab [10]. However, because of severe gastrointestinal toxicity associated with capecitabine in combination with irinotecan (CapeIRI or XELIRI), an effective alternative treatment to FOLFIRI has yet to be developed [4].

S-1 is a combination of tegafur, a pro-drug of 5-FU that consists of oral fluoropyrimidines, gimeracil (5-chloro-2,4-dihydoroxypyridine) and oteracil (potassium oxonate) at a molar ratio of 1:0.4:1 [11]. Gimeracil has a reversible competitive inhibitory effect on dihydropyrimidine dehydrogenase, a rate-limiting enzyme involved in the metabolic degradation of 5-FU. Oteracil reduces gastrointestinal toxicity and is effective against a wide range of carcinomas. Against metastatic colorectal cancer, S-1 showed a response rate of 39.5%, a PFS of 5.4 months and an overall survival time of 11.9 months when used as a monotherapy [12]. Because S-1 is expected to replace 5-FU/LV, there have been several prospective clinical trials in Japan using S-1 in combination with oxaliplatin (L-OHP or SOX) [13]. Clinical trials of S-1 combined with irinotecan (IRIS) were also conducted with various schedules or dosage regimens [14–16]. Among these, Yoshioka et al. [15] conducted phase I/II trials of sequential IRIS and the combined treatment of staggered irinotecan and S-1. These clinical trials were performed in order to avoid decreased therapeutic effects and increased toxicities caused by the inhibitory effect of 5-FU and its metabolites on the bioactivation of SN-38 from irinotecan [17, 18]. The authors reported on how this treatment regimen effectively avoided toxicity and rivaled the efficacy of previous FOLFIRI treatments; however, because the introduction of molecular targeted drugs in Japan was delayed, no studies were performed on the safety and efficacy of sequential IRIS in combination with bevacizumab. Thus, we report on the respective safety of sequential IRIS + bevacizumab and modified FOLFIRI (mFOLFIRI) + bevacizumab therapies against unresectable colorectal cancer. A secondary comparative study on the safety and efficacy of both therapies was also performed.

Patients and Methods

Patient Eligibility

The eligibility criteria were as follows: (1) patients histologically diagnosed with colorectal cancer; (2) patients with either an unresectable primary tumour or distal metastatic tumours; (3) an Eastern Cooperative Oncology Group performance status of 0 or 1; (4) the previous chemotherapy regimen had to be ≤1; (5) patients of post-operative adjuvant chemotherapy >6 months since last administration of drugs; (6) in the case of second-line therapy, first-line therapy had to be FOLFOX treatment; (7) internal organ function maintained, i.e. white blood cell count of 3,500–12,000/μl, platelet count ≥100,000/μl, aspartate aminotransferase (AST) ≤100 IU/l, alanine aminotransferase (ALT) ≤100 IU/l, total bilirubin ≤ 1.5 mg/dl, serum creatinine ≤1.2 mg/dl, serum creatinine clearance as estimated by Cockcroft-Gault equation ≥50 ml/min; (8) survival expected to be at least ≥3 months; and (9) written informed consent obtained from the patient for trial participation.

Exclusion criteria were as follows: (1) a history of abdominal irradiation; (2) any complications, such as intestinal paralysis, intestinal obstruction, poorly controlled diabetes, poorly controlled hypertension, unstable angina, hepatic cirrhosis, interstitial pneumonia, pulmonary fibrosis or severe pulmonary emphysema; (3) body cavity fluid retention requiring treatment; (4) poorly controlled peptic ulcerations; (5) concomitant gastrointestinal perforation or a history of perforation within 1 year prior to registration; (6) brain tumours or cerebral metastases confirmed on imaging; (7) concomitant symptoms of cerebrovascular nerve damage or any type of cardiac disease requiring treatment; (8) surgical treatment within 4 weeks prior to registration; (9) a bleeding tendency, coagulation disorder or excessive clotting factors; (10) awaiting or on treatment for chronic inflammatory disease such as rheumatoid arthritis, with any drugs that inhibit platelet function (aspirin or non-steroidal anti-inflammatory drugs); (11) women who are pregnant, may be pregnant, wish to become pregnant or are lactating; (12) men who wish their partner to become pregnant; (13) patients using irinotecan as post-operative adjuvant chemotherapy.

Treatment Methods

In the sequential IRIS + bevacizumab treatment regimen, on day 1, 7.5 mg/kg of bevacizumab was administered for >30 min, and 150 mg/m^2 of irinotecan was administered continuously for >90 min. Then, for the 2-week period from days 3 to 16, divided doses of S-1 were administered twice daily. The dosage of S-1 was as follows: body surface area (BSA) <1.25 m^2, 80 mg/day; BSA 1.25–1.5 m^2, 100 mg/day, and BSA >1.5 m^2, 120 mg/day as a 3-week course. Dosage for the mFOLFIRI + bevacizumab treatment regimen was as follows: 5 mg/kg of bevacizumab, 150 mg/m^2 of irinotecan, 200 mg/m^2 of L-leucovorin, 400 mg/m^2 of 5-FU by rapid intravenous infusion on day 1, and 2,400 mg/m^2 of 5-FU for 46 h by continuous intravenous infusion as a 2-week course. The treatment protocol period was set at 12 weeks in both groups, and treatment was continued until the criteria for discontinuation of the trial were met.

The criteria for commencement of treatment in each course were as follows: white blood cell count ≥3,000/μl, platelet count ≥75,000/μl (mFOLFIRI + bevacizumab) or ≥100,000/μl (IRIS + bevacizumab), AST ≤100 IU/l, ALT ≤100 IU/l, total bilirubin ≤1.5 mg/dl, and serum creatinine ≤1.2 mg/dl. In addition, diarrhoea of grade 0 and improvement in any other non-haematologic toxicity (excluding constipation, loss of appetite, loss of hair, chromatosis and dysgeusia) of grade ≤1 was required. In patients where the criteria for commencement of treatment were not met, treatment was delayed until all necessary requirements were completely satisfied. Treatment was discontinued in those patients where the criteria for commencement of treatment were not met even after a delay of ≥3 weeks.

