このたび、大腸癌治療ガイドライン医師用 2014 年版の「切除不能進行再発大腸がんに対する化学療法」に追記すべき臨床試験の結果が報告されましたので、下記の情報提供を行います。

（1）前治療歴を有する転移性大腸癌に対する TAS-102 単独療法：国内多施設ランダム化プラセボ対照第 II 相試験

論 文 名： TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomized, placebo-controlled phase 2 trial.

掲載雑誌名：Lancet Oncol 2012, 13: 993-1001

著者名；Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, Tsuji A, Yamaguchi K, Muro K, Sugimoto N, Tsuji Y, Moriwaki T, Esaki T, Hamada C, Tanase T, Ohtsu A.

試験のスポンサー名：大鵬薬品工業株式会社

試験デザイン

前治療歴を有する切除不能進行再発大腸癌患者を TAS-102 またはプラセボにそれぞれ 2:1 でランダム割り付けし、主要評価項目を全生存期間とした国内他施設第 II 相試験がおこなわれた。

本論文における結果の要約

2009 年 8 月から 2010 年 4 月までに TAS-102 群 112 名、プラセボ群 57 名が登録された。ほとんどの症例は国内で使用できる抗がん剤に不応な ECOGPS が 0-2 の患者であった。観察期間中央値 11.3 ヶ月の時点で，全生存期間中央値は TAS-102 療法群で 9.0 ヶ月，プラセボ群で 6.6 ヶ月であった（ハザード比 0.56, 80%信頼区間 0.44－0.71, 片側 p 値 0.0011）。TAS-102 療法の頻度の高い Grade3 以上の有害事象は血液毒性であり、好中球減少 50%及び白血球減少 28%であった。重篤な有害事象は TAS-102 群、プラセボ群でそれぞれ 19%, 9%であり、治療関連死亡は認めなかった。

本論文における結語

TAS-102 は標準治療に不応・不耐な転移性大腸がんに対して将来有望となる有効性を示し、忍容性も概ね良好であった。

（２）標準治療に不応な転移性大腸癌に対する TAS-102 単独療法

論文名：Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer.

掲載雑誌名：New Engl J Med 2015, 372: 1909-1919.

著者名；Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia- Carbonero R, Mizunuma N, Ymazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti H, Mizuguchi H, Makris L, Ito M, Ohstu A.

試験のスポンサー名：大鵬薬品工業株式会社

試験デザイン

標準治療に不応・不耐となった切除不能進行再発大腸癌患者を TAS-102 またはプラセボにそれぞれ 2:1 でランダム割り付けし、主要評価項目を全生存期間とした国際共同第 III 相試験(RECOURSE 試験)がおこなわれた。

本論文における結果の要約

2012 年 6 月から 2013 年 10 月までに、標準治療に不応で ECOG PS が 0-1 の 800 名が登録され、日本からは全体の約 1/3 の患者が登録された。前治療歴として、フルオロピリミジン、イリノテカン、オキサリプラチン、ベバシツマブは全例で使用され、KRAS 野生型の患者では抗 EGFR 抗体がほぼ 100%使用されていた。また、国内では 2013 年 5 月より販売されたばかりのレゴラフェニブも全体で 18%の患者に使用されていた。必要イベント数 574 に達した時点で，全生存期間中央値は TAS-102 療法群（534 名）で 7.1 ヶ月，プラセボ群（266 名）で 5.3 ヶ月であり，優越性が証明された（ハザード比 0.68，95%信頼区間 0.58－0.81，片側 p 値 <0.0001）。TAS-102 群において 1 名のみ敗血症性ショックによる治療関連死亡をみとめた。TAS-102 療法にて頻度の高い Grade3 以上の有害事象は血液毒性であり、好中球減少 38%及び白血球減少 21%であった。一方、非血液毒性は発熱性好中球減少症、倦怠感および食欲不振 4%、下痢 3%、と軽微であった。全生存期間におけるサブセット解析では、日本人とそれ以外の患者との間ではとくに交互作用はみとめなかった。

本論文における結語

標準治療に不応・不耐となった切除不能進行再発大腸癌に対して、TAS-102 は全生存期間の延長および優れた忍容性を示した。本試験の結果から、TAS-102 療法は、標準治療に不応になった切除不能進行再発大腸癌に対する治療としての新たな治療選択肢となりうる。

（3）両試験の結果を受けて、ガイドライン委員会のコメント

Yoshino T らにより国内で行われた TAS-102 単独投与と BSC とのランダム化比較第Ⅱ相試験にて有望な結果が得られたことにより国際共同第Ⅲ相試験である RECOURSE 試験が行われた。RECOURSE 試験の結果から、TAS-102 単独投与はフッ化ピリミジン、オキサリプラチン、イリノテカン、ベバシツマブ、および抗 EGFR 抗体全ての薬剤に対し不応/不耐となり、全身状態が良好に維持されている PS が 0-1 の大腸癌患者に対して生存期間が延長されることが示された。本試験における TAS-102 の有効性に関しては、CORRECT 試験（Lancet 2013, 381: 303-312)におけるレゴラフェニブの有効性とほぼ同等であった。また、TAS-102 の有効性に関して、*KRAS* 変異の有無、人種間（日本人と欧米人）には大きな影響を受けないことが示された。有害事象では骨髄抑制および発熱性好中球減少症に留意する必要があるが、後者の発生割合は 3.7%であり、適切なタイミングでの血液検査、さらには減量/休薬により、十分安全に管理が可能と思われる。

切除不能進行再発大腸癌に対する化学療法の治療アルゴリズムにおける TAS-102（トリフルリジン・チピラシル塩酸塩）の位置づけは、レゴラフェニブと同列に位置付けられると考えられる。すなわち、フッ化ピリミジン、オキサリプラチン、イリノテカン、ベバシツマブ、および抗 EGFR 抗体に対し不応/不耐となった患者に対しては、全身状態、およびそれぞれの薬剤の毒性プロファイルを考慮して、いずれかの薬剤を選択することになる。尚、トリフルリジン・チピラシル塩酸塩（トリフルリジンとして約 35mg/m^2/回）は 5 日間内服 2 日休薬を 2 回繰り返したのち 14 日間休薬する。これを 1 コースとして投与を繰り返すことになっており、これまでの経口剤に比べてやや複雑な服用法となっている。よって医師、外来看護師・薬剤師がチームとなって、より適切な服薬指導、コンプライアンス・副作用確認が必要となる。

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.

Funding Taiho Pharmaceutical.

Lancet Oncol 2012; 13: 993–1001

Published Online August 28, 2012 http://dx.doi.org/10.1016/S1470-2045(12)70345-5

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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.

