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Phase 3 RECOURSE Trial of TAS-102 Versus Placebo With Best Supportive Care in Patients With Metastatic Colorectal Cancer: European Subgroup

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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, which is different from 5-fluorouracil (5-FU)[2-4]
  - TPI improves the bioavailability of FTD[1,2]
- The mechanism of action (MOA) of TAS-102 is distinct from that of 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]
- The aim of this analysis was to evaluate efficacy and safety in the European subgroup in the RECOURSE trial.

Figure 1. Components of TAS-102

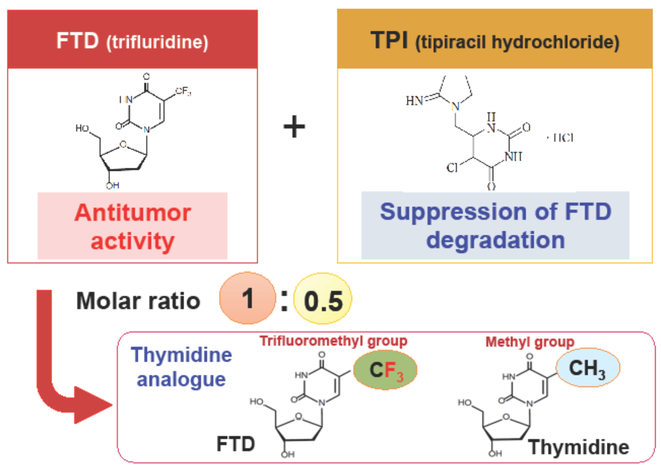
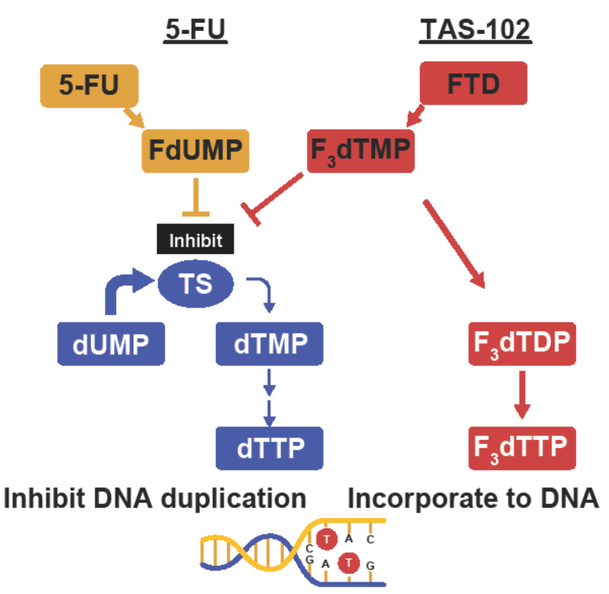


Figure 2. Differentiation of 5-Fluorouracil (5-FU) and TAS-102

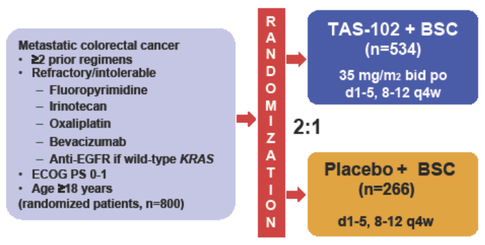


dTMP, deoxythymidine monophosphate; dTTP, deoxythymidine triphosphate; dUMP, deoxyuridine monophosphate; FdUMP, fluorodeoxyuridine monophosphate; FTD, trifluridine; TS, thymidylate synthase.

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 (DCR), and safety
  - Median OS and PFS were calculated using the Kaplan-Meier method, with corresponding 2-sided 95% confidence intervals (CIs) for the estimates
  - Tumors were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1
- A prespecified analysis was performed to compare outcomes and safety according to geographic subregion, although the study was not powered for each of these comparisons.

