ORIGINAL ARTICLE

Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer

Robert J. Mayer, M.D., Eric Van Cutsem, M.D., Ph.D., Alfredo Falcone, M.D., Takayuki Yoshino, M.D., Rocio Garcia-Carbonero, M.D., Ph.D., Nobuyuki Mizunuma, M.D., Ph.D., Kentaro Yamazaki, M.D., Yasuhiro Shimada, M.D., Josep Tabernero, M.D., Ph.D., Yoshito Komatsu, M.D., Ph.D., Alberto Sobrero, M.D., Eveline Boucher, M.D., Marc Peeters, M.D., Ph.D., Ben Tran, M.B., B.S., Heinz-Josef Lenz, M.D., Alberto Zaniboni, M.D., Howard Hochster, M.D., James M. Cleary, M.D., Hans Prenen, M.D., Ph.D., Fabio Benedetti, M.D., Hirokazu Mizuguchi, M.S., Lukas Makris, Ph.D., Masanobu Ito, M.S., and Atsushi Ohtsu, M.D., Ph.D., for the RECOURSE Study Group*

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.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Mayer at the Dana–Farber Cancer Institute, 450 Brookline Ave., Boston, MA 02215.

*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.

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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.

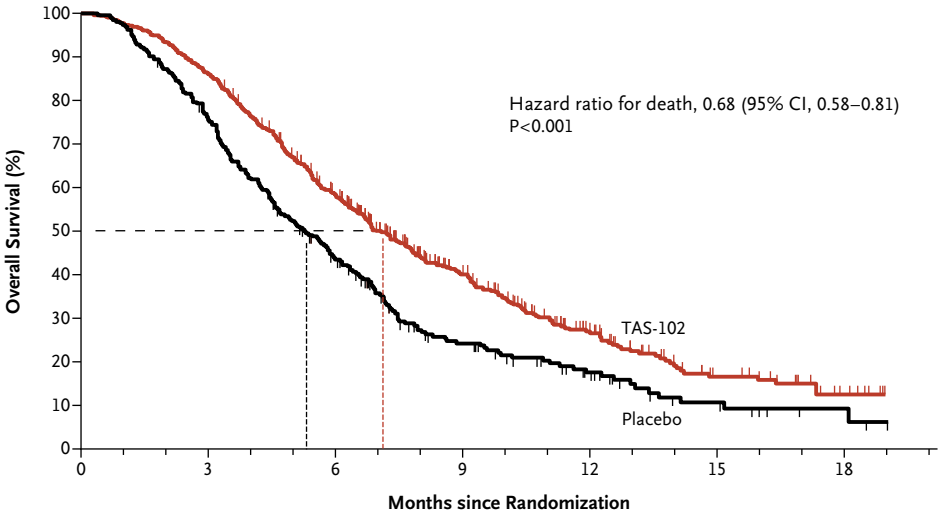
RESULTS

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

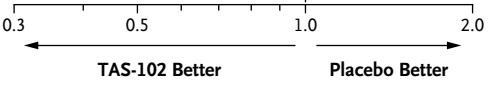


No. at Risk

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.