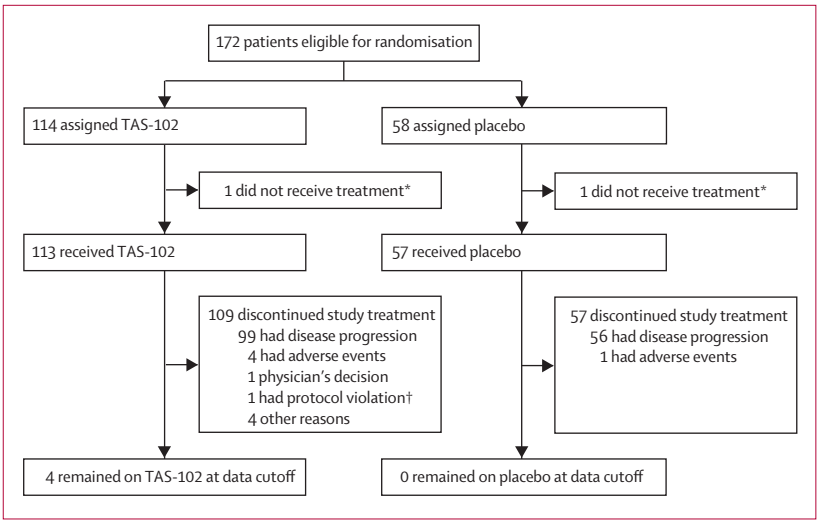

Figure 1: **Trial profile**
*One patient was randomly allocated to TAS-102 did not receive treatment because of aggravation of a rash related to previous chemotherapy and one patient allocated to placebo did not receive treatment because of occurrence of pulmonary thromboembolism; these patients were 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

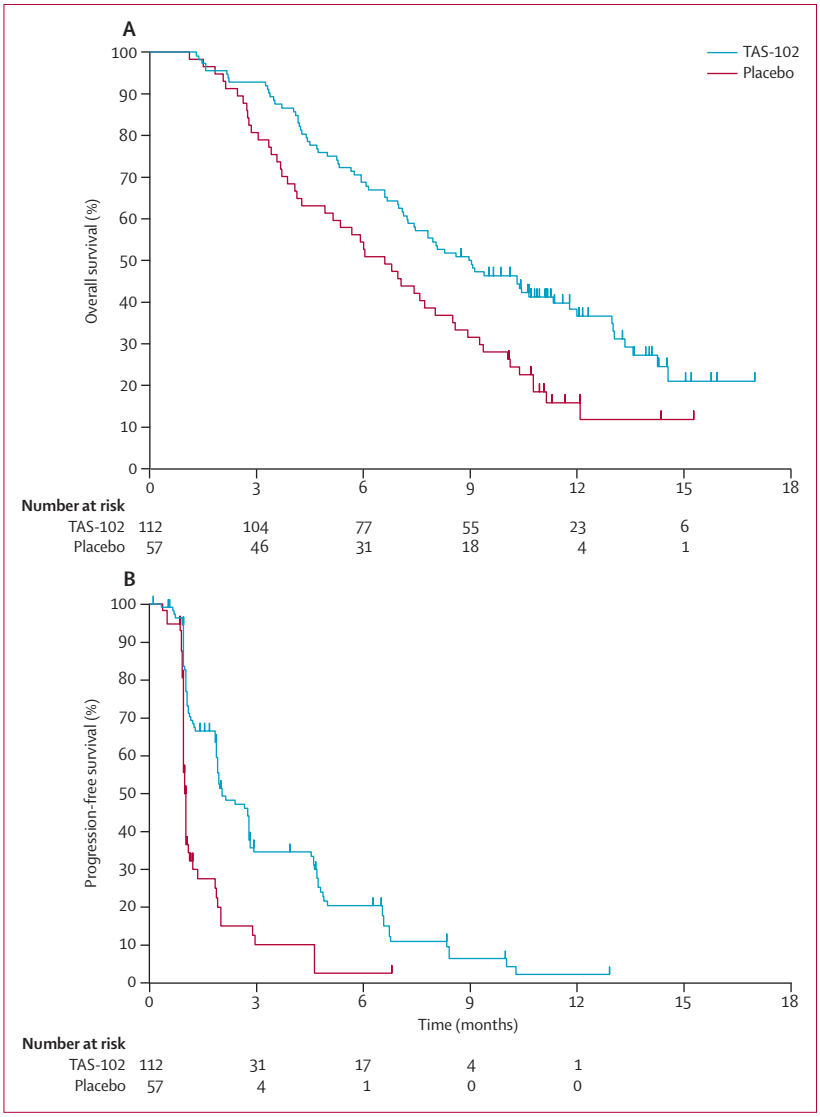

Figure 2: Kaplan-Meier curves of overall survival (A) and progression-free survival (B) as assessed by independent review committee

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).

