



# Clinical outcome of patients with chemorefractory metastatic colorectal cancer treated with trifluridine/tipiracil (TAS-102): a single Italian institution compassionate use programme

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## ABSTRACT

**Background** TAS-102 improves overall survival (OS) in patients with metastatic colorectal cancer (mCRC) refractory to standard treatments. However, predictive biomarkers of efficacy are currently lacking.

**Patients and methods** We treated a cohort of 43 chemorefractory mCRC patients treated with TAS-102, in a single institution expanded access, compassionate use programme. We stratified patients in two groups according to number of cycles received (<6 cycles and ≥6 cycles). OS, progression-free survival (PFS) and safety were evaluated.

**Results** Thirteen out of 43 patients (30%) obtained a clinically relevant disease control with TAS-102 therapy. Eleven of them were treated for ≥6 cycles with TAS-102, reaching a median PFS of 7.5 months (95% CI 5.8 to 9.2 months) and a median OS of 11.2 months (95% CI range not reached yet). A trend towards significance (p=0.08) between a good performance status and response to TAS-102 was observed. Further, 7 out of the 11 TAS-102 long-treated patients achieved a clinical benefit from a previous treatment with regorafenib. A significant correlation between regorafenib and TAS-102 clinical efficacy was observed (p=0.008). Six out of 13 regorafenib-naïve patients were treated with regorafenib after progression from TAS-102. All these patients achieved SD with a median duration of treatment with regorafenib of 6.1 months (range, 1.6–6.7).

**Conclusion** Patients with mCRC in good clinical conditions, even though having been heavily pretreated with all the available treatment options, could obtain a significant clinical benefit from treatment with TAS-102. Moreover, a previous clinical benefit obtained with regorafenib is potentially predictive of clinical efficacy of subsequent TAS-102 treatment.

## INTRODUCTION

Colorectal cancer (CRC) is one of the leading tumours worldwide and remains a big killer despite the improvements in terms of efficacy

## Key questions

### What is already known about this subject?

TAS-102 improves overall survival (OS) in patients with metastatic colorectal cancer (mCRC) refractory to standard treatments. However, considering the toxicity profiles and the lack of predictive biomarkers of response, the identification of which patients may derive a major benefit from TAS-102, remains an unmet clinical need.

### What does this study add?

We observed that some patients derived a long-term efficacy from TAS-102 treatment. In particular, a trend toward significance (p=0.08) between a good performance status and response to TAS-102 was observed as well as a previous response to regorafenib and TAS-102 clinical efficacy (p = 0.008). Furthermore, we also noticed that a cohort of patients treated with regorafenib after progression from TAS-102 were able to achieve a clinical benefit from regorafenib treatment.

### How might this impact on clinical practice?

Our analysis supports the concept that mCRC patients in good clinical conditions, even though heavily pretreated, could obtain a significant clinical benefit with TAS-102. A previous clinical benefit obtained with regorafenib has been found to be potentially predictive of clinical efficacy of subsequent TAS-102 treatment. Moreover, previous treatment with TAS-102 does not preclude the use of regorafenib as further line of treatment.

of systemic treatments during the recent years.<sup>1</sup>

TAS-102 is an oral combination of trifluridine (FTD), an antineoplastic thymidine-based nucleoside analogue, and of the thymidine phosphorylase inhibitor,

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**Table 1** Patient characteristics

Patient characteristics	TAS-102 n=43	
Age (years)	65 (range: 48–82)	%
Gender		
Male	31	72
Female	12	28
Race		
Caucasian	43	100
ECOG performance status		
0	27	63
1	14	32
2	2	5
Primary site of disease		
Right colon	11	26
Left colon	15	35
Rectum	17	39
RAS mutation		
Yes	27	63
No	16	37
Histology		
Adenocarcinoma	43	100
Number of previous systemic anticancer therapies (from diagnosis of metastatic disease)		
1	1	2
2	4	9
3	17	40
4	15	35
≥5	6	14
Number of metastatic sites		
1	5	12
2	19	44
≥3	19	44
Time from diagnosis of metastatic disease		
Median (months)		
<18 months	2	5
>18 months	41	95
Previous treatment with regorafenib		
Yes	30	70
No	13	30

ECOG, Eastern Cooperative Oncology Group.