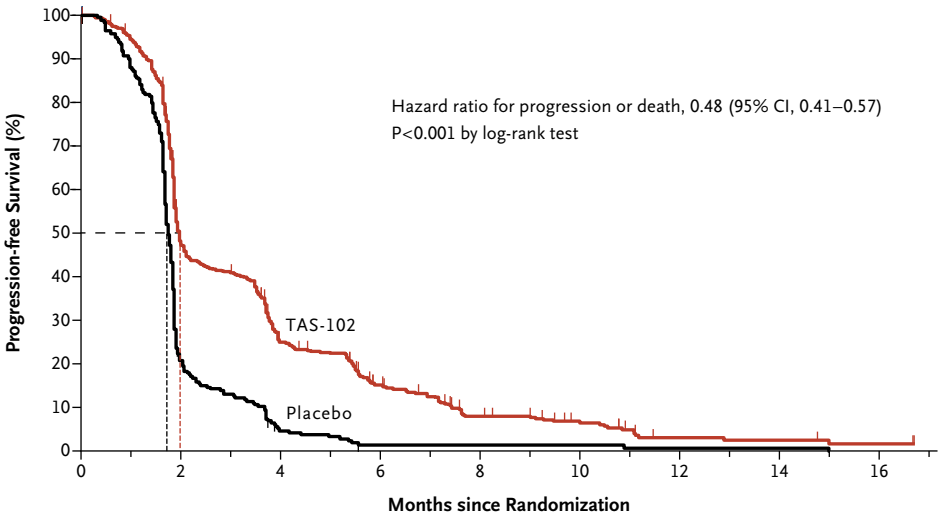
EFFICACY

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

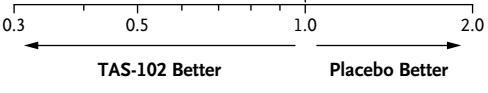


No. at Risk

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)



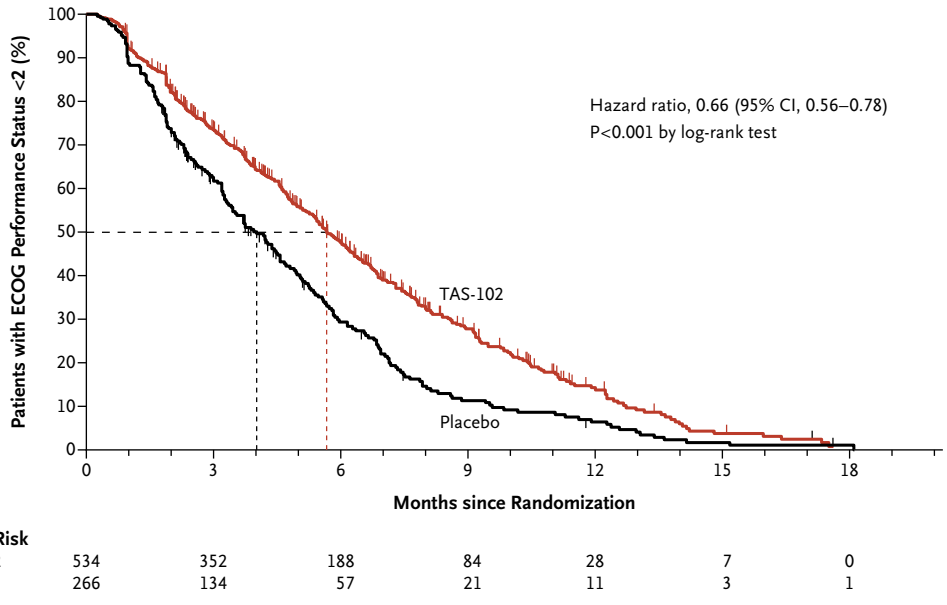


Figure 3. Time to ECOG Performance Status of 2 or Higher.

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.

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APPENDIX

The authors' affiliations are as follows: the Dana–Farber Cancer Institute, Boston (R.J.M, J.M.C.); University Hospitals, Leuven and KU Leuven, Leuven (E.V.C., H.P.), and Universitaire Ziekenhuizen Antwerp, Edegem (M.P.) — all in Belgium; University of Pisa, Pisa (A.F.), IRCCS Azienda Ospedaliera Universitaria San Martino–Istituto Nazionale per la Ricerca Sul Cancro, Genoa (A.S.), and the Fondazione Poliambulanza Istituto Ospedaliero, Brescia (A.Z.) — all in Italy; National Cancer Center Hospital East, Chiba (T.Y., A.O.), Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo (N.M.), Shizuoka Cancer Center, Shizuoka (K.Y.), National Cancer Center Hospital, Tokyo (Y.S.), Hokkaido University Hospital, Hokkaido (Y.K.), and Taiho Pharmaceutical, Tokyo (M.I.) — all in Japan; Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla, Seville (R.G.-C.), and Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona (J.T.) — all in Spain; Centre Eugène Marquis, Rennes, France (E.B.); Royal Melbourne Hospital, Melbourne, VIC, Australia (B.T.); University of Southern California Norris Comprehensive Cancer Center, Los Angeles (H.-J.L.); Yale Cancer Center, New Haven, CT (H.H.); Taiho Oncology, Princeton, NJ (F.B., H.M.); and Stathmi, New Hope, PA (L.M.).

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