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

- The European subgroup (n=403) consisted of 271 patients in the TAS-102 arm and 132 patients in the placebo arm (**Table 1**).
  - Both groups had a mean age of 62 years; 62% were male

Table 1. Patient Demographics and Baseline Characteristics: European Subgroup

	TAS-102 (n=271)	Placebo (n=132)	Overall EU (n=403)
Gender, male, n (%)	167 (61.6)	82 (62.1)	249 (61.8)
Age, y, mean (SD)	61.8 (10.0)	62.1 (10.4)	61.9 (10.1)
Race, n (%)			
Caucasian	229 (84.5)	119 (90.2)	348 (86.4)
Black/African American	1 (0.4)	0	1 (0.2)
Asian	1 (0.4)	1 (0.8)	2 (0.5)
Not collected	40 (14.8)	12 (9.1)	52 (12.9)
ECOG PS, n (%)			
0	138 (50.9)	68 (51.5)	206 (51.1)
1	133 (49.1)	64 (48.5)	197 (48.9)
KRAS status,[a] n (%)			
Wild type	123 (45.4)	68 (51.5)	191 (47.4)
Mutant	148 (54.6)	64 (48.5)	212 (52.6)
Time since diagnosis of first metastasis,[a] n (%)			
<18 months	61 (22.5)	24 (18.2)	85 (21.1)
≥18 months	210 (77.5)	108 (81.8)	318 (78.9)
Baseline renal function,[b] n (%)			
Normal (CrCL ≥90 mL/min)	164 (60.5)	72 (54.5)	236 (58.6)
Mild impairment (CrCL 60-89 mL/min)	86 (31.7)	41 (31.1)	127 (31.5)
Moderate impairment (CrCL 30-59 mL/min)	21 (7.7)	16 (12.1)	37 (9.2)
Missing	0	3 (2.3)	3 (0.7)
Baseline eGFR,[c] n (%)			
Normal (eGFR ≥90 mL/min/1.73 m²)	153 (56.5)	72 (54.5)	225 (55.8)
Mild impairment (eGFR 60-89 mL/min/1.73 m²)	92 (33.9)	42 (31.8)	134 (33.3)
Moderate impairment (eGFR 30-59 mL/min/1.73 m²)	18 (6.6)	12 (9.1)	30 (7.4)
Missing	8 (3.0)	6 (4.5)	14 (3.5)
Primary tumor site, n (%)			
Colon	176 (64.9)	81 (61.4)	257 (63.8)
Rectal	95 (35.1)	51 (38.6)	146 (36.2)
Number of prior regimens,[d] n (%)			
1	0	0	0
2	44 (16.2)	18 (13.6)	62 (15.4)
3	56 (20.7)	26 (19.7)	82 (20.3)
≥4	171 (63.1)	88 (66.7)	259 (64.3)
All prior systemic cancer therapeutic agents,[d,e] n (%)			
Bevacizumab	271 (100.0)	131 (99.2)	402 (99.8)
Cetuximab/panitumumab (if *KRAS* wild-type tumors)	131 (48.3)	75 (56.8)	206 (51.1)
Fluoropyrimidine[f]	271 (100.0)	132 (100.0)	403 (100.0)
Irinotecan	271 (100.0)	132 (100.0)	403 (100.0)
Oxaliplatin	271 (100.0)	132 (100.0)	403 (100.0)
Regorafenib	68 (25.1)	41 (31.1)	109 (27.0)
Other	237 (87.5)	114 (86.4)	351 (87.1)

CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; EU, European Union.
[a]As randomized.
[b]CrCL based on Cockroft-Gault using baseline creatinine.
[c]GFR (mL/min/1.73 m²) = 175 × (baseline creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American).
[d]Includes all prior systemic therapies (neoadjuvant, adjuvant, metastatic).
[e]Patients with multiple levels are counted in each applicable category.
[f]"Fluoropyrimidine" includes 5-FU–containing agents fluorouracil, capecitabine, doxifluridine, S-1, tegafur, and UFT.