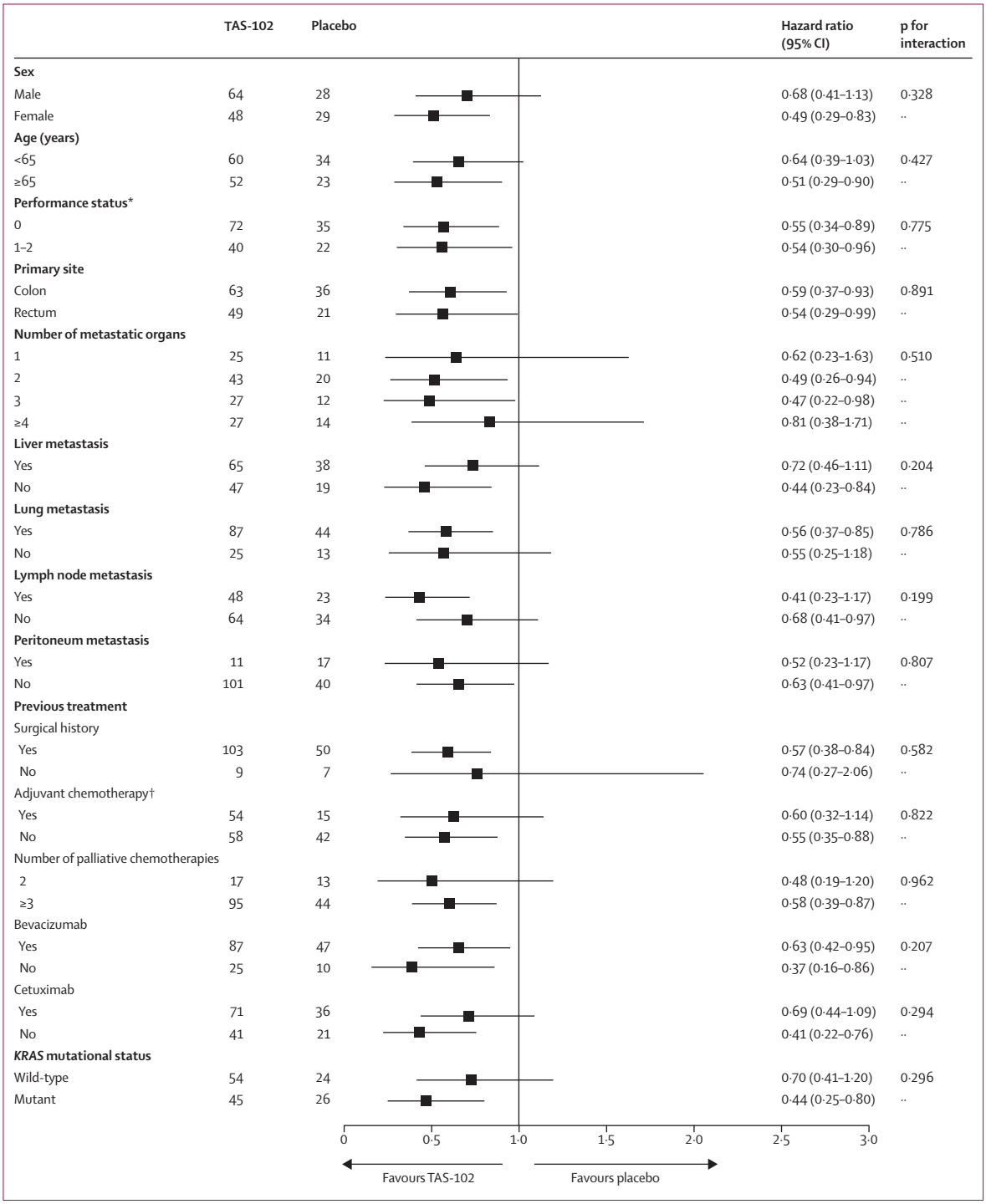

Figure 3: **Overall survival in prespecified subgroups**
*Eastern Cooperative Oncology Group criteria. †More patients received adjuvant chemotherapy in the TAS-102 group than in the placebo group, but this difference had no effect on the assessment of overall survival with the Cox proportional hazards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

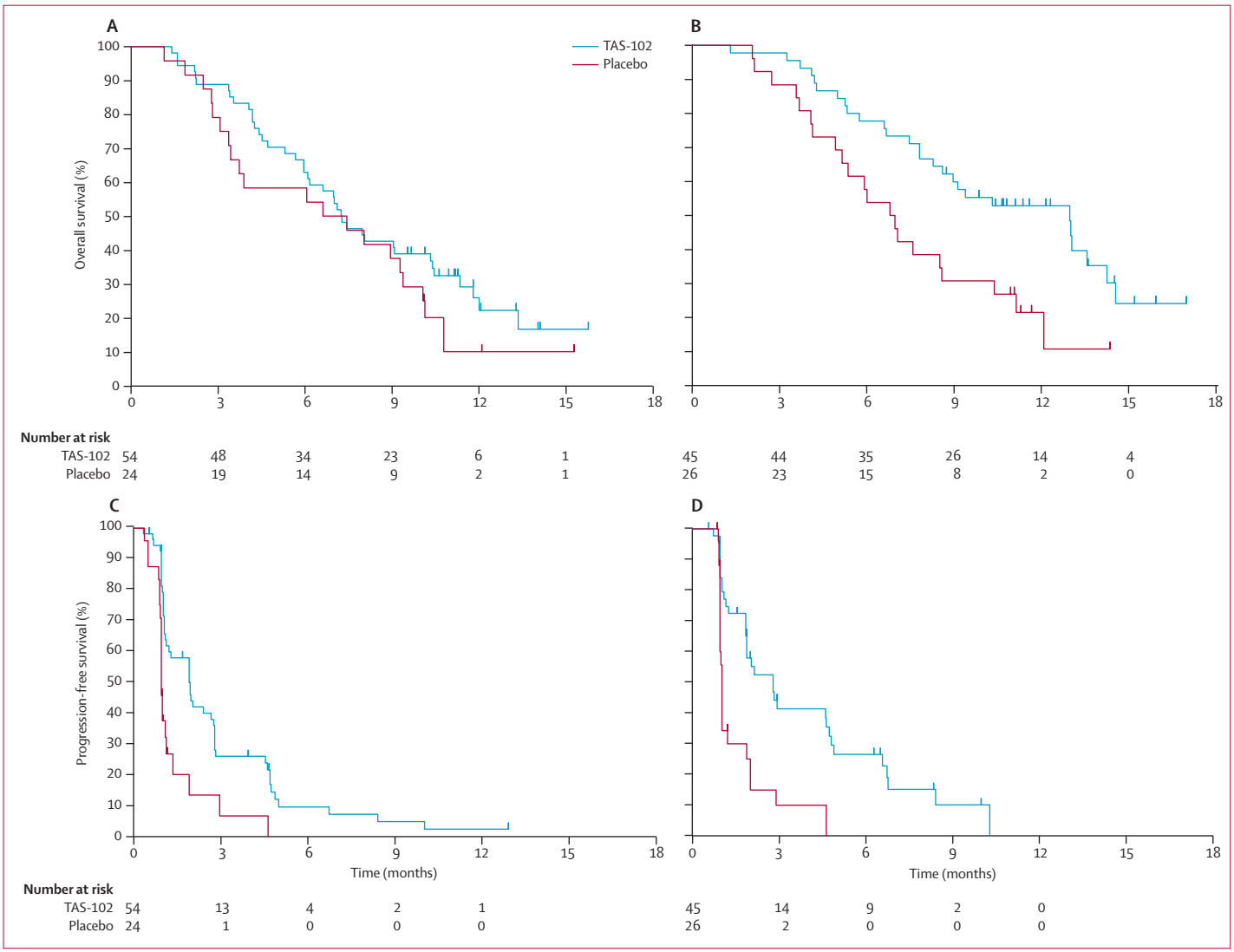

Figure 4: **Kaplan-Meier curves of overall survival and progression-free survival in patients with wild-type and mutant *KRAS***
(A) Overall survival of patients with wild-type *KRAS*. (B) Overall survival of patients with mutant *KRAS*. (C) Progression-free survival of patients with wild-type *KRAS*,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

Acknowledgments

This investigation was supported by Taiho Pharmaceutical. We thank the patients; their families; all the investigators who participated in the study (appendix); all of the committee members (Keisuke Aiba, Toshihiko Doi, Ichinosuke Hyodo, Atsushi Sato, Akira Tsuburaya, and Hiroyuki Uetake); and Masanobu Ito, Kenya Kosaka, and Mirai Sugiyama for their contributions to this report.

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ORIGINAL ARTICLE

Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer

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ABSTRACT

BACKGROUND

Early clinical trials conducted primarily in Japan have shown that TAS-102, an oral agent that combines trifluridine and tipiracil hydrochloride, was effective in the treatment of refractory colorectal cancer. We conducted a phase 3 trial to further assess the efficacy and safety of TAS-102 in a global population of such patients.

METHODS

In this double-blind study, we randomly assigned 800 patients, in a 2:1 ratio, to receive TAS-102 or placebo. The primary end point was overall survival.

RESULTS

The median overall survival improved from 5.3 months with placebo to 7.1 months with TAS-102, and the hazard ratio for death in the TAS-102 group versus the placebo group was 0.68 (95% confidence interval [CI], 0.58 to 0.81; P<0.001). The most frequently observed clinically significant adverse events associated with TAS-102 were neutropenia, which occurred in 38% of those treated, and leukopenia, which occurred in 21%; 4% of the patients who received TAS-102 had febrile neutropenia, and one death related to TAS-102 was reported. The median time to worsening performance status (a change in Eastern Cooperative Oncology Group performance status [on a scale of 0 to 5, with 0 indicating no symptoms and higher numbers indicating increasing degrees of disability] from 0 or 1 to 2 or more) was 5.7 months with TAS-102 versus 4.0 months with placebo (hazard ratio, 0.66; 95% CI, 0.56 to 0.78; P<0.001).