tipiracil hydrochloride, which is necessary for inhibiting the degradation of FTD by thymidine phosphorylase.<sup>2</sup> TAS-102 was first approved in Japan, based on results of a randomised phase II trial, in patients with metastatic colorectal cancer (mCRC) refractory to all standard therapies.<sup>3</sup> Subsequently, there was worldwide approval of

TAS-102 based on the results of the RECURSE trial, a large-scale global randomised phase III trial that evaluated the efficacy and safety of TAS-102 versus placebo in patients with mCRC refractory to all standard chemotherapies, including anti-angiogenic drugs and, when appropriate (RAS wild-type patients), anti-EGFR monoclonal antibodies (either cetuximab or panitumumab). The RECURSE study demonstrated a significant improvement in overall survival (OS), the primary end-point, from 5.3 months with placebo to 7.1 months with TAS-102 with an HR of 0.68 ( $p < 0.0001$ ). The study also reported a benefit in progression-free survival (PFS) from 1.7 months to 2.0 months in the TAS-102 arm with an HR of 0.48 ( $p < 0.001$ ).<sup>4</sup> The reported toxicities were mainly haematological, consisting in neutropenia, leucopenia, anaemia and thrombocytopenia, while the most frequent non-haematological toxicities were fatigue and diarrhoea.<sup>3–5</sup>

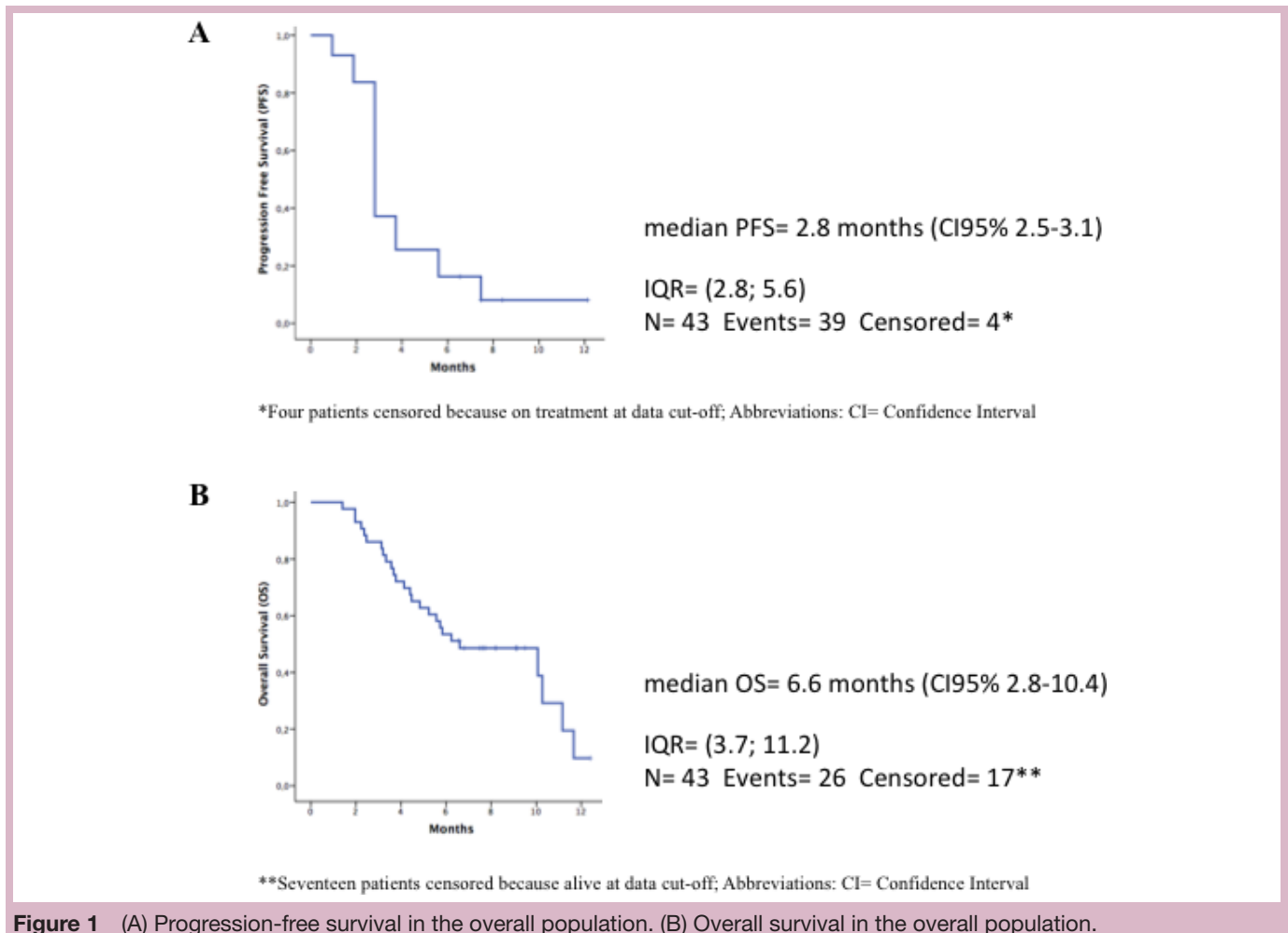
TAS-102 and the multitargeted tyrosine kinase inhibitor regorafenib represent the last approved drugs for the overgrowing population of patients with chemorefractory mCRC that still maintain a good clinical condition after failure of the two initial lines of treatment.<sup>6,7</sup> Unfortunately, we are currently lacking predictive biomarkers for efficacy for both drugs, and we do not know which is the best choice between the two therapeutic options or the best sequential treatment in this patient setting.