Efficacy

- Median OS in the European subgroup was 6.8 months in the TAS-102 group vs 4.9 months in the placebo group (HR=0.62; 95% CI, 0.48-0.80; $P=0.0002$) (**Table 2**; **Figures 4A** and **5**).
- Median PFS was 2.0 months in the TAS-102 group vs 1.7 months in the placebo group (HR=0.41; 95% CI, 0.33-0.52; $P<0.0001$) (**Table 2**; **Figures 4B** and **6**).
- DCR (complete response, partial response, or stable disease) was 42.1% with TAS-102 vs 12.5% with placebo (**Table 3**).

Table 2. Overall Survival and Progression-Free Survival for European Subgroup and Overall RECOURSE Population (ITT Population)

	European Subgroup		Overall	
	TAS-102 (n=271)	Placebo (n=132)	TAS-102 (n=534)	Placebo (n=266)
Median OS, months	6.8	4.9	7.1	5.3
HR (95% CI)	0.62 (0.48-0.80)		0.68 (0.58-0.81)	
P-value	0.0002		<0.0001	
Median PFS, months	2.0	1.7	2.0	1.7
HR (95% CI)	0.41 (0.33-0.52)		0.48 (0.41-0.57)	
P-value	<0.0001		<0.0001	

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

Figure 4. Forest Plots for Overall Survival (A) and Progression-Free Survival (B) for European Subgroup

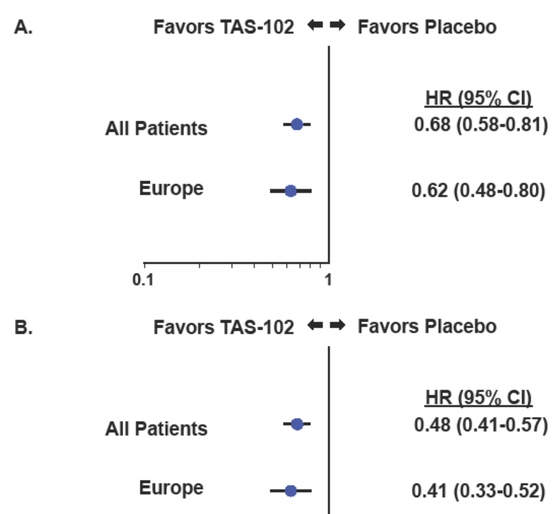


Figure 5. Kaplan-Meier Overall Survival for European Subgroup and Overall RECOURSE Population

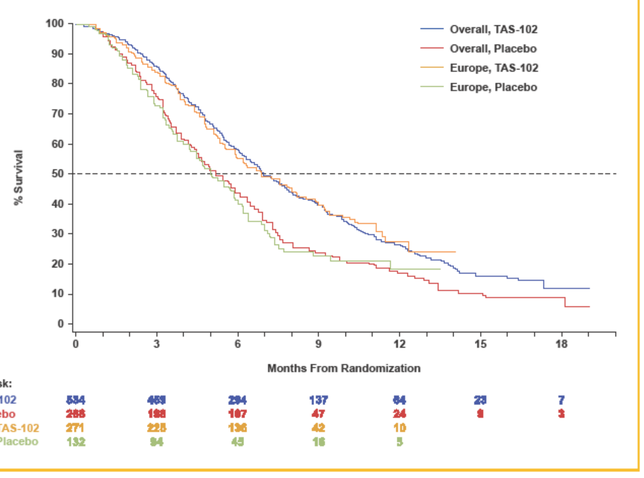


Figure 6. Kaplan-Meier Radiologic Progression-Free Survival for European Subgroup and Overall RECOURSE Population

