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Impact of trifluridine/tipiracil plus bevacizumab on tumor shrinkage and depth of response in refractory metastatic colorectal cancer: analysis of the SUNLIGHT trial

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ABSTRACT

Objectives: This *post hoc* analysis of the SUNLIGHT trial sought to assess the response to treatment with trifluridine/tipiracil (FTD/TPI) + bevacizumab and FTD/TPI in patients with refractory metastatic colorectal cancer using tumor shrinkage (TS), early TS (ETS), duration of TS (DTS) and depth of response (DpR) as response-related parameters.
Methods: TS was defined as any decrease from baseline of the sum of the longest diameter of target lesions. TS at first assessment was specified as ETS. DpR was defined as the maximum percentage change from baseline of the sum of the longest diameters of target lesions. DTS was defined as the time from first TS to first increase in tumor size, progressive disease, or death.
Results: In the FTD/TPI + bevacizumab group, 48 % had TS and 39 % had ETS. In the FTD/TPI group, 21 % had TS and 17 % had ETS. In patients achieving ETS, median DTS was prolonged with FTD/TPI + bevacizumab compared to FTD/TPI (3.8 versus 2.1 months; HR: 0.34 [95 % CI: 0.22, 0.53]; $P < 0.0001$). Magnitude of DpR was greater with FTD/TPI + bevacizumab than with FTD/TPI.
Conclusion: The survival benefit of treatment with FTD/TPI + bevacizumab versus FTD/TPI is likely associated with the improvement of ETS and DpR.

1. Introduction

The phase 3 SUNLIGHT trial demonstrated the benefit of treatment with trifluridine/tipiracil (FTD/TPI) + bevacizumab on overall survival (OS) and progression-free survival (PFS) compared to FTD/TPI in patients with metastatic colorectal cancer (mCRC) who had received no more than two lines of treatment and had progressed, or were intolerant to, their last line of treatment [1]. SUNLIGHT predominately recruited

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patients that had progressed after two previous lines of treatment (>90 %) [1]. Objective response rate (ORR) according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 [2] favored the FTD/TPI + bevacizumab arm (6.1 % and 1.2 % of patients in the FTD/TPI + bevacizumab and FTD/TPI treatment groups, respectively), which is a relatively modest improvement [1].

RECIST classifies partial response (PR) as tumor shrinkage (TS) of ≥ 30 % and progressive disease (PD) as tumor growth of ≥ 20 %, while any tumor growth or shrinkage between these two values is classified as stable disease (SD) [2]. In addition, RECIST does not consider timing, depth or duration of response. Thus, the population in SUNLIGHT with SD following treatment is heterogeneous, and includes patients with TS and patients with tumor growth outside of RECIST classifications of PD and PR [3].

It has been suggested that tumor evaluation using RECIST may not capture the full spectrum of response to treatment [4], and there is a need to explore different parameters to assess response to treatment in mCRC clinical trials, with a focus on dynamic changes of the target lesion. This is particularly relevant in the third line setting, in which ORR remains low and thus RECIST may be more equivocal than in earlier lines of treatment. Response-related parameters, such as early tumor shrinkage (ETS), duration of TS (DTS) and depth of response (DpR), have been shown to correlate with OS across a number of solid tumors, including mCRC [5–9].

Thus, the aim of this *post hoc* analysis of the SUNLIGHT trial was to assess response to treatment with FTD/TPI + bevacizumab and FTD/TPI using ETS, DTS and DpR and the association of these parameters with OS, PFS and global health status (GHS) from QLQ-C30 (Quality of Life Questionnaire Core 30, from European Organisation for Research and Treatment of Cancer).

2. Methods

2.1. Trial design and population

The design of the SUNLIGHT (NCT04737187) trial has been described previously [1,10]. Briefly, this study included patients aged ≥ 18 years old with histologically confirmed unresectable adenocarcinoma of the colon or rectum and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤ 1. The inclusion criteria for SUNLIGHT stated that patients must have progressed on their previous line of treatment and received no more than two previous chemotherapy regimens (including a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and an anti-EGFR monoclonal antibody for *RAS* wild-type patients) and had progressed, or were intolerant to, their last line of treatment.