CONCLUSIONS

In patients with refractory colorectal cancer, TAS-102, as compared with placebo, was associated with a significant improvement in overall survival. (Funded by Taiho Oncology–Taiho Pharmaceutical; RECOURSE ClinicalTrials.gov number, NCT01607957.)

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*A complete list of the investigators in the RECOURSE (Randomized, Double-Blind, Phase 3 Study of TAS-102 plus Best Supportive Care [BSC] versus Placebo plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapies) study is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Mayer and Van Cutsem contributed equally to this article.

N Engl J Med 2015;372:1909-19.
DOI: 10.1056/NEJMoa1414325

Fluoropyrimidines have long represented the cornerstone of treatment for colorectal cancer.[1] Such compounds act primarily as inhibitors of thymidylate synthase, the rate-limiting enzyme in the synthesis of pyrimidine nucleotides.[2] Fluorouracil has been combined with folinic acid (also known as leucovorin) to enhance the capacity of fluorouracil to bind to thymidylate synthase.[2] The addition of irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) to fluorouracil and folinic acid, in combination with either a vascular endothelial growth factor inhibitor (bevacizumab) or an epidermal growth factor inhibitor (e.g., cetuximab or panitumumab) if the tumor contains a wild-type *RAS* gene, represents contemporary standard therapy and has extended the median survival among patients with metastatic colorectal cancer to almost 30 months.[3,4]

TAS-102 is an orally administered combination of a thymidine-based nucleic acid analogue, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride. Trifluridine is the active cytotoxic component of TAS-102; its triphosphate form is incorporated into DNA, with such incorporation appearing to result in its antitumor effects.[5] Tipiracil hydrochloride is a potent inhibitor of thymidine phosphorylase and, when combined with trifluridine to form TAS-102, prevents the rapid degradation of the trifluridine, allowing for the maintenance of adequate plasma levels of the active drug.[6]

Preclinical xenograft studies in mice have shown that TAS-102 has antitumor activity against cell lines that are resistant to fluorouracil.[7,8] Results from clinical trials[9-12] have suggested that TAS-102 is effective when administered in 28-day cycles, each comprising 5 days of treatment followed by a 2-day rest period each week for 2 weeks, and then a 14-day rest period. A dose of 35 mg per square meter of body-surface area twice daily was recommended for further investigation on the basis of phase 1 studies involving patients from Japan[13] and from the United States.[14] TAS-102 was further evaluated in a double-blind, randomized, placebo-controlled, phase 2 trial involving 169 Japanese patients with metastatic colorectal cancer that was refractory to fluorouracil and to both irinotecan and oxaliplatin.[15] The median overall survival was 9.0 months in the TAS-102 group and 6.6 months in the placebo group (hazard ratio for death, 0.56; P=0.001). These experiences led to the development of a phase 3 study that was designed to further assess the efficacy and safety of TAS-102 in a global population of 800 patients with metastatic colorectal cancer whose cancer had been refractory to antitumor therapy or who had had clinically significant adverse events that precluded the readministration of those therapies.

METHODS

PATIENTS

Patients with biopsy-documented adenocarcinoma of the colon or rectum were eligible for participation in the study if they had received at least two prior regimens of standard chemotherapies, which could have included adjuvant chemotherapy if a tumor had recurred within 6 months after the last administration of this therapy; if they had either tumor progression within 3 months after the last administration of chemotherapy; or if they had had clinically significant adverse events from standard chemotherapies that precluded the readministration of those therapies. Eligibility also required knowledge of tumor status with regard to *KRAS* (i.e., wild-type or mutant), as reported by investigators. Patients were also required to have received chemotherapy with each of the following agents: a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and — for patients with *KRAS* wild-type tumors — cetuximab or panitumumab. In addition, patients had to be 18 years of age or older; have adequate bone-marrow, liver, and renal function; and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (on a scale of 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and higher numbers indicating increasing degrees of disability).

STUDY OVERSIGHT AND CONDUCT

This study was designed by the first two authors and the last author and by representatives of the sponsor of the study, Taiho Oncology–Taiho Pharmaceutical. The protocol is available with the full text of this article at NEJM.org. The first author prepared the first draft of the manuscript with input from the sponsor, and all the coauthors subsequently provided input and approved the manuscript. All the authors made the decision to submit the manuscript for publication.

An independent data and safety monitoring board regularly evaluated the conduct, evolving outcome, and safety of the study. The authors vouch for the accuracy and completeness of the data and for adherence to the study protocol. No one who is not an author contributed to the manuscript. The review board at each participating institution approved the study, which was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

STUDY DESIGN AND TREATMENT

Patients were randomly assigned, in a 2:1 ratio, to receive TAS-102 or placebo and were stratified according to tumor status with regard to wild-type or mutant *KRAS*, the time between first diagnosis of metastases and randomization (<18 months vs. ≥18 months), and geographic region (Japan or the United States, Europe, and Australia). Patients were unaware of the study-group assignments. TAS-102 (with each dose consisting of 35 mg per square meter) or placebo was administered twice daily, after morning and evening meals, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period, thus completing one treatment cycle. The regimen was repeated every 4 weeks. The protocol allowed for a maximum of three reductions in dose in decrements of 5 mg per square meter.

ASSESSMENTS

All patients received the best supportive care available but were not to receive other investigational antitumor agents or antineoplastic chemotherapy, hormonal therapy, or immunotherapy. No crossover between treatment groups was allowed before the final analysis of the primary end point. Patients were evaluated every 2 weeks while receiving treatment and every 8 weeks from the time they stopped treatment until their death or the trial cutoff date for data collection.

Radiologic assessments of tumors were performed by investigators every 8 weeks, and the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[16] was used to assess tumor responses. Treatment was continued until the determination of RECIST-defined[16] disease progression, clinical progression, the development of severe adverse events, withdrawal from the study, death, or a decision by the treating physician that discontinuation would be in the patient's best interest. Adverse events were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[17]

END POINTS

The primary end point was overall survival, which was defined as the time from randomization to death from any cause. Secondary end points included progression-free survival (the time from randomization to the first radiologic confirmation of disease progression or death from any cause), response rate (the proportion of patients whose best response was a complete or partial response), rate of disease control (the proportion of patients with a best response of complete or partial response or stable disease, with the assessment of stable disease made at least 6 weeks after randomization), and safety.

STATISTICAL ANALYSIS

The study was designed to have 90% power to detect a hazard ratio for death of 0.75 (a 25% reduction in risk) in the TAS-102 group as compared with the placebo group, with a one-sided type I error rate of 0.025. Given the treatment assignment ratio of 2:1 (TAS-102:placebo), we calculated that 800 patients had to be enrolled in the study, and at least 571 events (deaths) would be required for the primary analysis.