Here we report the efficacy and the safety results for a consecutive cohort of 43 chemorefractory, heavily pretreated mCRC patients who were treated with TAS-102 in an expanded access, compassionate use programme in our institution, with the aim to identify potential clinical predictors of TAS-102 activity.

## PATIENTS AND METHODS

### Patients

This expanded access, compassionate use programme was performed according to the Declaration of Helsinki. Institutional ethic committee approval was obtained as well as a written consent from each patient before receiving the first dose of TAS-102. This was a single-institution analysis of patients with mCRC who were treated with TAS-102 after failure of all standard therapies, including fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF therapies and anti-EGFR agents if RAS wild-type. The study population consisted of a consecutive cohort of 43 patients, older than 18 years with histologically confirmed adenocarcinoma of the colon or rectum, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. Data were collected from patients who received at least one TAS-102 dose according to the standard and registered schedule of 35 mg/m<sup>2</sup> twice daily, 5 days a week, for 2 weeks, followed by a 14-day rest period. Severity of adverse events (AEs) was graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4. We performed a weekly clinical visit during the first month with a physical and biochemistry assessment. The observational period of treatment with



TAS-102 comprised February 2016 to February 2017. Data cut-off was 28 February 2017. We stratified patients in two groups according to number of cycles received (<6 cycles and  $\geq 6$  cycles) and evaluated for each group OS, PFS and safety. Tumour response was evaluated every 8 weeks and assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1).

### Statistical analysis

We used the Kaplan-Meier method to estimate median PFS time. p Values were calculated using log-rank tests at a significance level of 5%. Differences between categorical data within subgroups were measured using parametrical tests,  $\chi^2$  and Fisher exact test, when adequate. All statistical analyses were performed using IBM-SPSS statistics V 22.0.

### RESULTS

Baseline demographic and clinical and pathological characteristics are listed in [table 1](#). In this respect, 41 out of 43 patients (95%) had a history of metastatic disease longer than 18 months and in 38 patients (88%), the number of metastatic sites were  $\geq 2$ . Thirty-eight out of 43 patients (89%) received  $\geq 3$  therapies for treatment of metastatic disease before TAS-102 and, of note, six patients (14%)

received  $\geq 5$  lines of therapies. In 30 out of 43 patients (70%), the last treatment before TAS-102 therapy consisted of regorafenib. The PS according to ECOG scale was 0 in 27 patients (63%) ([table 1](#)).

In the overall population, the median duration of treatment was 2.8 months (range 1–12.1 months). The median PFS was 2.8 months (95% CI 2.5 to 3.1 months) and the median OS was 6.6 months (95% CI 2.8 to 10.4 months) ([figure 1A,B](#)). Thirty-two out of 43 patients (74%) received <6 cycles of treatment with TAS-102, whereas 11 out of 43 patients (26%) were treated for  $\geq 6$  cycles, with four patients (9%) being still on treatment at the time of data cut-off (28 February 2017). To date, the longest-treated patient reached 12 cycles of treatment with TAS-102 and was still on treatment at the data cut-off time ([table 2](#)).