Patients were randomly assigned to receive FTD/TPI (35 mg/m^2 twice a day on days 1–5 and 8–12 every 28-day cycle) or FTD/TPI in combination with bevacizumab (5 mg/kg on days 1 and 15).

2.2. Assessments

Tumor evaluations were conducted according to RECIST version 1.1 and involved clinical examination of image-based assessments of the chest, abdomen, and pelvis at a minimum (other localizations could be included if clinically indicated) [2]. Tumor assessments were performed at baseline and every 2 cycles (8 weeks) until radiologic disease progression. After progression, follow-up OS assessments continued every 8 weeks, until death or end of study. At baseline, images obtained before receiving a patient's written informed consent could be used if the date of the images was within 28 days of randomization, and if they were in line with the methods and techniques used for tumor evaluation in this study.

For the QLQ-C30 analyses, patients that completed at least one questionnaire at baseline and during the study period were analyzed in their respective treatment groups. Baseline values, post-baseline values and changes from baseline in the GHS were collected at the beginning of each cycle of 28 days and at withdrawal visit. The QLQ-C30 consists of 30 questions and 15 scales including GHS quality of life (QoL) scale [11].

2.3. Endpoints

In this *post hoc* analysis, TS was defined as any decrease from baseline of the sum of the longest diameters of the target lesions. ETS was specified as TS occurring at the first tumor assessment (cycle 2 or before 8 weeks). DpR was defined as the maximum percentage change from baseline of the sum of the longest diameters of target lesions. DTS was defined as the time from first documented TS to the first documented increase in tumor size (from nadir), PD (clinical or radiological) or death, whichever came first.

2.4. Statistics

All analyses were performed in the tumor evaluable population (TUMEV), defined as all patients with measurable disease that had at least one evaluable baseline and post-baseline tumor assessment. Time to event endpoints were analyzed using Kaplan-Meier methodology and compared between treatment groups with a 2-sided log-rank test. Differences in TS/ETS rates and DpR between treatment groups were made using Fisher's exact test (two-sided) and two-sided Wilcoxon test, respectively.

A multivariate Cox proportional hazard regression analysis was performed to assess the relationship between ETS and OS/PFS. This analysis was adjusted for known prognostic factors (ECOG PS, location of primary disease, prior surgical resection, number of metastatic sites, neutrophil-to-lymphocyte ratio, prior bevacizumab) and stratification factors (geographic region, time since diagnosis of first metastasis, *RAS* mutational status). Statistical significance for factors were evaluated using Wald chi-square tests. An unstratified Cox regression model was used to assess the association between DpR and relative change from baseline at first tumor assessment, and both PFS and OS.

3. Results

Of 492 patients recruited in SUNLIGHT [1], 246 were randomized to each treatment group, and 227 and 218 were included in the TUMEV from the FTD/TPI + bevacizumab and FTD/TPI groups, respectively (Figure 1). In the FTD/TPI + bevacizumab group, 48 % and 39 % had TS and ETS, respectively (Figure 1). In the FTD/TPI group, 21 % and 17 % had TS and ETS, respectively (Figure 1). Baseline characteristics of patients in each treatment group, with and without TS and ETS are summarized in Table 1. No major differences in baseline characteristics were observed between the groups.

3.1. Tumor shrinkage and depth of response

The magnitude of DpR, TS and ETS was greater in the FTD/TPI + bevacizumab treatment group than the FTD/TPI treatment group. There was a 27.4 % difference in TS rate between treatment groups ($P < 0.0001$), and there was a 22.7 % difference in ETS rate between treatment groups ($P < 0.0001$). TS for each treatment group is summarized as a waterfall plot in Figure 2A.