Overall survival (the primary end point) and radiologically confirmed progression-free survival were analyzed in the intention-to-treat population with the use of a two-sided, stratified log-rank test, with the hazard ratio and two-sided 95% confidence intervals based on a stratified Cox model and the associated Kaplan–Meier survival estimates. The median follow-up time for survival was calculated by means of the reverse Kaplan–Meier method. Rates of objective response and disease control were compared with the use of Fisher's exact test in the subgroup of the intention-to-treat population that had measurable disease at baseline. Adverse events and laboratory abnormalities were summarized for all patients who received at least one dose of study drug. Time to worsening of ECOG performance status was analyzed with the same methods

Table 1. Baseline Characteristics of the Intention-to-Treat Population.*

Characteristic	TAS-102 (N=534)	Placebo (N=266)
Age — yr		
Median	63	63
Range	27–82	27–82
Sex — no. (%)		
Male	326 (61)	165 (62)
Female	208 (39)	101 (38)
Race — no. (%)†		
White	306 (57)	155 (58)
Asian	184 (34)	94 (35)
Black	4 (<1)	5 (2)
Region — no. (%)		
Japan	178 (33)	88 (33)
United States, Europe, and Australia	356 (67)	178 (67)
ECOG performance status — no. (%)‡		
0	301 (56)	147 (55)
1	233 (44)	119 (45)
Primary site of disease — no. (%)		
Colon	338 (63)	161 (61)
Rectum	196 (37)	105 (39)
KRAS mutation — no. (%)		
No	262 (49)	131 (49)
Yes	272 (51)	135 (51)
Time from diagnosis of metastases — no. (%)		
<18 mo	111 (21)	55 (21)
≥18 mo	423 (79)	211 (79)
Number of prior regimens — no. (%)		
2	95 (18)	45 (17)
3	119 (22)	54 (20)
≥4	320 (60)	167 (63)
Prior systemic anticancer agents — no. (%)		
Fluoropyrimidine	534 (100)	266 (100)
Irinotecan	534 (100)	266 (100)
Oxaliplatin	534 (100)	266 (100)
Bevacizumab	534 (100)	265 (>99)
Anti-EGFR monoclonal antibody	278 (52)	144 (54)
Regorafenib	91 (17)	53 (20)
Refractory to fluoropyrimidine — no. (%)		
As part of any prior treatment regimen	524 (98)	265 (>99)
At time of last exposure	497 (93)	240 (90)
As part of last regimen before study entry	311 (58)	144 (54)

* Baseline demographic and disease characteristics were well balanced between the two study groups. EGFR denotes epidermal growth factor receptor.
† Race was self-reported.
‡ Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale of 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and higher numbers indicating increasing degrees of disability.

Figure 1 (facing page). Kaplan–Meier Curves for Overall Survival and Forest Plot of Subgroup Analyses.

Kaplan–Meier curves for overall survival are shown in Panel A. A total of 364 patients (68%) in the TAS-102 group and 210 (79%) in the placebo group have died. The median overall survival was 7.1 months in the TAS-102 group (vertical red dashed line) and 5.3 months in the placebo group (vertical black dashed line). At 6 months, 58% of the patients in the TAS-102 group and 44% of the patients in the placebo group were alive; at 12 months, 27% and 18%, respectively, were alive. The median follow-up time was 11.8 months. A forest plot of subgroup analyses is shown in Panel B. Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale of 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and higher numbers indicating increasing degrees of disability.

used to assess overall survival. All subgroup analyses, as well as the time to worsening ECOG performance status, were prespecified in the protocol or statistical analysis plan before the data were unblinded. Multivariate Cox regression analysis was performed to examine the effect of all prespecified factors (prognostic and predictive) on the overall survival effect of TAS-102.

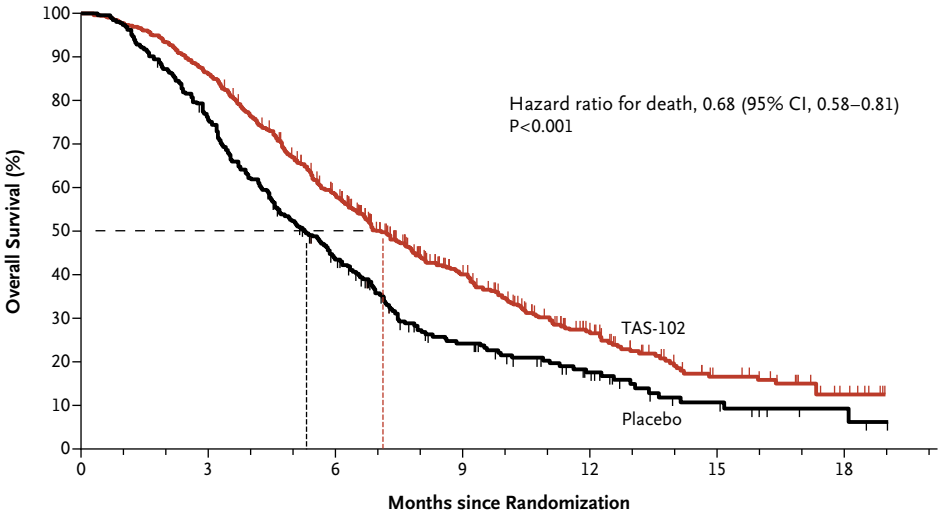
RESULTS

PATIENTS

Between June 17, 2012, and October 8, 2013, a total of 1002 patients were screened for eligibility, of whom 800 underwent randomization, with 534 assigned to receive TAS-102 and 266 assigned to receive placebo (intention-to-treat population) (details regarding the disposition of patients are provided in Fig. S1 in the Supplementary Appendix, available at NEJM.org). Treatment was initiated in 798 patients, with 533 receiving TAS-102 and 265 receiving placebo (safety-analysis population). All treated patients received their assigned study drug according to the randomization schema, and 760 could be evaluated for assessment of tumor response (tumor-response population).

Baseline demographic and disease characteristics were well balanced between the two study groups (Table 1). All the patients had received prior chemotherapy regimens containing a fluoropyrimidine, oxaliplatin, and irinotecan; all but one patient (in the placebo group) had received bevacizumab. All but two patients (one patient in each study group) with *KRAS* wild-type tumors

A Overall Survival

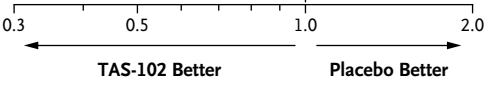


No. at Risk

TAS-102	534	459	294	137	64	23	7
Placebo	266	198	107	47	24	9	3

B Overall Survival

Subgroup	No. of Patients	Hazard Ratio (95% CI)
All patients	800	0.68 (0.58–0.81)
KRAS status		
Wild type	393	0.58 (0.45–0.74)
Mutant	407	0.80 (0.63–1.02)
Time since diagnosis of first metastases		
<18 mo	166	0.84 (0.58–1.21)
≥18 mo	634	0.64 (0.53–0.78)
Geographic region		
Japan	266	0.75 (0.57–1.00)
United States, Europe, and Australia	534	0.64 (0.52–0.80)
Sex		
Male	491	0.69 (0.56–0.87)
Female	309	0.68 (0.51–0.90)
Age		
<65 yr	448	0.74 (0.59–0.94)
≥65 yr	352	0.62 (0.48–0.80)
ECOG performance status		
0	448	0.73 (0.58–0.93)
1	352	0.61 (0.48–0.79)
Primary tumor site		
Colon	499	0.68 (0.55–0.85)
Rectum	301	0.64 (0.48–0.85)
Disease refractory to fluoropyrimidine (as part of last prior regimen)	455	0.75 (0.59–0.94)
Prior use of regorafenib		
Yes	144	0.69 (0.45–1.05)
No	656	0.69 (0.57–0.83)
No. of prior regimens		
2	140	1.05 (0.68–1.63)
3	173	0.74 (0.51–1.08)
≥4	487	0.59 (0.47–0.73)
No. of metastatic sites		
1–2	477	0.69 (0.54–0.87)
≥3	323	0.68 (0.52–0.88)