The criteria common to both groups for discontinuation of bevacizumab treatment were as follows: (1) any grade of haemoptysis, gastrointestinal perforation, reversible leucoencephalopathy syndrome; (2) grade ≥3 thromboembolism, haemorrhage or hypersensitivity reaction, and (3) grade 4 proteinuria or hypertension. In patients with grade 2 haemorrhage, treatment was withdrawn until improvement to grade 0, and treatment was discontinued in patients where grade 2 haemorrhage recurred. Treatment was discontinued in patients with grade 3 hypertension that could not be controlled by medication. Treatment was withdrawn in the following situation: patients with grade 2 or 3 proteinuria until proteinuria was ≤2 g as determined by 24-hour urine collection analyses, with grade 3 or 4 liver dysfunction until improvement to either grade 1 or baseline, and in instances of recurrence.

In the IRIS group, S-1 administration was stopped if any of the following adverse effects occurred during the course: (1) grade ≥3 leucopenia or neutropenia in addition to other grade ≥3 non-haematological toxicity, until patient recovery; (2) grade ≥2 thrombocytopenia, diarrhoea, stomatitis, nausea or vomiting; (3) serum creatinine ≥1.5× the upper limit of normal, and (4) AST or ALT ≥100 IU/l. Any patients exhibiting grade ≥4 leucopenia or neutropenia, grade ≥3 thrombocytopenia, diarrhoea, stomatitis, nausea or vomiting, non-haematological toxicity, or AST or ALT ≥200 IU/l during the study were administered a lower dosage of IRIS in the next course of treatment. The low dosage of S-1 (level 1) was 50 mg/day for BSA <1.25 m^2, 80 mg/day for BSA 1.25–1.50 m^2, and 100 mg/day for BSA >1.5 m^2. For irinotecan, level 1 was 120 mg/m^2 and level 2 was 100 mg/m^2; no increase was made once dosage decreased. Also, in the mFOLFIRI + bevacizumab regimen, dosage was reduced in patients with grade ≥4 leucopenia or neutropenia, grade ≥3 thrombocytopenia, diarrhoea, stomatitis, nausea or vomiting or non-haematological toxicity as follows: 120 mg/m^2 of irinotecan and 200 mg/m^2 of 5-FU (bolus) for level 1, and 100 mg/m^2 of irinotecan, 200 mg/m^2 of 5-FU (bolus) and 2,000 mg/m^2 of 5-FU (infusion) for level 2.

With regard to safety data, the patients' health status was observed and blood samples were tested during weekly medical examinations by the attending physician until 4 weeks after commencing treatment and repeated after the fifth week at the start of each new course of treatment. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0, and effectiveness was observed according to the Response Evaluation Criteria in Solid Tumors 1.0. Computed tomographic scans were performed every 6 weeks. Effectiveness was judged comprehensively using blinded tests on the treatment methods by 3 or more physicians not including primary physicians.

Interim Analysis about Safety

After 3 cases have been registered in each group, registration was stopped to evaluate the safety of the two treatments (step 1). After the confirmation of the safety of the two treatments by the efficacy and safety evaluation committee, registration was reopened with 60 patients enrolled (30 per group; step 2).

Statistical Analysis

While attempting to detect a frequency of ≥10% with 95% probability for the occurrence of adverse events, we determined that the sample size would include 30 patients in each experimental group or 60 patients overall in the two experimental groups [19]. Patients' background, safety and efficacy data were summarized as frequencies and percentages. The χ^2 test was used to compare between groups, while the Kaplan-Meier method was used to analyse PFS.

Results

Patient Background

From November 2007 to February 2010, 60 patients were registered from the 12 institutes of the Tohoku Clinical Oncology Research and Education Society. These patients were randomly assigned to either the mFOLFIRI + bevacizumab or sequential IRIS + bevacizumab groups, with 30 patients in each group. Patient backgrounds are presented in table 1; the median age was 62.5 (range 46–77) and 62 years (range 31–73) in the mFOLFIRI + bevacizumab and sequential IRIS + bevacizumab group, respectively. Many patients were receiving first-line treatment (24 patients in the mFOLFIRI + bevacizumab group and 23 patients in the IRIS + bevacizumab group). No significant bias was seen between the two groups.

Safety Verification Test (Step 1)

Step 1 of this trial was to register 3 patients at a time into the two experimental chemotherapy regimen groups and evaluate the initial safety for 12 weeks. The last patient was registered in April 2008 when patient registration was temporarily suspended and initial safety was assessed. Except for 1 patient in the mFOLFIRI + bevacizumab group with gastrointestinal perforation (G3), no other severe adverse events occurred. Because international phase III and verification trials in combination with FOLFOX treatment in a Japanese population cite gastrointestinal perforation as an expected adverse event, the efficacy and safety evaluation committee recommended proceeding to step 2 while maintaining utmost vigilance with regard to patient safety.

Safety Verification Trial (Step 2)

By February 2010, 60 patients had been registered in the study, including the 6 patients from step 1 and were randomly allocated to the two experimental groups (table 1). Although one adverse event of gastrointestinal perforation (G5) was observed in the mFOLFIRI + bevacizumab group, this was determined to be due to progression of an underlying disease (table 2) and not due to the experimental treatment. With regard to G3/4 haematological toxicities in the mFOLFIRI + bevacizumab and sequential IRIS + bevacizumab treatment groups, neutropenia was seen at a rate of 48 and 38%, respectively. Although statistical differences were not observed, G3/4 gastrointestinal toxicities were more frequent in the mFOLFIRI + bevacizumab group than in the sequential IRIS + bevacizumab group (anorexia 17.9 and 3.4%, nausea 7.1 and 0%, diarrhoea 14.3 and 6.9%, respectively). G3/4 severity in hypertension, which is the representative adverse event of bevacizumab, was confirmed as 3.6% in the mFOLFIRI + bevacizumab group, whereas it was not observed in the sequential IRIS + bevacizumab group. No patient experienced severe proteinurea, thrombosis or haemorrhage in either group.

