O-0010

KRAS and *BRAF* Gene Subgroup Analysis in the Phase 3 RECOURSE Trial of TAS-102 Versus Placebo in Patients With Metastatic Colorectal Cancer

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Introduction

- TAS-102 is an oral combination treatment comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine (FTD), and the thymidine phosphorylase inhibitor, tipiracil hydrochloride (TPI), at a molar ratio of 1:0.5 (weight ratio, 1:0.471) (**Figure 1**).[1,2]
  - FTD is incorporated into DNA, causing DNA dysfunction[2-4]
  - TPI improves the bioavailability of FTD[1,2]
- The mechanism of action (MOA) of TAS-102 is distinct from that of 5-fluorouracil (5-FU), a uracil analogue (**Figure 2**).
  - The primary MOA of 5-FU is believed to be the inhibition of thymidylate synthase (TS), which leads to depletion of deoxythymidine triphosphate and inhibition of DNA replication[5,6]
  - The monophosphate form of FTD also inhibits TS, but this is not believed to be the primary MOA when dosed orally[4]
- In the phase 3 RECOURSE trial in patients with metastatic colorectal cancer (mCRC) refractory to standard therapies, TAS-102 demonstrated a significant improvement compared with placebo in median overall survival (OS) (7.1 vs 5.3 months; hazard ratio [HR]=0.68; *P*<0.0001) and progression-free survival (PFS) (2.0 vs 1.7 months; HR=0.48; *P*<0.0001).[7]
- This analysis was performed to evaluate efficacy and safety in the RECOURSE trial based on *KRAS* and *BRAF* mutation gene status as reported by investigators.

Figure 1. Components of TAS-102

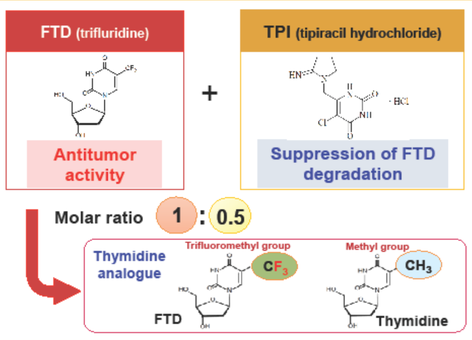
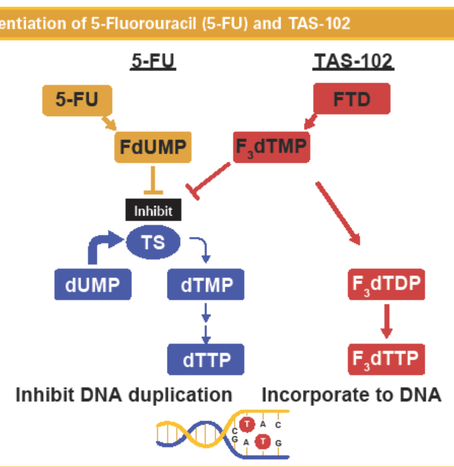


Figure 2. Differentiation of 5-Fluorouracil (5-FU) and TAS-102

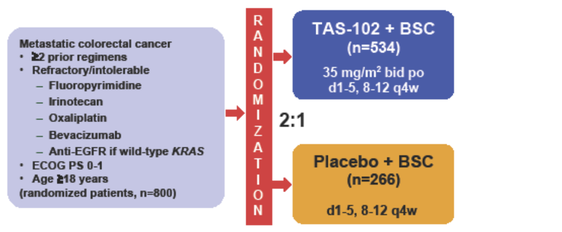


dTMP, deoxythymidine monophosphate; dTTP, deoxythymidine triphosphate; dUMP, deoxyuridine monophosphate; FdUMP, fluorodeoxyuridine monophosphate; FTD, trifluridine; TS, thymidylate synthase.

Methods

- RECOURSE was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial (**Figure 3**).[7]
  - Eligible patients with mCRC had received ≥2 prior lines of therapy, including fluoropyrimidines, irinotecan, oxaliplatin, and bevacizumab, and cetuximab or panitumumab for patients with *KRAS* wild-type tumors
  - The primary endpoint was OS; secondary endpoints included PFS, overall response rate, disease control rate, and safety
  - Median OS and PFS were calculated using the Kaplan-Meier method, with corresponding 2-sided 95% confidence intervals (CIs) for the estimates
- Prespecified analyses of RECOURSE compared efficacy and safety of TAS-102 vs placebo in subgroups of patients who had tumors that were wild type or mutant for *KRAS* and *BRAF*; mutation status was determined according to site practice as reported by investigators.
- The primary endpoint (OS) and key secondary efficacy endpoint (PFS) were evaluated using univariate and multivariate analyses for stratification (eg, status) and prespecified (eg, status) factors.