had received cetuximab or panitumumab. Regorafenib, an oral multikinase inhibitor, became available for the management of previously treated colorectal cancer during the course of the study; 17% of the patients in the TAS-102 group, as compared with 20% of those in the placebo group, had received this drug. A large percentage of patients in both study groups — 93% of patients receiving TAS-102 and 90% of those receiving placebo — had disease that had been refractory to fluoropyrimidines when they were last exposed to this class of drugs. Moreover, 58% of the patients receiving TAS-102 and 54% of the patients receiving placebo had disease that had been refractory to fluoropyrimidine when that drug was administered as part of their last treatment regimen before study entry.

Patients in the TAS-102 group received the study drug for a mean (±SD) of 12.7±12.0 weeks (median, 6.7; range, 0.1 to 78.0), and patients in the placebo group received the study drug for a mean of 6.8±6.1 weeks (median, 5.7; range, 0.1 to 63.7). Patients assigned to the TAS-102 group received 89% of the planned dose during the course of the study (mean dose intensity, 155.1±20.0 mg per square meter per week), and patients in the placebo group received 94% of the planned dose (mean dose intensity, 165.3±16.5 mg per square meter per week). The planned dose reflects the total targeted dose while patients were receiving treatment. Patients in the placebo group were treated for a smaller interval overall, but their adherence to the targeted dose was slightly higher.

Figure 2 (facing page). Kaplan–Meier Curves for Progression-free Survival and Forest Plot of Subgroup Analyses.

Kaplan–Meier curves for progression-free survival are shown in Panel A. A total of 472 patients (88%) in the TAS-102 group and 251 (94%) in the placebo group had an event of progression or death. The median progression-free survival was 2.0 months in the TAS-102 group (vertical red dashed line) and 1.7 months in the placebo group (vertical black dashed line). Tumor assessments were performed every 8 weeks. A forest plot of subgroup analyses is shown in Panel B.

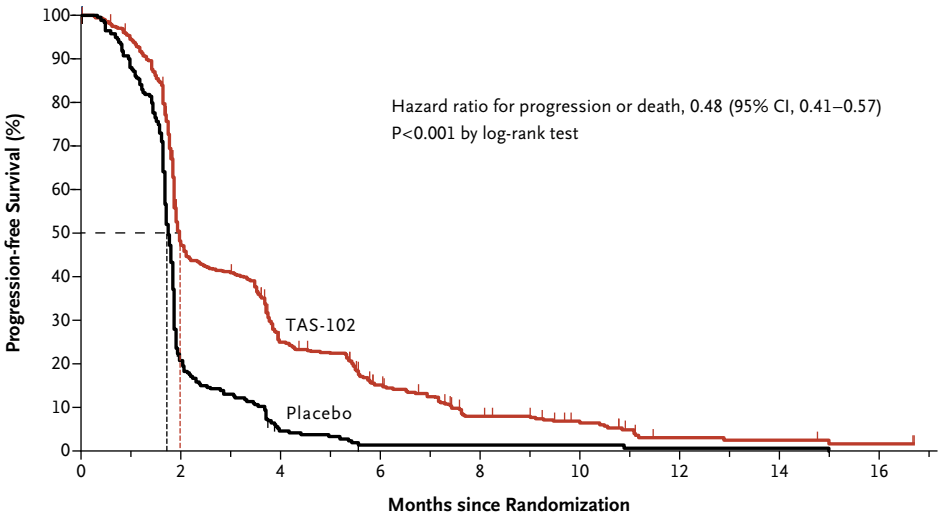
EFFICACY

The number of events (deaths) required to determine efficacy for the primary analysis was 571. At the time that the target was reached (574 deaths), the median overall survival was 7.1 months (95% confidence interval [CI], 6.5 to 7.8) in the TAS-102 group and 5.3 months (95% CI, 4.6 to 6.0) in the placebo group. The hazard ratio for death (TAS-102 vs. placebo) was 0.68 (95% CI, 0.58 to 0.81; P<0.001) (Fig. 1A). The 1-year overall survival rates were 27% and 18%, respectively. The overall survival benefit with TAS-102 was observed in essentially all prespecified subgroups (Fig. 1B), including subgroups defined according to each of the three stratification factors (i.e., *KRAS* status, time between first diagnosis of metastases and randomization, and geographic region). In the multivariate Cox regression analysis, none of the factors were identified as being predictive; all P values for treatment interaction were more than 0.20. Three factors were identified as prognostic: time since diagnosis of first metastasis, ECOG performance status, and number of metastatic sites. However, the magnitude of the TAS-102 treatment effect, after adjustment for all three factors, was maintained (hazard ratio, 0.69; 95% CI, 0.58 to 0.81). In particular, the efficacy of TAS-102 was documented in patients with disease that had been refractory to fluorouracil when that drug had been administered as a component of the last treatment regimen before study entry and in patients who had previously been treated with regorafenib. The median progression-free survival was 2.0 months (95% CI, 1.9 to 2.1) in the TAS-102 group and 1.7 months (95% CI, 1.7 to 1.8) in the placebo group. The hazard ratio for progression (TAS-102 vs. placebo) was 0.48 (95% CI, 0.41 to 0.57; P<0.001) (Fig. 2A). The effect of TAS-102 on progression-free survival was observed in all prespecified subgroups (Fig. 2B).

In the tumor-response population (502 patients in the TAS-102 group and 258 in the placebo group), 8 patients in the TAS-102 group had a partial response, and 1 patient in the placebo group was reported to have a complete response, resulting in objective response rates of 1.6% with TAS-102 and 0.4% with placebo (P=0.29). Disease control (complete or partial response or stable disease, assessed at least 6 weeks after randomization) was achieved in 221 patients (44%) in the TAS-102 group and 42 patients (16%) in the placebo group (P<0.001).