Comparison of Efficacy

The treatment methods were blind, and efficacy was compared by judging the response rate with a 3-person decision committee. The overall response rate (ORR) in the mFOLFIRI + bevacizumab group versus the sequential IRIS + bevacizumab group was 61.5% [95% confidence interval (CI) 40–80] and 72.0% (95% CI 51–86), respectively (table 3). Two patients showed complete response in the sequential IRIS + bevacizumab group. The median PFS was 324 days (95% CI 247–475) in the mFOLFIRI + bevacizumab group and 345 days (95% CI 312–594) in the sequential IRIS + bevacizumab group (fig. 1). Statistical significance was not observed between the two groups (p = 0.71).

Table 1. Characteristics of patients

	mFOLFIRI + bevacizumab (n = 30)	IRIS + bevacizumab (n = 30)
Age, years		
Median	62.5	62
Range	46–77	31–73
Males/females	18/12	17/13
ECOG performance status		
0	24	27
1	6	3
Primary legion		
Colon	17	17
Rectum	12	13
Both	1	0
Cancer		
Advanced	22	20
Recurrent	8	10
Histology		
Well	7	7
Moderately	20	22
Poor	2	0
Other	1	1
Primary site		
Yes	5	6
No	25	24
Number of metastases		
1	17	16
2	9	10
3	4	4
Adjuvant chemotherapy		
Yes	5	7
No	25	23
Prior chemotherapy		
Yes	24	25
No	6	5

ECOG = Eastern Cooperative Oncology Group.

Discussion

Systemic chemotherapy against unresectable or recurrent colorectal cancer was developed on the basis of the successful combination therapy of 5-FU and L-leucovorin. Continuous 5-FU infusion and cytotoxic drugs (e.g. irinotecan and L-OHP, as well as other molecular target-

Table 2. Adverse events of the two treatments

Adverse event	mFOLFIRI + bevacizumab							IRIS + bevacizumab							p value (χ^2 test; G3,4)
	G0	G1	G2	G3	G4	G5	grade >3, %	G0	G1	G2	G3	G4	G5	grade >3, %	
Non-haematological															
Anorexia	10	5	8	5			17.9	13	10	5	1			3.4	0.076
Nausea	10	7	9	2			7.1	16	11	2				0.0	0.143
Vomiting	20	6	1	1			3.6	28			1			3.4	0.980
Diarrhoea	12	12		4			14.3	15	11	1	2			6.9	0.364
Mucositis	17	10	1				0.0	23	6					0.0	(-)
Fatigue	14	8	4	2			7.1	17	9	3				0.0	0.143
GI perforation	26			1		1	7.1	29						0.0	0.143
Bleeding	20	7	1				0.0	21	8					0.0	(-)
Hypertension	20	3	2	1			3.6	24	2	1				0.0	0.304
Proteinuria	20	3	2				0.0	22	2	3				0.0	(-)
Haematological															
Leucopenia	5	6	12	4			14.3	12	3	9	5			17.2	0.409
Neutropenia	3[1]		11	8	5		48.1	12[1]		6	7	4		37.9	0.598
Thrombopenia	23	4					0.0	22	6		1			3.4	0.286

GI = Gastrointestinal. [1] Frequency of G0 and G1.

Table 3. Overall response of the two treatments

	mFOLFIRI + bevacizumab	IRIS + bevacizumab
CR	0	2
PR	16	16
SD	8	5
PD	2	2
NE	4	5
Total	30	30
RR, %	61.5 (40.1–79.8)	72.0 (CI 50.6–86.2)

Figures in parentheses are 95% CIs.
CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated.

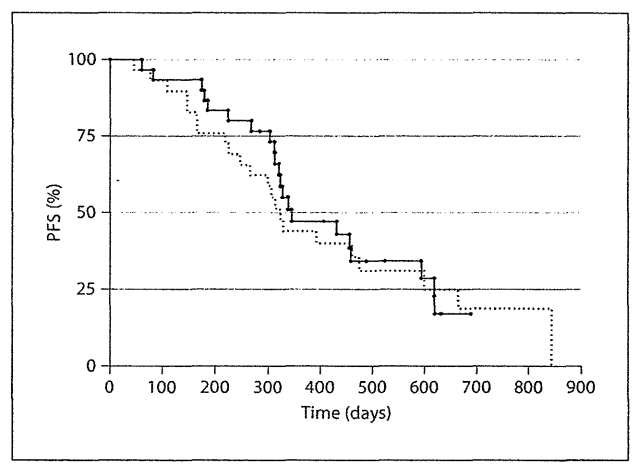

Fig. 1. Kaplan-Meier PFS curves of patients with metastatic colorectal cancer treated with mFOLFIRI + bevacizumab (dotted line) and IRIS + bevacizumab (solid line).

ed drugs, such as bevacizumab, cetuximab and panitumumab) are used concomitantly or sequentially to yield a median survival time that exceeds 2 years; however, continuous 5-FU infusion necessitates the insertion of a peripherally inserted central catheter or CV port, which can increase infection and thromboembolism risks. In order to circumvent these drawbacks, novel treatment options with oral fluoropyrimidines are being developed to replace the need for 5-FU infusions. The oral fluoropyrimidine S-1 exhibits a lower frequency of diarrhoea and hand-foot syndrome when compared with capecitabine, and S-1 has a higher tolerance level among Japanese people. Therefore, treatments such as SOX and IRIS are being developed in Japan to replace FOLFOX and FOLFIRI therapies, and it has been suggested that S-1 may be

able to replace 5-FU/LV [12–14]. Furthermore, because molecular targeted drugs, such as bevacizumab, cetuximab and panitumumab, have been introduced into routine clinical use in Japan, it has become important to evaluate the safety and efficacy of combined therapies on the basis of these drugs and on the new oral fluoropyrimidines.

Prior to this study, we tested the safety and efficacy of sequential IRIS therapy, which we found to have a low toxicity and high efficacy [13]. In this study, among patients with G3 or higher haematological toxicities, no significant differences between the two groups were observed with regard to neutropenia and/or leucopenia, although a lower trend was observed in the sequential IRIS + bevacizumab group. Muro et al. [16] performed a phase II/III trial comparing mFOLFIRI with irinotecan + S-1 therapy as a second line of treatment for patients with unresectable recurrent colorectal cancer. Although their administration method differed from our sequential IRIS therapy, as Muro et al. [16] did not use bevacizumab in their study, the frequency of G3/4 neutropenia in the mFOLFIRI (150 mg/m^2/2 weeks of irinotecan) and IRIS groups showed a similar trend to our data (52.1 and 36.2%, respectively), indicating that IRIS exhibits less neutropenic toxicity.