Figure 3. RECOURSE Study Design



- **Treatment continuation until progression, unacceptable toxicity, or patient refusal**
- **Multicenter, randomized, double-blind, placebo-controlled, phase 3**
  - **Stratification: *KRAS* status, time from diagnosis of metastatic disease, region**
- **Sites: 13 countries, 114 sites**
- **Enrollment: June 2012 to October 2013**

bid, twice daily; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; po, by mouth.

Results

Baseline Characteristics

- Of the 800 RECOURSE patients, 394 (49.3%) had *KRAS* wild-type tumors (63.7% male, mean age 62.0 years); 406 (50.8%) had *KRAS* mutant tumors (59.1% male, mean age 61.1 years) (**Tables 1** and **2**).
  - *KRAS* status is per assignment on the case report form
- Treatment groups were well balanced with respect to *KRAS* status, including *KRAS* mutation types.

Table 1. *KRAS* and *BRAF* Status in RECOURSE

	TAS-102 (n=534)	Placebo (n=266)	Total (N=800)
KRAS status,[a] n (%)			
Wild type	260 (48.7)	134 (50.4)	394 (49.3)
Mutant	274 (51.3)	132 (49.6)	406 (50.8)
KRAS mutation type, n (%)			
Codon 12	201 (37.6)	102 (38.3)	303 (37.9)
Codon 13	55 (10.3)	28 (10.5)	83 (10.4)
Other	6 (1.2)	3 (1.2)	9 (1.2)
Unknown	26 (4.9)	8 (3.0)	34 (4.3)
BRAF status, n (%)			
Wild type	75 (14.0)	41 (15.4)	116 (14.5)
Mutant	4 (0.7)	4 (1.5)	8 (1.0)
Missing	455 (85.2)	221 (83.1)	676 (84.5)

[a]As per assignment on the case report form.

Results (cont'd)

Table 2. Patient Demographics and Baseline Characteristics by *KRAS* Status (ITT Population)