The addition of TAS-102 to best supportive care, as compared with placebo plus best supportive care, resulted in a significant delay in the worsening of ECOG performance status from

A Overall Progression-free Survival

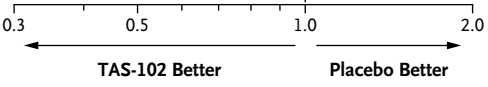


No. at Risk

TAS-102	534	238	121	66	30	18	5	4	2
Placebo	266	51	10	2	2	2	1	1	0

B Progression-free Survival According to Subgroup

Subgroup	No. of Patients	Hazard Ratio (95% CI)
All patients	800	0.48 (0.41–0.57)
KRAS status		
Wild type	393	0.48 (0.38–0.60)
Mutant	407	0.49 (0.39–0.61)
Time since diagnosis of first metastases		
<18 mo	166	0.60 (0.43–0.85)
≥18 mo	634	0.45 (0.38–0.54)
Geographic region		
Japan	266	0.58 (0.44–0.75)
United States, Europe, and Australia	534	0.43 (0.35–0.53)
Sex		
Male	491	0.54 (0.44–0.67)
Female	309	0.40 (0.30–0.53)
Age		
<65 yr	448	0.52 (0.42–0.65)
≥65 yr	352	0.41 (0.32–0.52)
ECOG performance status		
0	448	0.49 (0.40–0.61)
1	352	0.47 (0.37–0.61)
Primary tumor site		
Colon	499	0.50 (0.41–0.62)
Rectum	301	0.45 (0.34–0.59)
Disease refractory to fluoropyrimidine (as part of last prior regimen)	455	0.51 (0.41–0.63)
Prior use of regorafenib		
Yes	144	0.53 (0.36–0.78)
No	656	0.47 (0.39–0.56)
No. of prior regimens		
2	140	0.59 (0.39–0.88)
3	173	0.44 (0.30–0.63)
≥4	487	0.44 (0.36–0.54)
No. of metastatic sites		
1–2	477	0.44 (0.35–0.54)
≥3	323	0.55 (0.43–0.71)



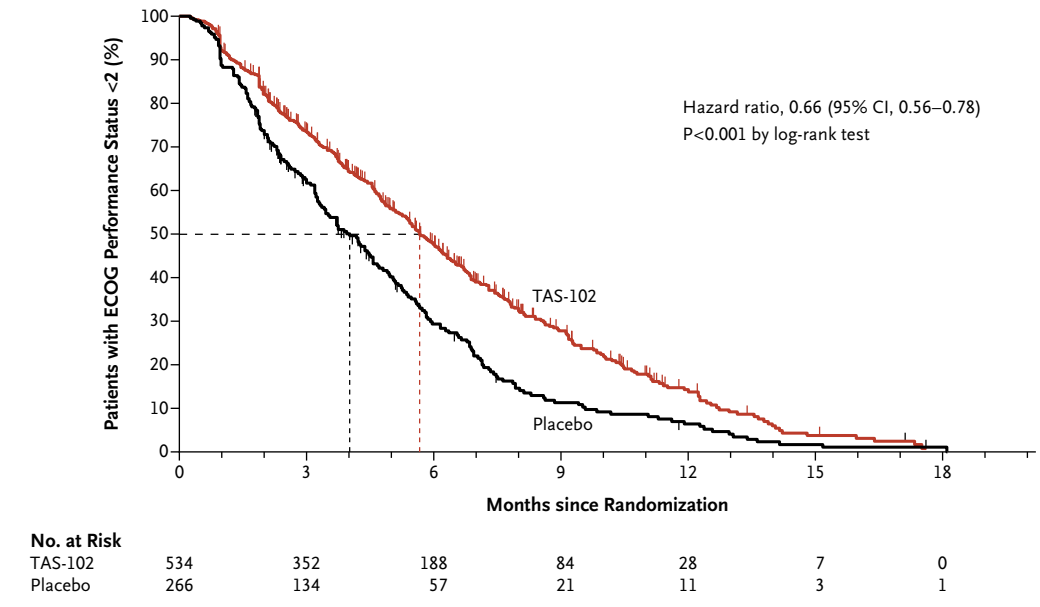


Figure 3. Time to ECOG Performance Status of 2 or Higher.

A total of 383 patients (72%) in the TAS-102 group and 216 (81%) in the placebo group had a worsening of ECOG performance status from 0 or 1 to 2 or higher during the course of the study. The median time to worsening of ECOG performance status to 2 or higher was 5.7 months in the TAS-102 group (vertical red dashed line), and 4.0 months in the placebo group (vertical black dashed line)

the baseline of 0 or 1 to 2 or higher (Fig. 3). The median time to an ECOG performance status of 2 or higher was 5.7 months in the TAS-102 group versus 4.0 months in the placebo group, with a hazard ratio of 0.66 (95% CI, 0.56 to 0.78; P<0.001). The number of patients receiving additional systemic therapy after participation in the trial was balanced between the two groups, with approximately 42% in each group receiving such therapy.

SAFETY AND ADVERSE EVENTS

In an assessment of patients in the TAS-102 group who began at least two cycles of treatment, 53% had a delay of 4 days or more in beginning their next cycle owing to toxicity; the delay in approximately half of this subgroup extended for 8 days or more. In the TAS-102 group, a total of 73 patients (14%) required dose reductions (with 53 patients [10%] having a single dose reduction, 18 [3%] having two reductions, and 2 [<1%] having three reductions). Adverse events resulted in the withdrawal of 4% of the patients receiving TAS-102 and 2% of the patients receiving placebo.

Overall, adverse events of grade 3 or higher occurred more frequently in the TAS-102 group than in the placebo group (in 69% vs. 52% of the patients) (Table 2). Among the 533 patients who received TAS-102, 38% had neutropenia of grade 3 or higher, 4% had febrile neutropenia, and 9% received granulocyte colony-stimulating factor; one treatment-related death resulting from septic shock was reported. The incidence of anemia of grade 3 or higher was greater in the TAS-102 group than in the placebo group (18% vs. 3% of the patients), as was the incidence of thrombocytopenia of grade 3 or higher (5% vs. <1%). Patients in the TAS-102 group were also more likely than those in the placebo group to have nausea of grade 3 or higher (2% vs. 1%), vomiting (2% vs. <1%), and diarrhea (3% vs. <1%). However, no clinically meaningful differences were noted with respect to the development of serious hepatic or renal dysfunction, anorexia, stomatitis, hand–foot syndrome, or cardiac events. Alopecia was reported in 7% of the patients receiving TAS-102 as compared with 1% of those receiving placebo.

Table 2. Frequency of Adverse Events and Laboratory Abnormalities.*

Event	TAS-102 (N=533)		Placebo (N=265)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any event — no. (%)	524 (98)	370 (69)	247 (93)	137 (52)
Any serious event — no. (%)	158 (30)		89 (34)	
Most common events — no. (%)†				
Nausea	258 (48)	10 (2)	63 (24)	3 (1)
Vomiting	148 (28)	11 (2)	38 (14)	1 (<1)
Decreased appetite	208 (39)	19 (4)	78 (29)	13 (5)
Fatigue	188 (35)	21 (4)	62 (23)	15 (6)
Diarrhea	170 (32)	16 (3)	33 (12)	1 (<1)
Abdominal pain	113 (21)	13 (2)	49 (18)	10 (4)
Fever	99 (19)	7 (1)	37 (14)	1 (<1)
Asthenia	97 (18)	18 (3)	30 (11)	8 (3)
Events associated with fluoropyrimidine treatment — no. (%)				
Febrile neutropenia	20 (4)	20 (4)	0	0
Stomatitis	43 (8)	2 (<1)	17 (6)	0
Hand–foot syndrome	12 (2)	0	6 (2)	0
Cardiac ischemia‡	2 (<1)	1 (<1)	1 (<1)	1 (<1)
Laboratory abnormalities — no./total no. (%)§				
Neutropenia	353/528 (67)	200/528 (38)	2/263 (<1)	0
Leukopenia	407/528 (77)	113/528 (21)	12/263 (5)	0
Anemia	404/528 (77)	96/528 (18)	87/263 (33)	8/263 (3)
Thrombocytopenia	223/528 (42)	27/528 (5)	21/263 (8)	1/263 (<1)
Increase in alanine aminotransferase level	126/526 (24)	10/526 (2)	70/263 (27)	10/263 (4)
Increase in aspartate aminotransferase level	155/524 (30)	23/524 (4)	91/262 (35)	16/262 (6)
Increase in total bilirubin	189/526 (36)	45/526 (9)	69/262 (26)	31/262 (12)
Increase alkaline phosphatase level	205/526 (39)	42/526 (8)	118/262 (45)	28/262 (11)
Increase in creatinine level	71/527 (13)	5/527 (<1)	32/263 (12)	2/263 (<1)