Among patients treated for  $\geq 6$  cycles, the median duration of treatment was 7.5 months (range 5.6–12.1 months), the median PFS was 7.5 months (95% CI 5.8 to 9.2 months) and the median OS was 11.2 months (95% CI range not reached yet).

Regarding response to treatment, 13 out of 43 patients (30%) achieved a clinical response with TAS-102 therapy ([figure 2](#)). In particular, two patients (5%) obtained a partial response (PR) and 11 patients (26%) a stable disease

**Table 2** Correlation between clinical characteristics and duration of treatment

Patient characteristics	Patients treated <6 cycles n=32	Patients treated ≥6 cycles n=11	p Value
<b>Median age (years)</b>	<b>65</b>	<b>63</b>	<b>0.65</b>
<b>Gender</b>			
Male	23	8	0.83
Female	9	3	
<b>Race</b>			
Caucasian	32	11	1
<b>ECOG performance status</b>			
0	17	10	0.08
1	13	1	
2	2	0	
<b>Primary site of disease</b>			
Right colon	6	5	0.43
Left colon/rectum	26	6	
<b>RAS mutation</b>			
Yes	20	7	0.94
No	12	4	
<b>Histology</b>			
Adenocarcinoma	32	11	-
<b>Number of previous systemic anticancer therapies (from the diagnosis of metastatic disease)</b>			
1	0	1	0.30
2	4	0	
3	12	5	
4	12	3	
≥5	4	2	
<b>Number of metastatic sites</b>			
1	3	2	0.68
2	14	5	
3	15	4	
<b>Time from diagnosis of metastatic disease</b>			
<b>Median (months)</b>			
<18 months	2	0	0.40
>18 months	30	11	
<b>Pretreatment with regorafenib</b>			
Yes	22	8	0.80
No	10	3	
<b>Best response with regorafenib</b>			
SD/PR	5	7	0.008
No response	17	2	

ECOG, Eastern Cooperative Oncology Group; PR, partial response; SD, stable disease.

(SD). Eleven out of 13 patients achieving a response have been treated for ≥6 cycles of TAS-102, whereas two patients achieved an SD maintained for five cycles and then experienced a clinical progression of disease.

Thirty out of 43 patients (70%) received a previous treatment with regorafenib, with PR or SD in 11 cases. Comparing treatment outcomes for regorafenib and/or TAS-102 therapies, we found that seven patients achieved

a clinical benefit (PR or SD) with both drugs (figure 2). The regorafenib pretreated patients reached a median PFS of 2.8 months (95% CI 2.3 to 3.2 months) and a median OS of 5.8 months (95% CI 2.1 to 9.6 months) by treatment with TAS-102. On the other hand, the 13 regorafenib-naïve patients (30%) achieved a median PFS of 2.8 months and a median OS of 10.3 months following TAS-102 therapy. Four out of 13 (31%) regorafenib-naïve patients achieved a clinical benefit from TAS-102 treatment with 3 SD and 1 PR. Of note, at data cut-off time, six regorafenib-naïve patients were treated with regorafenib after progression from TAS-102. In these six patients, the median duration of treatment with regorafenib was 6.1 months (range 1.6–6.7) with stable disease as best response, which was observed in all of them. Of the two patients with PR following TAS-102 treatment, one was not pretreated with regorafenib, while the other achieved an SD that lasted for 12 cycles with regorafenib therapy. This latter patient was still on treatment with TAS-102 (12 cycles ongoing) at the time of data cut-off.