	KRAS Wild Type			*KRAS* Mutant		
	TAS-102 (n=260)	Placebo (n=134)	Total (N=394)	TAS-102 (n=274)	Placebo (n=132)	Total (N=406)
Gender, male, n (%)	168 (64.6)	83 (61.9)	251 (63.7)	158 (57.7)	82 (62.1)	240 (59.1)
Age, y, mean (SD)	62.1 (10.33)	61.6 (9.46)	62.0 (10.03)	60.9 (10.09)	61.4 (11.51)	61.1 (10.56)
Race, n (%)						
Caucasian	139 (53.5)	82 (61.2)	221 (56.1)	167 (60.9)	73 (55.3)	240 (59.1)
Black/African American	2 (0.8)	1 (0.7)	3 (0.8)	2 (0.7)	4 (3.0)	6 (1.5)
Asian	97 (37.3)	43 (32.1)	140 (35.5)	87 (31.8)	51 (38.6)	138 (34.0)
Not collected	22 (8.5)	8 (6.0)	30 (7.6)	18 (6.6)	4 (3.0)	22 (5.4)
ECOG PS, n (%)						
0	149 (57.3)	63 (47.0)	212 (53.8)	152 (55.5)	84 (63.6)	236 (58.1)
1	111 (42.7)	71 (53.0)	182 (46.2)	122 (44.5)	48 (36.4)	170 (41.9)
Time since diagnosis of first metastasis,[a] n (%)						
<18 months	39 (15.0)	18 (13.4)	57 (14.5)	72 (26.3)	37 (28.0)	109 (26.8)
≥18 months	221 (85.0)	116 (86.6)	337 (85.5)	202 (73.7)	95 (72.0)	297 (73.2)
Baseline renal function,[b] n (%)						
Normal (CrCL ≥90 mL/min)	153 (58.8)	73 (54.5)	226 (57.4)	154 (56.2)	72 (54.5)	226 (55.7)
Primary tumor site, n (%)						
Colon	155 (59.6)	80 (59.7)	235 (59.6)	183 (66.8)	81 (61.4)	264 (65.0)
Rectal	105 (40.4)	54 (40.3)	159 (40.4)	91 (33.2)	51 (38.6)	142 (35.0)
Number of prior regimens,[c] n (%)						
1	0	0	0	0	0	0
2	25 (9.6)	8 (6.0)	33 (8.4)	70 (25.5)	37 (28.0)	107 (26.4)
3	50 (19.2)	22 (16.4)	72 (18.3)	69 (25.2)	32 (24.2)	101 (24.9)
≥4	185 (71.2)	104 (77.6)	289 (73.4)	135 (49.3)	63 (47.7)	198 (48.8)
All prior systemic cancer therapeutic agents,[c,d] n (%)						
Bevacizumab	260 (100.0)	133 (99.3)	393 (99.7)	274 (100.0)	132 (100.0)	406 (100.0)
Cetuximab/panitumumab	262 (100.0)	131 (100.0)	393 (100.0)	16 (5.9)	13 (9.6)	29 (7.1)
Cetuximab	186 (71.5)	104 (77.6)	290 (73.6)	15 (5.5)	9 (6.8)	24 (5.9)
Panitumumab	115 (44.2)	52 (38.8)	167 (42.4)	6 (2.2)	4 (3.0)	10 (2.5)
Fluoropyrimidine*	260 (100.0)	134 (100.0)	394 (100.0)	274 (100.0)	132 (100.0)	406 (100.0)
Irinotecan	260 (100.0)	134 (100.0)	394 (100.0)	274 (100.0)	132 (100.0)	406 (100.0)
Oxaliplatin	260 (100.0)	134 (100.0)	394 (100.0)	274 (100.0)	132 (100.0)	406 (100.0)
Regorafenib	40 (15.4)	31 (23.1)	71 (18.0)	51 (18.6)	22 (16.7)	73 (18.0)
Other	228 (87.7)	116 (86.6)	344 (87.3)	243 (88.7)	121 (91.7)	364 (89.7)

CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention to treat.
[a]As randomized.
[b]CrCL based on Cockcroft-Gault using baseline creatinine.
[c]Includes all prior systemic therapies (neoadjuvant, adjuvant, metastatic).
[d]Patients with multiple levels are counted in each applicable category.
*"Fluoropyrimidine" includes 5-FU–containing agents fluorouracil, capecitabine, doxifluridine, S-1, tegafur, and UFT.

Efficacy

- OS favored TAS-102 vs placebo across both *KRAS* subgroups (**Table 3**; **Figure 4**).
  - In the *KRAS* wild-type subgroup, median OS was 8.0 months with TAS-102 vs 5.7 months with placebo (HR=0.58, 95% CI, 0.45-0.74; *P*<0.0001)
  - In the *KRAS* mutant subgroup, median OS was 6.5 months with TAS-102 vs 4.9 months with placebo (HR=0.80, 95% CI, 0.63-1.02; *P*=0.0712)
- In an exploratory analysis of treatment factor interactions using a Cox proportional hazards (CPH) model, *KRAS* status was not predictive of treatment outcome, with an interaction *P*-value=0.4213.
  - *P*-value for interaction with treatment from full model plus the 2-way interaction with just the factor shown (ie, separate models including only 1 factor crossed with treatment)
  - The CPH model included the following factors identified using a stepwise selection process: *KRAS* status, time since diagnosis of first metastasis, region, primary tumor site, Eastern Cooperative Oncology Group performance status, and number of metastatic sites
- Results for PFS also favored TAS-102 across *KRAS* subgroups (**Table 3**; **Figure 5**).
  - In the *KRAS* wild-type subgroup, median PFS was 2.1 months with TAS-102 vs 1.7 months with placebo (HR=0.48, 95% CI, 0.38-0.60; *P*<0.0001)
  - In the *KRAS* mutant subgroup, median PFS was 1.9 months with TAS-102 vs 1.8 months with placebo (HR=0.49, 95% CI, 0.39-0.61; *P*<0.0001)
- Disease control rate (complete response, partial response, or stable disease) was 45.8% with TAS-102 vs 21.4% with placebo in the *KRAS* wild-type subgroup, and 42.2% with TAS-102 vs 11.4% with placebo in the *KRAS* mutant subgroup (**Table 4**).