In patients achieving TS, median DTS was 3.7 months in patients treated with FTD/TPI + bevacizumab and 2.2 months in patients treated with FTD/TPI (HR: 0.55 [95 % CI: 0.38, 0.78]; $P = 0.00082$; Figure 2B). In patients achieving ETS, median DTS was 3.8 months in patients treated with FTD/TPI + bevacizumab and 2.1 months in patients treated with FTD/TPI (HR: 0.34 [95 % CI: 0.22, 0.53]; $P < 0.0001$; Figure 2C). The magnitude of DpR was greater with FTD/TPI + bevacizumab treatment than with FTD/TPI treatment in the TUMEV and in those with TS and ETS (Supplementary Table 1).

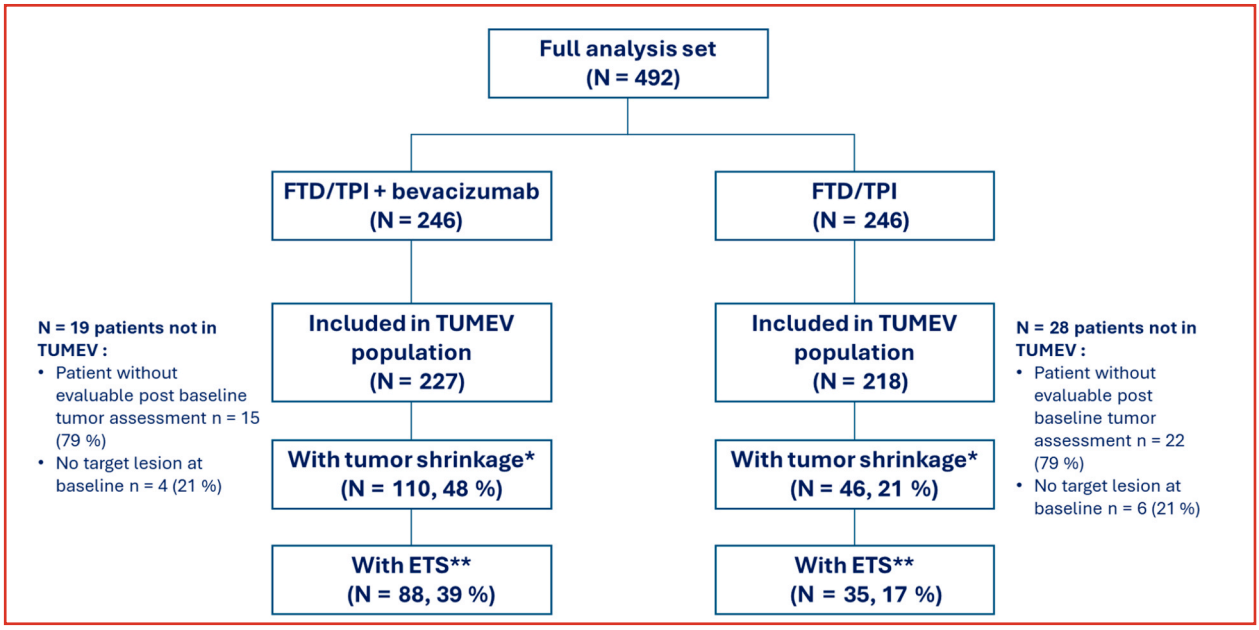
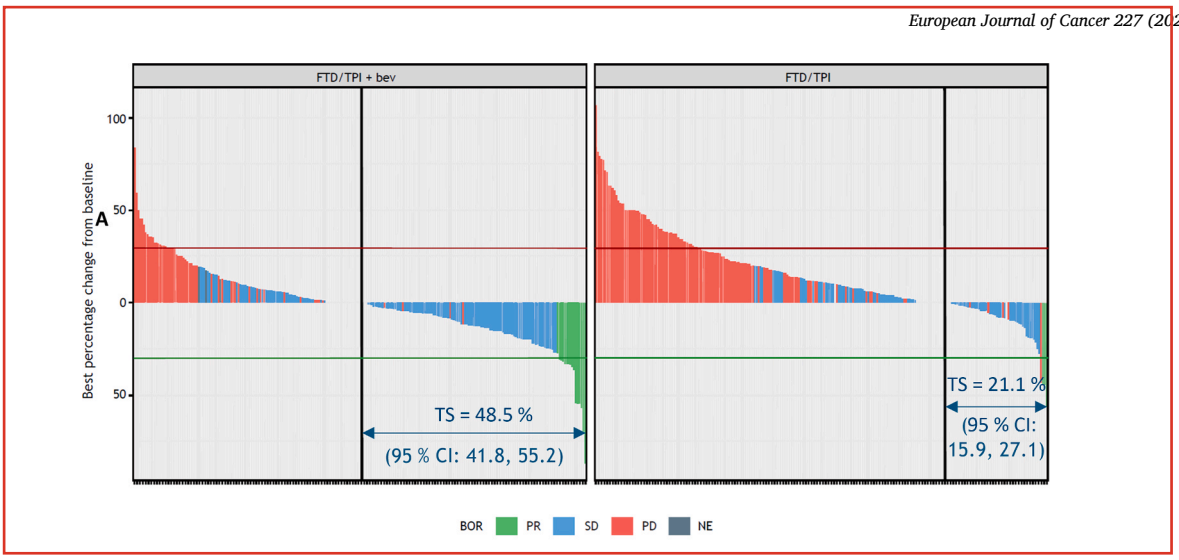