The incidence of gastrointestinal toxicity observed in this study in the mFOLFIRI + bevacizumab group was nearly identical to that in the FOLFIRI group (43.2–53.6%) as reported by a BICC-C study [4]. As with haematological toxicities, the frequency of non-haematological toxicity was lower in the sequential IRIS + bevacizumab group than in the mFOLFIRI + bevacizumab group. Furthermore, the frequency of reported gastrointestinal toxicities, such as loss of appetite (11%) and diarrhoea (20.5%), in the sequential IRIS + bevacizumab group of our study tended to be lower than that in the IRIS group in the study of Muro et al. [16]. This difference may be due to the following reasons: (1) all patients in the study of Muro et al. [16] were undergoing second-line treatment, and (2) the different administration method used placed a greater emphasis on irinotecan dose intensity than our sequential IRIS method. Muro et al. [16] also mentioned that raising the dose intensity of irinotecan was among the effective strategies for patients resistant to oxaliplatin-based chemotherapy; however, with regard to these adverse events, we believe that raising the dose intensity of S-1 rather than that of irinotecan is the better strategy for first-line treatment with regard to safety. Finally, as regards efficacy, the median PFS in both groups was about nearly a year. Although the number of patients in the current study was small, the level of efficacy seems to be higher than that in previous studies. The data on overall survival time are currently being analysed in a follow-up study.

Recently, Yamada et al. [20] reported the results of a phase II study on IRIS combined with bevacizumab (SIRB study). In the SIRB regimen, S-1 is administered on days 1–14 of a 21-day cycle, but the dose intensity of S-1, irinotecan and bevacizumab was equivalent to that of the sequential IRIS + bevacizumab regimen. Toxicity in the SIRB regimen was low and manageable (G3/4 neutropenia 26%, G3/4 anorexia 12%, G3/4 diarrhoea 8%). The ORR was 67% (95% CI 52.1–79.1) and the median PFS was 373 days (95% CI 299–440), which is comparable with our sequential IRIS + bevacizumab therapy.

From these results, we concluded that the combination of S-1, irinotecan and bevacizumab could be an effective primary therapy in Japanese patients, compared with mFOLFIRI + bevacizumab. Moreover, this regimen could reduce the risk of infection because it does not require a CV port. Therefore, sequential IRIS + bevacizumab therapy, a very promising treatment method, should be developed further in a larger randomized clinical trial. We are currently in the process of planning a phase III clinical trial in Japan comparing IRIS + bevacizumab with CapOX/FOLFOX + bevacizumab.

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前立腺がんの地域連携クリティカルパスにおけるバリアンス分析

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要旨：2007年11月から千葉県がんセンター泌尿器科は，千葉県内の泌尿器科開業医師との地域医療連携を開始するにあたり泌尿器がんの地域連携クリティカルパスを作成した。2011年10月現在，前立腺がん5種のクリティカルパスを運用しており症例数は1,460例であった。今回われわれは，2007年11月から2008年10月までの1年間に3種類の前立腺がんクリティカルパスが適応となった248例を対象として全例のバリアンス分析を行った。運用成績としてはクリティカルパス適応継続例が213例（86%），バリアンス例が35例（14%）であった。前立腺がん3種類のクリティカルパスのアウトカム設定条件は適切であったと考えられた。しかしバリアンス例の中には「連携から外れた症例」が23例（9%）みられており，クリティカルパスのアウトカム設定に診療連携の継続を追加することが必要と思われた。

key words 地域連携クリティカルパス，前立腺がん，バリアンス

はじめに

2007年のがん対策推進基本計画およびがん診療連携拠点病院の指定要件の見直しに伴い，がん診療連携拠点病院では5大がんを中心とした地域連携クリティカルパスの整備が求められている[1, 2]。

千葉県がんセンター泌尿器科では拠点病院に集中する患者数の緩和を目的に，主に千葉県内の泌尿器科開業医と医療連携をすすめる方法を模索していた。そこで前立腺特異抗原（PSA）を用いた前立腺がん地域連携クリティカルパスを3種類開発した[3]。開始時期は2007年11月で，地域連携クリティカルパスの整備ががん診療連携拠点病院の指定要件となる前であった。2012年3月現在，前立腺がん5種のクリティカルパスを運用しており，症例数は1,600例であった。今回われわれは2007年11月から2008年10月までの1年間に3種類の前立腺がんクリティカルパスが適応となった248例を対象に運用状況の調査とバリアンス解析を行い，クリティカルパスの妥当性について検討を行った。

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I 対象・方法

対象は2007年11月から2008年10月までの1年間に前立腺がん地域連携クリティカルパスを適用した248例である。地域連携クリティカルパスは3種類ありそれぞれの適応条件（**表1**）と症例数を以下に示す[3]。

PSA経過観察クリティカルパス：PSA高値（4.0ng/ml以上）で前立腺生検を施行し結果が陰性であった症例：110例，前立腺全摘術後経過観察クリティカルパス：限局性前立腺がんに対し前

表1　前立腺特異抗原（PSA）を用いた3種類の地域連携クリティカルパス

地域連携クリティカルパスの名称	対象患者	適応開始条件	アウトカムの設定	バリアンス発生時
PSA経過観察	PSA高値/生検陰性	PSA 4.0ng/ml以上，前立腺生検：陰性	PSA定期検査：生検時の1.4倍未満を確認	前回の生検時のPSA1.4倍以上⇒パス運用開始施設へ再紹介
前立腺全摘後	限局性前立腺癌/前立腺全摘除術後	PSA 0.2ng/ml未満，尿失禁の改善	PSA定期検査：PSA 0.2ng/ml未満を確認	PSA 0.2ng/ml以上⇒パス運用開始施設へ再紹介
内分泌療法	前立腺癌/内分泌療法	PSA 4.0ng/ml未満	PSA定期検査：PSA 2.0ng/ml未満を確認	PSA 2.0ng/ml以上⇒パス運用開始施設へ再紹介