Table 3. Overall Survival and Progression-Free Survival: Overall RECOURSE Population and by *KRAS* Status

	Overall RECOURSE Population		*KRAS* Wild Type		*KRAS* Mutant	
	TAS-102 (N=534)	Placebo (N=266)	TAS-102 (n=262)	Placebo (n=131)	TAS-102 (n=272)	Placebo (n=135)
Median OS, months (95% CI)	7.1 (6.5-7.8)	5.3 (4.6-6.0)	8.0 (6.9-9.2)	5.7 (4.5-6.6)	6.5 (5.6-7.1)	4.9 (4.2-6.1)
P-value	<0.0001		<0.0001		0.0712	
Median PFS, months (95% CI)	2.0 (1.9-2.1)	1.7 (1.7-1.8)	2.1 (1.9-2.7)	1.7 (1.7-1.9)	1.9 (1.9-2.1)	1.8 (1.7-1.8)
HR (95% CI)	0.68 (0.58-0.81)		0.58 (0.45-0.74)		0.80 (0.63-1.02)	
P-value	<0.0001		<0.0001		0.0712	
Median PFS, months (95% CI)	2.0 (1.9-2.1)	1.7 (1.7-1.8)	2.1 (1.9-2.7)	1.7 (1.7-1.9)	1.9 (1.9-2.1)	1.8 (1.7-1.8)
HR (95% CI)	0.48 (0.41-0.57)		0.48 (0.38-0.60)		0.49 (0.39-0.61)	
P-value	<0.0001		<0.0001		<0.0001	

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Figure 4. Kaplan-Meier Overall Survival by *KRAS* Status

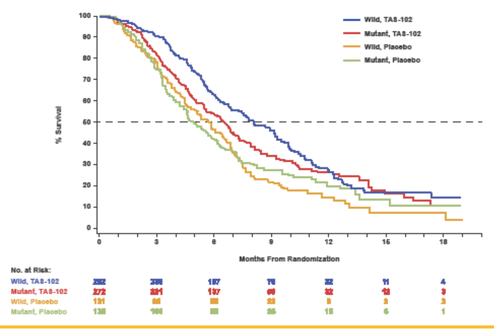


Figure 5. Kaplan-Meier Radiologic Progression-Free Survival by *KRAS* Status

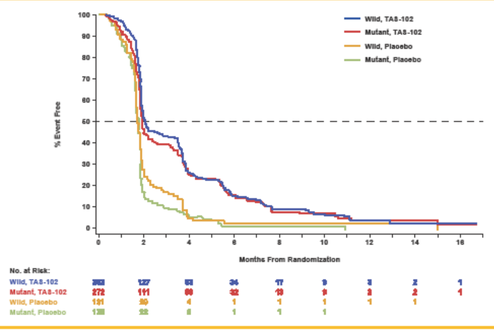


Table 4. Best Overall Response According to *KRAS* Status

	KRAS Wild Type		*KRAS* Mutant	
	TAS-102 (n=253)	Placebo (n=126)	TAS-102 (n=249)	Placebo (n=132)
Best overall response, n (%)				
Complete and partial response	7 (2.8)	1 (0.8)	1 (0.4)	0
Disease control rate*	116 (45.8)	27 (21.4)	105 (42.2)	15 (11.4)

*Disease control rate = complete response + partial response + stable disease.

Safety

- There were no overall differences in incidence of adverse events (AEs), grade ≥3 AEs, or serious AEs for patient subgroups based on *KRAS* status (**Table 5**).
- In the TAS-102 group, patients with *KRAS* mutant vs *KRAS* wild-type tumors had a higher incidence (≥5%) of diarrhea (35.2% vs 28.5%), asthenia (21.6% vs 14.6%), and decreased appetite (43.2% vs 34.6%); patients with *KRAS* wild-type vs *KRAS* mutant tumors had a higher incidence of neutropenia (41.7% vs 34.2%), leukopenia (24.3% vs 18.6%), and thrombocytopenia (7.7% vs 2.6%) (**Table 6**).
  - In the TAS-102 group, there was an increase in hematologic AEs for patients with *KRAS* wild-type vs *KRAS* mutant tumors; the difference was significant for thrombocytopenia and borderline for febrile neutropenia, anemia, and neutropenia based on 95% CIs (**Table 7**)
- Dose intensity was similar for patients with *KRAS* wild-type and mutant tumors (**Table 8**).