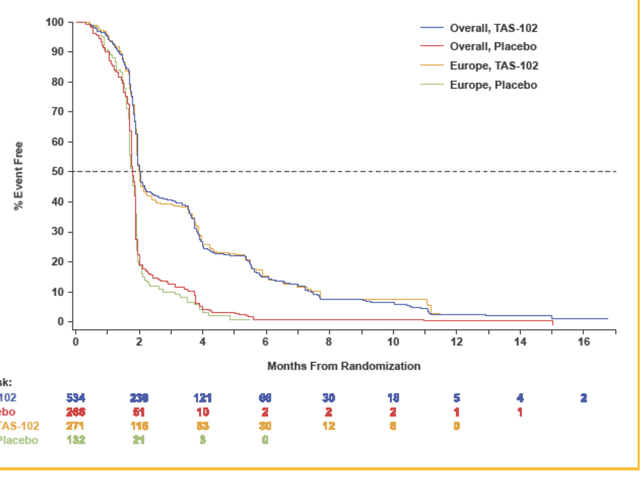


Table 3. Response Rates for European Subgroup

	TAS-102 (n=254)	Placebo (n=128)
Best overall response, n (%)		
Complete or partial response	3 (1.2)	0
Disease control rate[a]	107 (42.1)	16 (12.5)

[a]Disease control rate = complete response + partial response + stable disease.

Safety

- Adverse events (AEs) are shown in **Table 4**.
  - The most common grade ≥3 laboratory abnormality was neutropenia (37.3% in the TAS-102 group vs 0% in placebo)

Table 4. Adverse Events in European Subgroup (As-Treated Population)

	TAS-102 (n=270)	Placebo (n=131)
Any AE, n (%)	266 (98.5)	120 (91.6)
Grade ≥3 AEs, n (%)	191 (70.7)	72 (55.0)
Most common grade ≥3 AEs (≥5% in TAS-102 group)		
Asthenia	18 (6.7)	8 (6.1)
General physical health deterioration	15 (5.6)	9 (6.9)
Laboratory abnormalities,[a] n (%)		
Neutropenia[b]	100 (37.3)	0
Leukopenia[b]	50 (18.7)	0
Lymphocytopenia[c]	41 (15.6)	11 (8.6)
Anemia[b]	39 (14.6)	3 (2.3)
Thrombocytopenia[b]	11 (4.1)	0
Serious AEs	82 (30.4)	42 (32.1)

AE, adverse event.
[a]Selected grade ≥3 laboratory parameters that worsened from baseline by ≥1 grade at any cycle.
[b]TAS-102 (n=268), placebo (n=129).
[c]TAS-102 (n=262), placebo (n=128).

- In the overall RECOURSE study, most common grade ≥3 nonhematologic AEs included fatigue (3.9% vs 5.7%), decreased appetite (3.6% vs 4.9%), and asthenia (3.4% vs 3.0%), and most common grade ≥3 laboratory abnormalities included neutropenia (37.9% vs 0%), leukopenia (21.4% vs 0%), anemia (18.2% vs 3.0%), and thrombocytopenia (5.1% vs 0.4%), in the TAS-102 vs placebo groups, respectively.

Conclusions

- In the RECOURSE study, the clinical and statistically significant improvements in overall survival and progression-free survival observed in the overall population were observed in the European subgroup, with TAS-102 vs placebo.
- No new safety signals were seen in this European subpopulation of patients with metastatic colorectal cancer refractory to standard therapies.

References 1. Emura T et al. *Int J Oncol.* 2005;27(2):449-455. **2.** Temmink OH et al. *Cancer Sci.* 2007;98(6):779-789. **3.** Sakamoto K et al. *Int J Oncol.* 2015;46(6):2327-2334. **4.** Tanaka N et al. *Oncol Rep.* 2014;32(6):2319-2326. **5.** Longley DB et al. *Nat Rev Cancer.* 2003;3(5):330-338. **6.** Wilson PM et al. *Nat Rev Clin Oncol.* 2014;11(5):282-298. **7.** Mayer RJ, Van Cutsem E, et al. *N Engl J Med.* 2015;372(20):1909-1919.

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