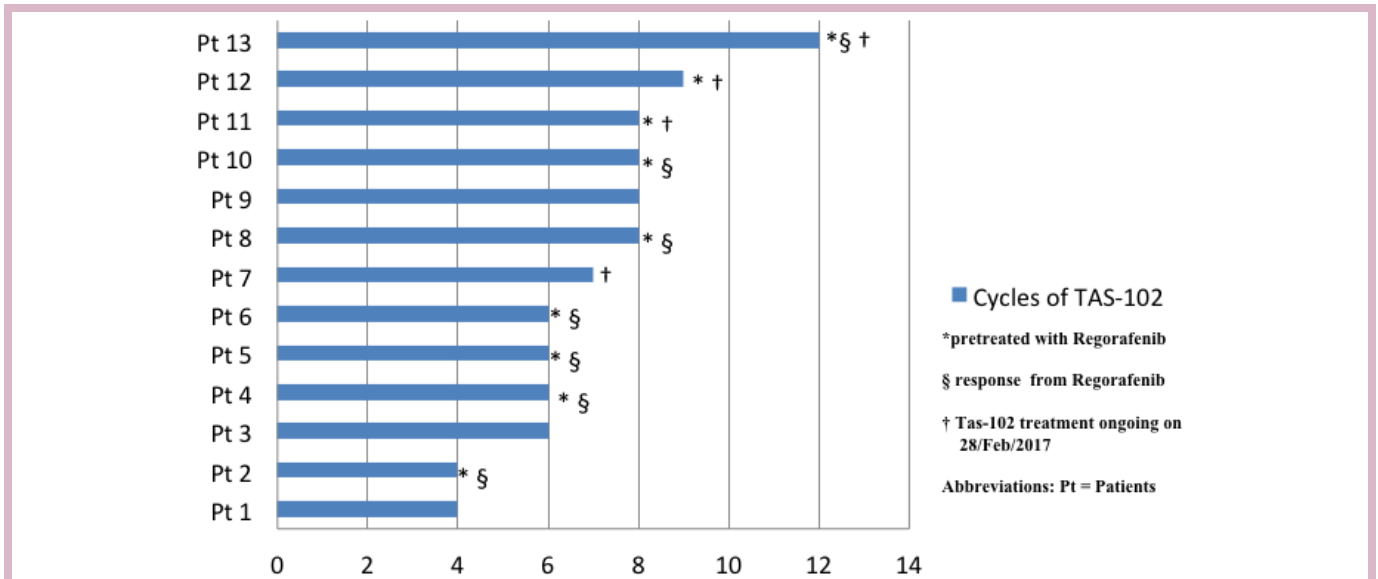
The observed adverse events (AEs) during TAS-102 treatment were mostly haematological toxicities, occurring principally from days 15 to 21 during the first cycle of treatment. In particular, 35% of patients had neutropenia of grade 3 or 4, with only 7% experiencing febrile neutropenia, while anaemia of grade 3 or 4 was observed in 19% of patients treated with TAS-102. The non-haematological AEs registered were fatigue of grade 3 and 4 in 5% of patients and nausea of any grade in 14% of patients (table 3).

Eleven out of 43 patients (26%) required a dose modification due to AEs. In particular, six patients (14%) required one dose level reduction (to 30 mg/m<sup>2</sup>) during the first five cycles of treatment, mainly for haematological AEs, such as neutropenia or febrile neutropenia; one patient required a similar dose reduction for fatigue. Four patients reduced the dose starting from the sixth cycle for neutropenia, whereas only one patient required a two dose levels reduction (to 25 mg/m<sup>2</sup>) for recurrent febrile neutropenia (table 4).

Finally, the reasons of TAS-102 treatment discontinuation were radiological progression of disease in 35 out of 43 patients (82%), worsening of clinical conditions in 4 patients (9%), while 4 patients were still on treatment at the time of data cut-off.

## DISCUSSION

Medical treatment of mCRC has been greatly improved during the last two decades resulting in significantly better patient outcome. However, after failure of the first two lines of therapy, standard treatment options are few. Although widely common in clinical practice, re-challenge therapy with previously used drugs is not supported by prospective and randomised clinical studies.<sup>8</sup> To date, only TAS-102 and regorafenib have demonstrated in two randomised phase III trials, RECOURSE and CORRECT, respectively, a significant improvement in OS in patients with mCRC who have previously received all the available treatments. Both drugs demonstrated a consistent and