Table 5. Adverse Events by *KRAS* Status (As-Treated Population)

	KRAS Wild Type		*KRAS* Mutant	
	TAS-102 (n=260)	Placebo (n=133)	TAS-102 (n=273)	Placebo (n=132)
Any AE, n (%)	258 (99.2)	124 (93.2)	266 (97.4)	123 (93.2)
Grade ≥3 AEs, n (%)	177 (68.1)	69 (51.9)	193 (70.7)	68 (51.5)
Serious AEs, n (%)	84 (32.3)	42 (31.6)	74 (27.1)	47 (35.6)

AEs, adverse events.

Table 6. Adverse Events by *KRAS* Status

	KRAS Wild Type		*KRAS* Mutant	
	TAS-102 (n=260)	Placebo (n=133)	TAS-102 (n=273)	Placebo (n=132)
Most common AEs (≥15% in any TAS-102 group), n (%)				
Nausea	126 (48.5)	31 (23.3)	132 (48.4)	32 (24.2)
Fatigue	91 (35.0)	29 (21.8)	97 (35.5)	33 (25.0)
Decreased appetite	90 (34.6)	41 (30.8)	118 (43.2)	37 (28.0)
Diarrhea	74 (28.5)	19 (14.3)	96 (35.2)	14 (10.6)
Pyrexia	42 (16.2)	21 (15.8)	56 (20.5)	16 (12.1)
Asthenia	38 (14.6)	17 (12.8)	59 (21.6)	13 (9.8)
Laboratory abnormalities,[a] n (%)				
Neutropenia[b]	108 (41.7)	0	92 (34.2)	0
Leukopenia[b]	63 (24.3)	0	50 (18.6)	0
Lymphocytopenia[c]	59 (23.0)	11 (8.5)	53 (20.0)	15 (11.4)
Anemia[b]	55 (21.2)	6 (4.6)	41 (15.2)	2 (1.5)
Thrombocytopenia[b]	20 (7.7)	1 (0.8)	7 (2.6)	0

AEs, adverse events.
[a]Selected grade ≥3 laboratory parameters that worsened from baseline by ≥1 grade at any cycle.
[b]*KRAS* wild type: TAS-102 (n=259), placebo (n=131); *KRAS* mutant: TAS-102 (n=269), placebo (n=132).
[c]*KRAS* wild type: TAS-102 (n=257), placebo (n=130); *KRAS* mutant: TAS-102 (n=265), placebo (n=132).

Table 7. Relative Risk of Selected Adverse Events for *KRAS* Wild Type vs Mutant: TAS-102 Group (As-Treated Population; ≥3% in Either *KRAS* Group)[a]

	KRAS Wild Type (n=260)	*KRAS* Mutant (n=273)	RR Mutant vs Wild Type (95% CI)
Grade ≥3 hematologic events, n (%)			
Clinical findings			
Febrile neutropenia	14 (5.4)	6 (2.2)	0.41 (0.16-1.05)
Laboratory abnormalities			
Anemia	55 (21.2)	41 (15.2)	0.71 (0.49-1.02)
Neutropenia	108 (41.7)	92 (34.2)	0.81 (0.65-1.01)
Thrombocytopenia	20 (7.7)	7 (2.6)	0.33 (0.14-0.78)
Grade ≥3 nonhematologic events, n (%)			
Clinical findings			
Asthenia	6 (2.3)	12 (4.4)	1.90 (0.73-5.00)
Decreased appetite	9 (3.5)	10 (3.7)	1.06 (0.44-2.56)
Diarrhea	7 (2.7)	9 (3.3)	1.22 (0.46-3.24)
Fatigue	10 (3.8)	11 (4.0)	1.05 (0.45-2.43)
Vomiting	8 (3.1)	3 (1.1)	0.36 (0.10-1.33)
Laboratory investigations			
AST increased	10 (3.9)	13 (4.9)	1.24 (0.55-2.77)
Alkaline phosphatase increased	19 (7.3)	23 (8.6)	1.15 (0.64-2.07)
Bilirubin increased	26 (10.1)	19 (7.1)	0.70 (0.39-1.23)
Potassium decreased	10 (3.9)	5 (1.9)	0.48 (0.16-1.37)
Any grade nonhematologic events, n (%)			
Cardiac (arrhythmic)	8 (3.1)	7 (2.6)	0.83 (0.31-2.27)
Thromboembolic events (arterial and venous)	12 (4.6)	9 (3.3)	0.71 (0.31-1.67)

AST, aspartate aminotransferase; RR, relative risk.
[a]*KRAS* status is per assignment on the case report form.