表2　地域連携クリティカルパスバリアンスの35例の内訳

PSA値の上昇	9例　(4%)
連携医療機関での継続受診なし ●医療機関での継続受診あり（16例） ●医療機関での継続受診なし（7例） ●連絡とれず（1例）	23例　(9%)
その他	3例　(1%)
合計	35例　(14%)

(%)：全症例（248例）に対する割合

立腺全摘除術を施行しPSAが低値である（0.2ng/ml未満）：69例，内分泌療法クリティカルパス：内分泌療法を開始しPSAが基準値（4.0ng/ml）未満まで低下し内分泌療法を継続していく：69例であった。連携医療機関での血清PSA値の測定間隔についてはPSA経過観察クリティカルパスの場合4～6ヵ月ごととし，前立腺全摘後および内分泌療法後クリティカルパスでは3ヵ月ごとと規定している[3]。地域連携クリティカルパスのアウトカムは**表1**のように設定した[3]。

千葉県がんセンター地域医療連携室が主だった連携医療機関13施設への患者の受診状況を調査し，地域連携クリティカルパスのバリアンス分析を行った。連携医療機関で受診状況を把握できていない患者については，地域医療連携室の担当者が患者へ直接電話し受診の有無や現在の通院状況などの聞き取り調査を行った。

Ⅱ　結　果

今回の1年間において新規治療総数に占めるクリティカルパス登録の割合は，PSA経過観察クリティカルパスでは，前立腺針生検334例中72例（22%），前立腺全摘後クリティカルパスでは，手術症例115例中14例（12%），内分泌療法クリティカルパスでは，新規治療開始88例中10例（11%）であった。それ以外は，2007年10月以前の症例の適応であった。

受診状況の調査の結果，クリティカルパス適用継続は213例（86%）であり，バリアンス発生が35例（14%）であった。バリアンスの内訳は，PSA値の上昇9例（4%），連携医療機関に継続受診なし23例（9%），その他3例（1%）であった（**表2**）。

連携医療機関に継続受診しなかった23例(9%)を検討すると，連携医以外の医療機関での継続あり16例（6%）（当センター再受診4例を含む），医療機関への受診なし7例（3%），連絡とれず1例（0.4%）であった。

医療機関への受診なし7例をクリティカルパス別にみると，PSA経過観察が5例で前立腺全摘後は2例であった。この7症例はいずれも検診を利用することでPSAの経過を自己管理していた。

クリティカルパス別にバリアンス例を検討すると，PSA経過観察が110例中22例（20%）と最も多く，次いで前立腺全摘後69例中9例（13%），内分泌療法69例中4例(6%)の順であった(**図1**)。

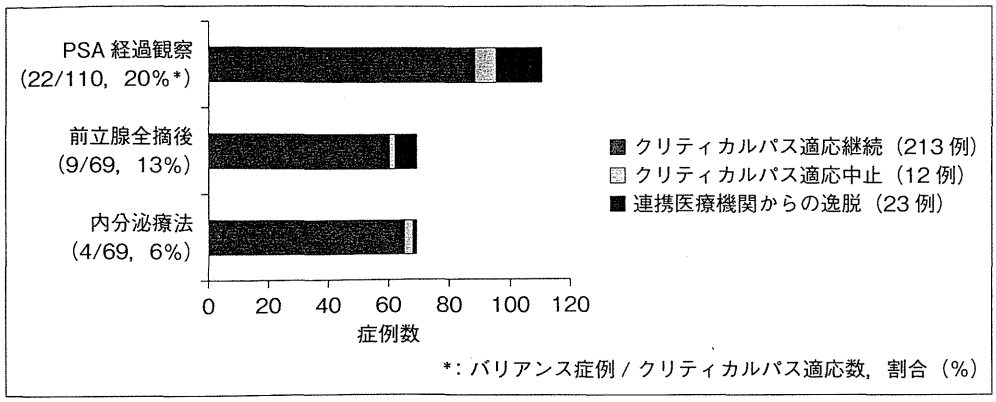

図1 地域連携クリティカルパス別のバリアンスの割合

Ⅲ 考 察

従来の地域連携では多くの場合，中核病院から地域医療機関（多くは開業医師）へ紹介された後は連携先の担当医師が判断し治療が行われてきた。医療レベルの高い中核病院で治療方針が決定した後，自宅近くの医療機関で治療を継続して受けられることは患者にとっての大きなメリットである。しかし紹介後の治療内容は担当医師の裁量に委ねられることが多く，再紹介のタイミングを逸すれば病状の悪化につながりかねず患者が不利益を被りかねない。また，地域医療を担う医師にとっても高リスク症例を担当することは大きなストレスとなる。特にがん患者の再紹介はがんの再発や進展を見逃すリスクを伴うため，良性疾患を中心に患者治療を行っている地域医療機関からあまり望まれない傾向にある。

地域医療機関に紹介される患者と連携先の担当医師双方のメリットとなる様に，われわれのクリティカルパスはアウトカムの設定すなわち再紹介の時期を明確に設定してある。再紹介の時期が明確になることで患者にがん診療の質と安心を保証するだけでなく，地域医療機関の担当医師にかかるストレスも軽減することができたと考えられる。ただし，がん診療の質を高く保っていくためには，バリアンス分析に基づくクリティカルパスの改善を図る必要がある。これまでに地域連携クリティカルパスの運用を開始したという報告は多くみられるが，十分なクリティカルパスの運用数があり，かつバリアンス分析も行った報告は少ない。今回われわれが行ったのは前立腺がんクリティカルパス3種類についての妥当性の検討とバリアンスの解析である。これまでのクリティカルパスにおけるバリアンスの収集方法は大きく3方式に分けられている。それぞれ，①ゲートウェイ方式：設定されたアウトカムが達成されなかった場合をバリアンスとして収集する方法，②センチネル方式：重要なアウトカム（クリニカルインディケーター）が達成されなかった場合のみをバリアンスとして収集する方法，③オールバリアンス方式：設定されたアウトカムだけでなく，すべての患者状態・医療ケア行為に対する異常をバリアンスとして収集する方法，である[4]。今回の検討では，ゲートウェイ方式をとりバリアンスの収集を行った。この収集方法によるバリアンスの発生は248例中35例（14%）であった。バリアンス35例の内訳はPSA経過観察クリティカルパスが最も多く同クリティカルパス適用例のうち20%，次に前立腺全摘後クリティカルパスの13%であった。内分泌療法クリティカルパスはバリアンス発生率が適用例のうち6%と低値だった。経過観察のみでなく治療を続ける必要があるクリティカルパスでは，継続して医療機関を受診する必要性があり，クリティカルパスの継続に関連すると考えられた。