**Figure 2** Outcome of TAS-102 responder patients with regorafenib.

similar benefit over placebo, leading to their approval in third-line treatment of patients with chemorefractory mCRC.<sup>4,7</sup> However, considering the toxicity profiles and the lack of predictive biomarkers of response, the identification of which patients may derive a major benefit from TAS-102 or regorafenib therapy and which is the best sequence of treatment remain an unmet clinical need. As reported in a retrospective analysis of a series of patients treated with regorafenib and TAS-102, the different pattern of toxicities of the two drugs could represent a useful driver that could guide physicians choice between the two agents.<sup>9</sup> Hamauchi and colleagues found a significant correlation between high-grade neutropenia (G3-G4 according to Common Terminology Criteria for Adverse Events 4.3) during the first cycle of treatment, with better clinical efficacy of TAS-102 and hypothesised whether the absence of neutropenia could indicate an insufficient dose of drug.<sup>10</sup> Promising results have also been published by Suenaga and colleagues about the

Adverse event		Any grade	Grade ≥3
Haematological	Neutropenia	21 (49%)	15 (35%)
	Anaemia	20 (46%)	8 (19%)
	Trombocytopenia	16 (37%)	3 (7%)
	Febrile neutropenia	—	3 (7%)
Non-haematological	Fatigue	7 (16%)	2 (5%)
	Nausea	6 (14%)	—
	Vomiting	—	—
	Diarrhoea	1	—

Grade of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4

predictive and prognostic role of genetic variants of DNA repair-related genes for the efficacy of TAS-102.<sup>11</sup>

In the present analysis, we have evaluated a consecutive cohort of 43 patients with chemorefractory mCRC treated with TAS-102. Here we have reported a median PFS of 2.8 months with a median OS of 6.6 months, which are in agreement with the 2.0 months of PFS and the 7.1 months of OS reported in the phase III RECURSE trial. The safety profile of TAS-102 was also concordant with previous reports. In particular, we did not find unexpected AEs and the reported toxicities were mainly haematological, occurring principally from days 15 to 21 of the first cycle.<sup>5</sup>

The patient population that we report in the current study was heavily pretreated (89% of patients received ≥3

Number of cycles	<6 n=32	≥6 n=11	Total 43
Number of patients with reduced dose	6	5	11 (26%)
Patients requiring one dose level reduction: 30 mg/m <sup>2</sup>	6	4	10 (23%)
Toxicities:	Neutropenia G4 (three patients)	Neutropenia G4 (four patients)	
	Febrile neutropenia (two patients)	Fatigue G3 (one patient)	
Patients requiring two dose levels reduction: 25 mg/m <sup>2</sup>	0	1	1 (2%)
Toxicities:	-	Febrile neutropenia (one patient)	

treatments for metastatic disease before TAS-102) with more than two metastatic sites, and had a long course of metastatic disease (95% of patients had a history of metastatic disease longer than 18 months). Thirteen patients out of 43 patients (30%) obtained a clinically relevant disease control with TAS-102 therapy, with 7 of these 13 patients (54%) having achieved a clinical benefit from the previous line of treatment with regorafenib. Four patients, who obtained a clinical benefit with regorafenib, did not respond to TAS-102 therapy. Taken together, these data support the observation that previous treatment with regorafenib does not preclude a clinical response to TAS-102. Furthermore, the results of the present study suggest that a previous clinical benefit obtained with regorafenib could be more likely associated with clinical efficacy of subsequent TAS-102 treatment ( $p=0.008$ ) (table 2). Interestingly, at the data cut-off time, 6 out of the 13 regorafenib-naïve patients after progression from TAS-102 could be subsequently treated with regorafenib. Therefore, also previous treatment with TAS-102 does not preclude the use of regorafenib as further line of treatment in this heavily pretreated population of patients with chemorefractory mCRC.

Finally, as recently reported in a study from our Institution on a consecutive series of 123 patients with chemorefractory mCRC treated with regorafenib, a good ECOG PS and a long history of metastatic disease were significantly associated with better clinical outcome from regorafenib.<sup>12</sup> The current analysis seems to confirm a trend between the good ECOG PS and response to TAS-102 ( $p=0.08$ ), supporting the concept that patients with mCRC in good clinical conditions, even though heavily pretreated with all available treatment options for first and second line, could obtain a significant clinical benefit with TAS-102.

## CONCLUSION

Patients with chemorefractory mCRC in good clinical conditions, even though having been heavily pretreated with all the available treatment options, could obtain a significant clinical benefit from treatment with TAS-102. Moreover, a previous clinical benefit obtained with regorafenib is potentially predictive of clinical efficacy of subsequent TAS-102 treatment.

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