Table 8. Exposure to Study Medication by *KRAS* Status (As-Treated Population)[a]

	KRAS Wild Type		*KRAS* Mutant	
	TAS-102 (n=260)	Placebo (n=133)	TAS-102 (n=273)	Placebo (n=132)
Total dose administered, mg/m², mean (SD)	2355.1 (1744.86)	1565.5 (1120.39)	2152.3 (1601.64)	1448.4 (917.64)
Dose intensity, mg/m²/week,[b] mean (SD)	155.36 (17.629)	165.42 (16.248)	154.76 (21.989)	165.09 (16.844)
Relative dose intensity (ratio to planned), mean (SD)	0.888 (0.1007)	0.945 (0.0928)	0.884 (0.1257)	0.943 (0.0963)

SD, standard deviation.
[a]*KRAS* status is per assignment on the case report form.
[b]*P*=0.7284 (t-test) comparing dose intensity (mg/m²/week) of mutant and wild type.

BRAF Wild Type and Mutant

- *BRAF* status was provided for ~15% of intention-to-treat patients: 116 (14.5%) had *BRAF* wild-type tumors and 8 (1.0%) had *BRAF* mutant tumors (**Tables 1** and **9**).
- The small number of patients with *BRAF* status identified, especially *BRAF* mutant, precludes any meaningful analysis of OS or PFS (**Table 10**).
- The small *BRAF* status sample size makes it difficult to draw any conclusions regarding differences in incidence of AEs (**Table 11**) or clinical laboratory abnormalities.

Table 9. Patient Demographics and Baseline Characteristics by *BRAF* Status (ITT Population)

	BRAF Wild Type			*BRAF* Mutant		
	TAS-102 (n=75)	Placebo (n=41)	Total (N=116)	TAS-102 (n=4)	Placebo (n=4)	Total (N=8)
Gender, male, n (%)	52 (69.3)	26 (63.4)	78 (67.2)	2 (50.0)	2 (50.0)	4 (50.0)
Age, y, mean (SD)	60.7 (11.45)	60.3 (10.60)	60.5 (11.11)	53.8 (17.31)	65.0 (8.76)	59.4 (14.05)
Race, n (%)						
Caucasian	47 (62.7)	28 (68.3)	75 (64.7)	4 (100.0)	4 (100.0)	8 (100.0)
Black/African American	2 (2.7)	0	2 (1.7)	0	0	0
Asian	12 (16.0)	8 (19.5)	20 (17.2)	0	0	0
Not collected	14 (18.7)	5 (12.2)	19 (16.4)	0	0	0
ECOG PS, n (%)						
0	47 (62.7)	23 (56.1)	70 (60.3)	2 (50.0)	2 (50.0)	4 (50.0)
1	28 (37.3)	18 (43.9)	46 (39.7)	2 (50.0)	2 (50.0)	4 (50.0)
KRAS status,[a] n (%)						
Wild type	42 (56.0)	26 (63.4)	68 (58.6)	3 (75.0)	2 (50.0)	5 (62.5)
Mutant	33 (44.0)	15 (36.6)	48 (41.4)	1 (25.0)	2 (50.0)	3 (37.5)
Time since diagnosis of first metastasis,[a] n (%)						
<18 months	21 (28.0)	8 (19.5)	29 (25.0)	1 (25.0)	2 (50.0)	3 (37.5)
≥18 months	54 (72.0)	33 (80.5)	87 (75.0)	3 (75.0)	2 (50.0)	5 (62.5)
Baseline renal function,[b] n (%)						
Normal (CrCL ≥90 mL/min)	49 (65.3)	24 (58.5)	73 (62.9)	3 (75.0)	1 (25.0)	4 (50.0)
Primary tumor site, n (%)						
Colon	42 (56.0)	23 (56.1)	65 (56.0)	0	4 (100.0)	4 (50.0)
Rectal	33 (44.0)	18 (43.9)	51 (44.0)	4 (100.0)	0	4 (50.0)
Number of prior regimens,[c] n (%)						
1	0	0	0	0	0	0
2	15 (20.0)	4 (9.8)	19 (16.4)	0	0	0
3	17 (22.7)	6 (14.6)	23 (19.8)	0	2 (50.0)	2 (25.0)
≥4	43 (57.3)	31 (75.6)	74 (63.8)	4 (100.0)	2 (50.0)	6 (75.0)
All prior systemic cancer therapeutic agents,[c,d] n (%)						
Bevacizumab	75 (100.0)	41 (100.0)	116 (100.0)	4 (100.0)	4 (100.0)	8 (100.0)
Cetuximab	38 (50.7)	24 (58.5)	62 (53.4)	3 (75.0)	1 (25.0)	4 (50.0)
Panitumumab	12 (16.0)	11 (26.8)	23 (19.8)	1 (25.0)	1 (25.0)	2 (25.0)
Fluoropyrimidine*	75 (100.0)	41 (100.0)	116 (100.0)	4 (100.0)	4 (100.0)	8 (100.0)
Irinotecan	75 (100.0)	41 (100.0)	116 (100.0)	4 (100.0)	4 (100.0)	8 (100.0)
Oxaliplatin	75 (100.0)	41 (100.0)	116 (100.0)	4 (100.0)	4 (100.0)	8 (100.0)
Regorafenib	18 (24.0)	13 (31.7)	31 (26.7)	0	1 (25.0)	1 (12.5)
Other	63 (84.0)	34 (82.9)	97 (83.6)	4 (100.0)	4 (100.0)	8 (100.0)

CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention to treat.
[a]As randomized.
[b]CrCL based on Cockcroft-Gault using baseline creatinine.
[c]Includes all prior systemic therapies (neoadjuvant, adjuvant, metastatic).
[d]Patients with multiple levels are counted in each applicable category.
*"Fluoropyrimidine" includes 5-FU–containing agents fluorouracil, capecitabine, doxifluridine, S-1, tegafur, and UFT.

Table 10. OS and PFS by *BRAF* Status

	BRAF Wild Type		*BRAF* Mutant	
	TAS-102 (n=75)	Placebo (n=41)	TAS-102 (n=4)	Placebo (n=4)
Median OS, months (95% CI)	6.1 (5.2-9.7)	5.5 (3.9-7.0)	5.4 (2.2-6.2)	NR (0.8-NR)
HR (95% CI)	0.73 (0.44-1.18)		0.58 (0.03-10.25)	
P-value	0.1963		0.7065	
Median PFS, months (95% CI)	1.9 (1.8-2.1)	1.7 (1.6-1.8)	1.5 (1.0-2.0)	1.7 (0.8-1.9)
HR (95% CI)	0.56 (0.36-0.88)		0.58 (0.03-10.25)	
P-value	0.0110		0.7065	

CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

Table 11. Adverse Events by *BRAF* Status (As-Treated Population)

	BRAF Wild Type		*BRAF* Mutant	
	TAS-102 (n=75)	Placebo (n=40)	TAS-102 (n=4)	Placebo (n=4)
Any AE, n (%)	75 (100.0)	40 (100.0)	4 (100.0)	4 (100.0)
Grade ≥3 AEs, n (%)	50 (66.7)	19 (47.5)	2 (50.0)	2 (50.0)
Serious AEs, n (%)	25 (33.3)	11 (27.5)	1 (25.0)	0

AEs, adverse events.

Conclusions

- In the RECOURSE study, improvements in overall survival (OS) and progression-free survival (PFS) were observed in patients with *KRAS* wild-type and mutant tumors who received TAS-102 vs placebo, with a favorable safety profile.
- While the effect on PFS was the same for *KRAS* wild-type and mutant groups, the OS shows a more pronounced effect on wild-type with a hazard ratio of 0.6 and 0.8, respectively.
- Although similar results were seen for OS and PFS with respect to *BRAF* status, the small patient sample size precludes evaluation.

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