今回の検討でクリティカルパス適用後に「連携医療機関を一度も受診していない」や「一度は受診したが継続的な受診をしていない」などの連携医療機関からの逸脱症例が23例（9%）みられた。これはわれわれのクリティカルパスが千葉県がんセンターへの定期的な受診を義務付ける循環式ではないための特有の現象と思われた。連携診療が継続されていくことが地域医療クリティカルパスにおいての重要なアウトカムであるため，今後は連携診療の継続の有無についてもバリアンスとして検出する必要があると考えられた。今回の検討

を踏まえて，これまでのアウトカムに「診療計画に沿って，定期的な検査が行える」を追加し，連携診療の継続の有無をバリアンスに加えて今後の分析を行っていく予定である。

連携から外れたものが23例（9%）あることの1つの原因としてクリティカルパスについて説明不足があげられる。外来診療での限られた診療時間内では，担当医師がクリティカルパスの運用についての説明を詳細に行い，且つ，患者側が今後の治療や経過観察がどのように行われていくのかを十分に理解を得ることは困難と考えられた。今回のバリアンス解析をもとに対策としてわれわれの施設では，患者の地域連携クリティカルパスへの理解と診療の継続を高める目的で「地域連携コーディネータ」を任命し泌尿器科外来へ配置している。専任の地域連携コーディネータが中心となり，患者オリエンテーション用パンフレットと地域連携の啓発リーフレットを作成し，これを用いて患者へ説明することで，オリエンテーションの質の均一化を図った。また，患者へ質の高い地域医療連携の提供をするために，地域連携コーディネータが外来担当看護師へのパスに関する教育を行っている。

がん治療後経過観察目的での地域連携クリティカルパス導入を試みる医療施設が多くなる中，実際には運用されている症例数が少ないため，その多くがバリアンス解析の報告まで至っていない。今回われわれは，地域連携クリティカルパス導入開始後の運用例248例のバリアンス解析を行った。今回の検討でがんの再発や連携診療の継続がアウトカムとなることが改めて認識された。われわれの地域連携クリティカルの質の向上を図るためには，今回のバリアンス解析を基にさらにクリティカルパスの設計を見直していくと同時に，患者支援の充実及びネットワークづくりの強化を図る必要があると考えられた。

クリティカルパスと医療コストの関係性については，現時点では以下の効果が考えられる。当センターでは千葉市以外の遠隔地から通院する場合が多いため，患者や付き添う家族が負担する交通費や通院にかかる時間が軽減できる。また，クリティカルパスの登録は平成24年3月まで1,600例である。これらの患者が1人あたりすべて3ヵ月に1度当センターに受診するとして単純計算で年間6,400回受診が必要である。年間55週とすると1日あたり23人の外来受診が増える。これだけの患者の受診を減らしていることは，外来の負担軽減に結びついていると思われる。

今後の問題点として，多くの症例が地域連携クリティカルパスの適応となることが予想されるため，運用数の増加に伴い，運用例すべてを連携の枠内で把握することが困難になることがあげられる。このため，患者状況の効率的な収集方法を開発する必要がある。今後，地域連携クリティカルパス導入開始後2年まではアンケート法によるバリアンスの解析を行い，その結果と今回の分析結果とを比較し，患者の通院状況をより簡便に把握する方法を検討開発する予定である。さらに今回の検討から個々の地域連携クリティカルパスの改定に取り組む予定である。

結　語

千葉県がんセンター泌尿器科では千葉県内の泌尿器科開業医を中心とした地域医療機関との連携を開始するにあたり，前立腺がんの治療や経過観察を目的とした地域連携クリティカルパスを作成導入している。運用開始1年を経過した時点で前立腺がんにおける3種類の地域連携クリティカルパスのバリアンス分析を行った結果，アウトカムの設定は良好だった。一方，バリアンス例の中には，診療連携から外れた症例が一定数みられており，地域連携クリティカルパスのアウトカム設定に診療連携の継続を追加することが今後の課題と思われた。

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Abstract

Variance Analysis of Regional Cooperation Critical Pathway for Prostate Cancer

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Beginning in November 2007, we at the Department of Urology of the Chiba Cancer Center developed critical pathways for urological cancer in association with regional private clinics of urologists, and we commenced regional medical cooperation. As of October 2011, we have employed 5 prostate cancer-related critical pathways on 1460 cases. We analyzed variance for 248 cases in which the three regional cooperation critical pathways about prostate cancer were used for 1 year until October 2008. We performed the analysis by surveying urologists at the cooperating medical institutions. The paths were followed on 213 cases (86%), but they were dropped with 35 cases (14%) "variance of the critical pathways." Based on these results, considering the outcome setting conditions, we thought that the current level of use of regional cooperation critical pathways was appropriate. However, since 9% of the cases "veered away from the paths," we thought that it would be necessary to add "continuous cooperative medical treatment" to future critical pathways outcomes.

key words：regional cooperation critical pathway, prostate cancer, variance

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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/m^2 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/m^2 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.