* All adverse events were grading according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
† Adverse events of any grade that are listed as most common occurred in 10% or more of patients in the TAS-102 group and in a greater percentage in that group than in the placebo group.
‡ Events included acute myocardial infarction, angina pectoris, and myocardial ischemia.
§ The denominator for the percentage of patients with laboratory abnormalities is the number of patients with at least one postbaseline measurement during treatment.

DISCUSSION

The results of this placebo-controlled, double-blind, phase 3 clinical trial conducted in Japan and in the United States, Europe, and Australia confirmed the results of previous assessments of oral TAS-102 in patients with metastatic colorectal cancer who had already undergone extensive treatment: TAS-102 was associated with a clinically relevant prolongation of overall survival in essentially all treatment subgroups. The superiority of TAS-102 over placebo was also evident in

analyses of the control of clinical disease and the time to disease progression as determined by radiographic assessment (i.e., progression-free survival) and in the assessment of symptoms (i.e., deterioration of performance status). This superiority is particularly meaningful given that more than 90% of the study patients had disease that had been refractory to treatment with fluoropyrimidines when they were last exposed to such drugs and that more than 50% had disease that was refractory to treatment in which a fluoropyrimidine was a component of their most recent treatment regimen; these observations provide clinical support for prior preclinical data[5] that indicated that the mechanism of action of TAS-102 differs from that of fluoropyrimidines. In addition, the clinical benefit associated with TAS-102 was maintained irrespective of prior treatment with regorafenib.

Neutropenia was the most frequently observed clinically meaningful adverse event (grade 3 or 4), occurring in 38% of patients treated with TAS-102. Among the 533 patients who received TAS-102, febrile neutropenia occurred in 4%, and adverse events resulted in one death, which was attributed to septic shock. Grade 3 or 4 stomatitis, hand–foot syndrome, and coronary spasm, which are associated with the use of fluoropyrimidines, were encountered in less than 1% of the patients treated with TAS-102.

Trifluridine, the active component of TAS-102, was developed approximately 50 years ago,[18,19] at about the same time that fluorouracil was introduced. Although early clinical trials showed that trifluridine had antitumor activity,[20] the required dosing schedule had a toxicity profile that was not considered feasible for long-term administration, and further drug development was discontinued. The subsequent availability of the thymidine phosphorylase inhibitor, tipiracil hydrochloride, and its later combination with trifluridine to form TAS-102 approximately 15 years ago allowed for a more constant pharmacokinetic level of the drug to be maintained with an acceptable toxicity profile,[6] a development that led to the preclinical and clinical studies that resulted in this trial.[6]

The assessment of tumor status with regard to *KRAS* showed that 49% of the patients had wild-type tumors and 51% had mutant tumors. Benefit from treatment with TAS-102 was observed in both patient subgroups.Only 15% of tumor specimens were assessed for *BRAF* status — a patient cohort that was not sufficient to determine the extent of the benefit of TAS-102 in these cases.

In summary, TAS-102 was shown to have clinical activity in a large population of Japanese and Western patients with heavily pretreated metastatic colorectal cancer, including those whose disease was refractory to fluorouracil. Such benefit was observed across essentially all prespecified patient subgroups and was validated by means of a multivariate analysis. TAS-102 was associated with few serious adverse events, with neutropenia being the most frequently observed adverse event.

Presented in part at the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer, Barcelona, June 25–28, 2014; and the ESMO Congress, Madrid, September 26–30, 2014.

Supported by Taiho Oncology–Taiho Pharmaceutical.

Dr. Falcone reports receiving lecture fees from Roche, Bayer, Merck Serono, Sanofi, and Amgen, travel support from Roche, Bayer, Merck Serono, and Amgen, and grant support and fees for serving on advisory boards from Roche, Bayer, Merck Serono, Sanofi, Eli Lilly, and Amgen; Dr. Yoshino, receiving lecture fees from Merck Serono, Chugai, and Takeda and grant support from Daiichi-Sankyo, Bayer Yakuhin, Eli Lilly, Pfizer, Yakult, Chugai, and Sumitomo Dainippon; Dr. Mizunuma, receiving lecture fees from Taiho Oncology; Dr. Yamazaki, receiving lecture fees from Taiho Oncology, Chugai, Takeda, Yukult, Merck, Bristol-Myers Squibb, and Bayer; Dr. Shimada, receiving lecture fees from Taiho Oncology, Chugai, Yakult, and Bayer and grant support from Taiho Oncology, Chugai, Yakult, Eli Lilly, and Novartis; Dr. Tabernero, receiving consulting fees from Amgen, Boehringer Ingelheim, Celgene, Chugai, Imclone, Eli Lilly, Merck, Merck Serono, Millennium, Novartis, Roche, Sanofi, and Taiho Oncology; Dr. Komatsu, receiving lecture fees and investigator fees from Pfizer and grant support, investigator fees, and study drugs from Taiho Oncology, Takeda, Chugai, Bayer, Novartis, Eli Lilly, Yakult, Merck Serono, Bristol-Myers Squibb, Sumitomo Dainippon Pharma, GlaxoSmithKline, AstraZeneca, and Daiichi-Sankyo; Dr. Sobrero, receiving fees for serving on advisory boards and participating in satellite symposia from Amgen, Bayer, Merck Serono, Roche, and Sanofi; Dr. Peeters, receiving fees for lectures and for serving on advisory boards from Amgen, Bayer, Merck Serono, Sanofi, and Sirtex; Dr. Makris, receiving consulting fees from Taiho Oncology and fees for statistical consulting from small biotech companies; and Dr. Ohtsu, receiving consulting fees from Eisai, Daiichi-Sankyo, Merck Serono, Chugai, and Novartis. Drs. Benedetti, Mizuguchi, and Ito report being employees of Taiho Oncology and Taiho Pharmaceutical. No other conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the participating patients and their families; the study team, site staff, and operations staff; Toshihiko Doi, M.D., at the National Cancer Hospital East, Japan, for his contribution to the development of the study protocol; and Manuel Aivado, M.D., Ph.D., who was previously an employee of Taiho Oncology, for his contribution to the study.

APPENDIX

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