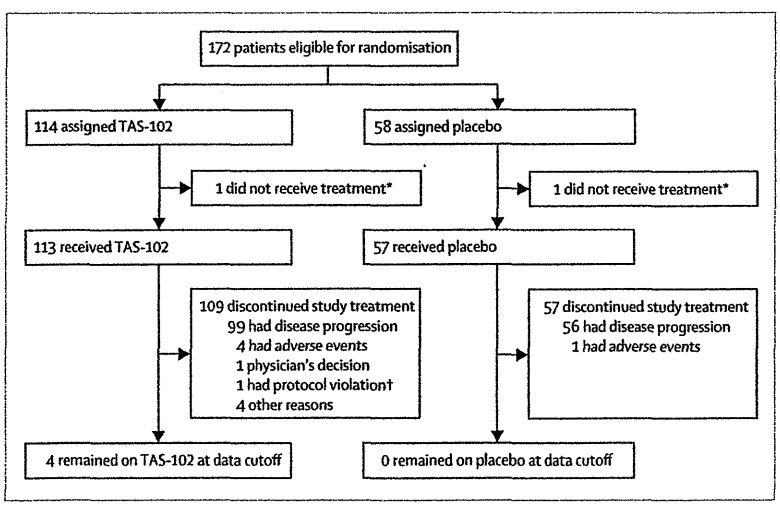

Figure 1: **Trial profile**
*One patient was randomly allocated to TAS-102 did not receive treatment because of aggravation of a rash related to previous chemotherapy and one patient allocated to placebo did not receive treatment because of occurrence of pulmonary thromboembolism; these patients were 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/m^2 TAS-102 was taken orally twice a day after meals (ie, 70 mg/m^2 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

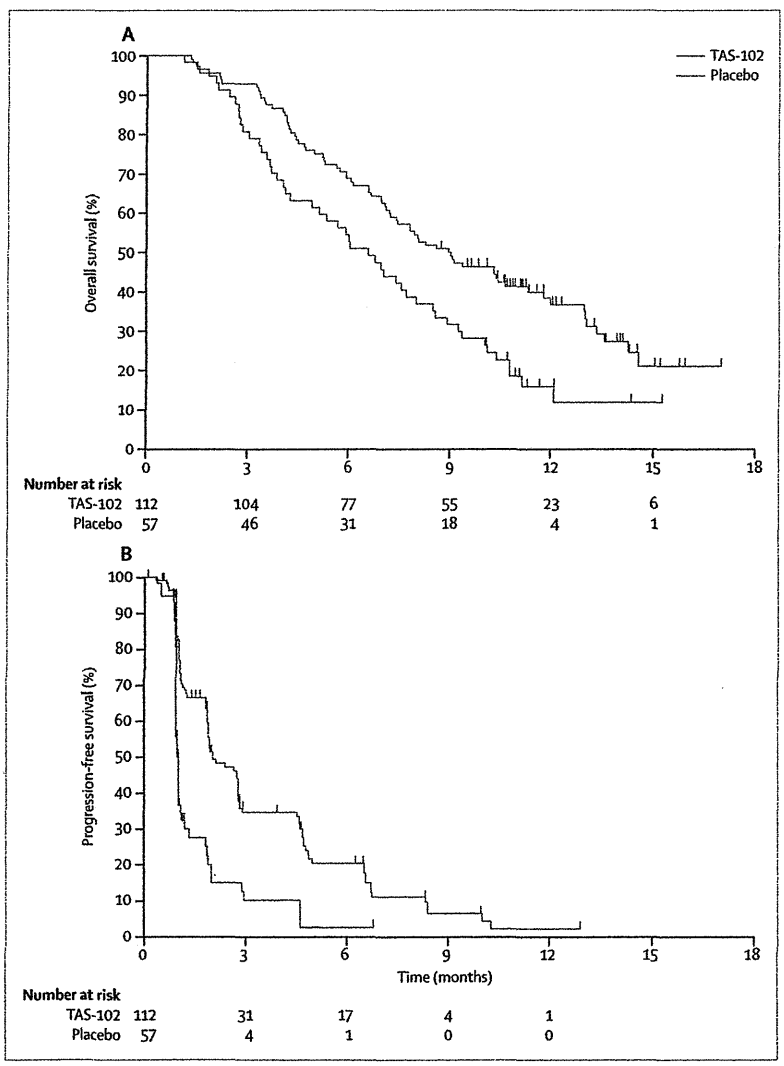

Figure 2: **Kaplan-Meier curves of overall survival (A) and progression-free survival (B) as assessed by independent review committee**

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).

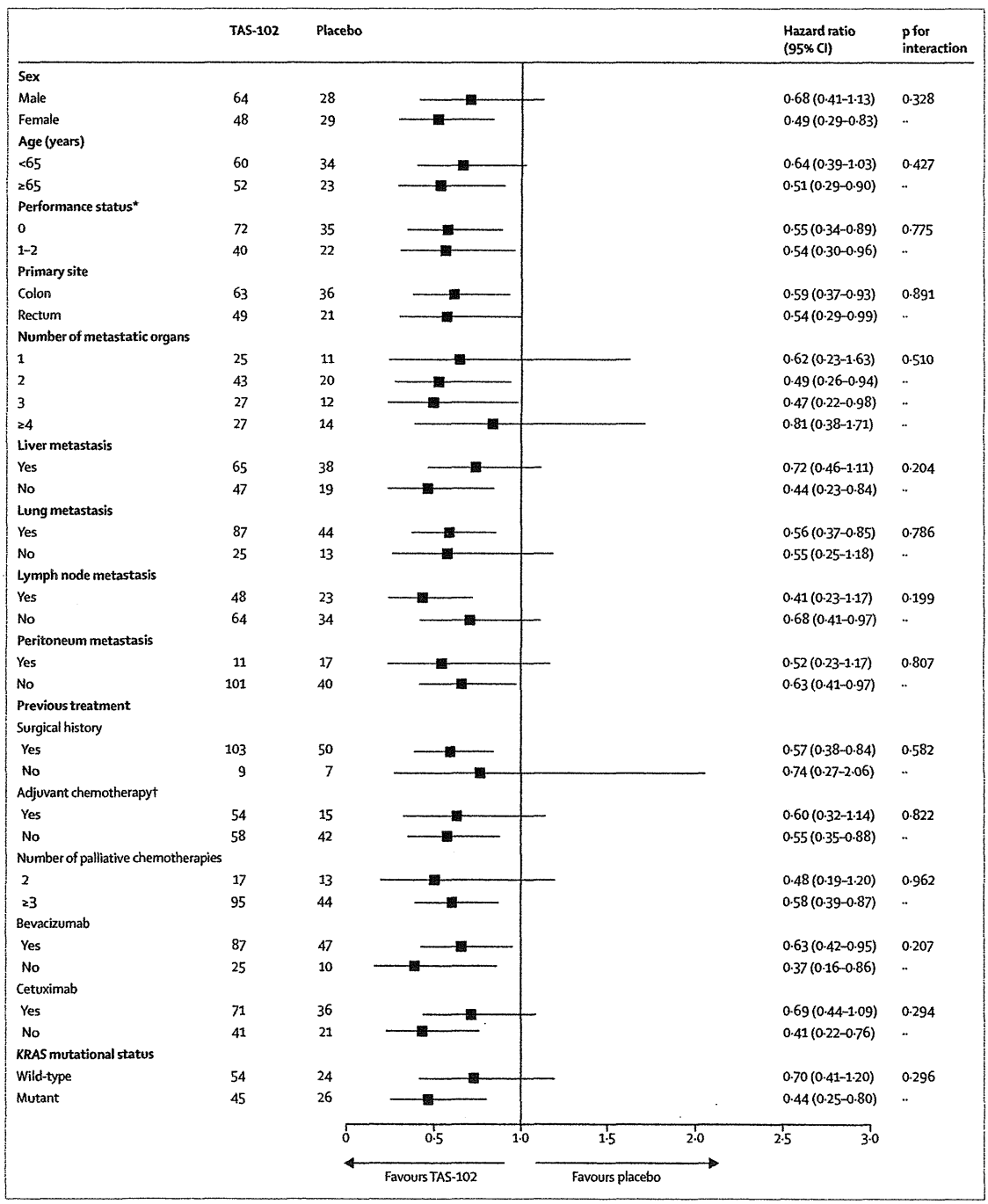

Figure 3: **Overall survival in prespecified subgroups**
*Eastern Cooperative Oncology Group criteria. †More patients received adjuvant chemotherapy in the TAS-102 group than in the placebo group, but this difference had no effect on the assessment of overall survival with the Cox proportional hazards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

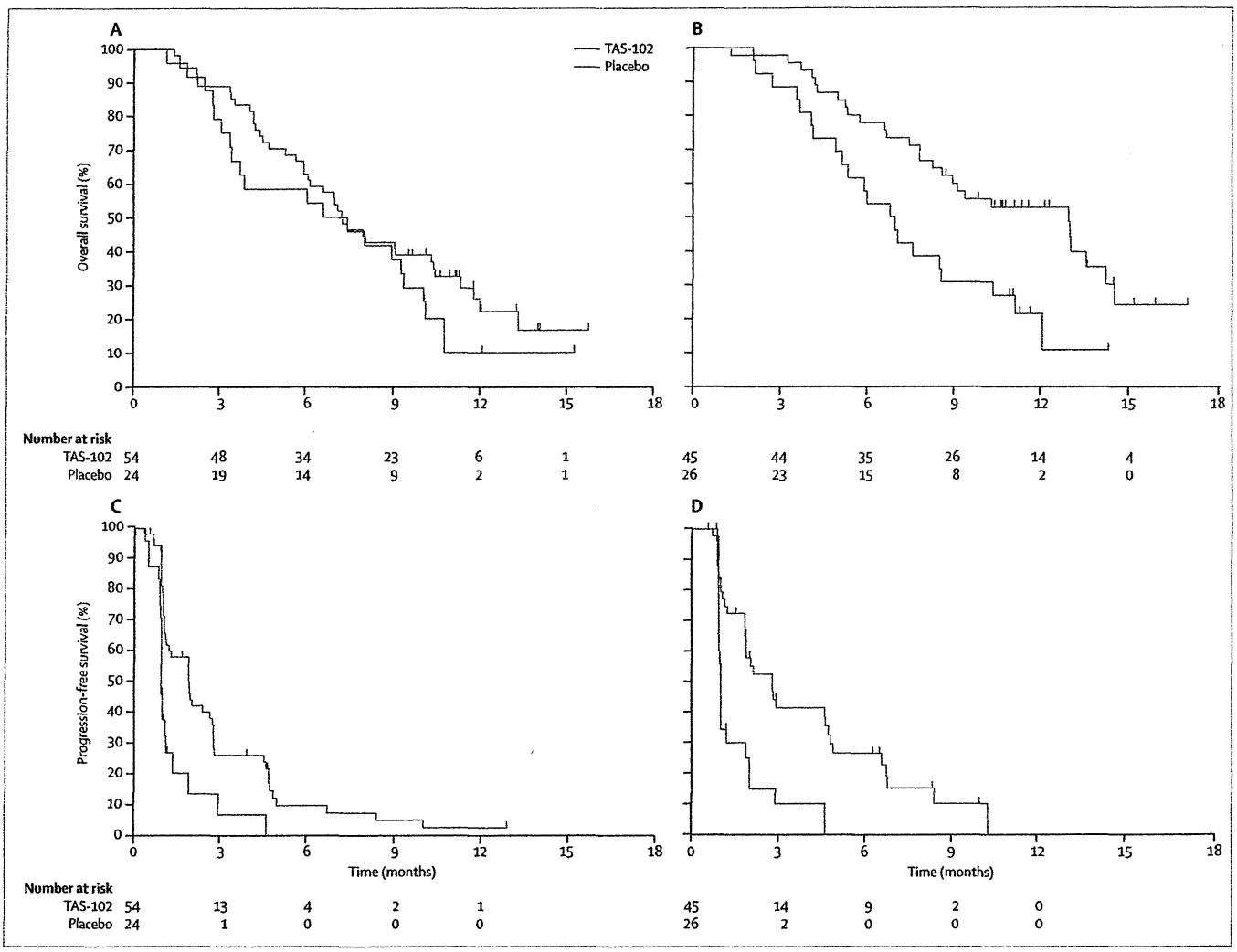

Figure 4: **Kaplan-Meier curves of overall survival and progression-free survival in patients with wild-type and mutant *KRAS***
(A) Overall survival of patients with wild-type *KRAS*. (B) Overall survival of patients with mutant *KRAS*. (C) Progression-free survival of patients with wild-type *KRAS*, 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/m^2 *vs* 25 mg/m^2), 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.