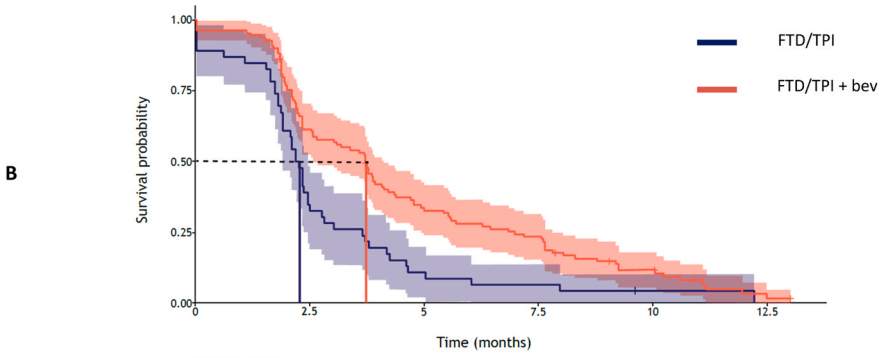
Fig. 1. CONSORT diagram summarizing the populations used for analysis (original CONSORT diagram for the SUNLIGHT study published in Prager et al. [1]). *Tumor shrinkage is defined as any decrease in sum of the longest diameter of the target lesion. **ETS is defined as tumor shrinkage that occurred before or at cycle 2 or 8 weeks. Percentages shown here are of the TUMEV. ETS, early tumor shrinkage. FTD/TPI, trifluridine/tipiracil. TUMEV, tumor evaluable population.

Table 1
Baseline characteristics and disease characteristics of patients with and without TS and ETS.

	With TS		Without TS		With ETS		Without ETS	
	FTD/TPI + bev (n = 110)	FTD/TPI (n = 46)	FTD/TPI + bev (n = 117)	FTD/TPI (n = 172)	FTD/TPI + bev (n = 88)	FTD/TPI (n = 35)	FTD/TPI + bev (n = 139)	FTD/TPI (n = 183)
Mean (SD) age, years	61.6 (10.0)	63.6 (10.4)	61.1 (12.4)	62.4 (11.2)	62.1 (9.2)	63.4 (11.2)	60.9 (12.4)	62.5 (11.0)
Gender, n (%)								
Female	52 (47.3)	21 (45.7)	62 (53.0)	81 (47.1)	41 (46.6)	15 (42.9)	73 (52.5)	87 (47.5)
Male	58 (52.7)	25 (54.4)	55 (47.0)	91 (52.9)	47 (53.4)	20 (57.1)	66 (47.5)	96 (52.5)
Ethnic origin, n (%)								
White	98 (94.2)	43 (95.6)	100 (95.2)	153 (96.2)	78 (94.0)	33 (97.1)	120 (95.2)	163 (95.9)
Black or African American	1 (1.0)	0 (0.0)	2 (1.9)	3 (1.9)	1 (1.2)	0 (0.0)	2 (1.6)	3 (1.8)
Other	5 (4.8)	2 (4.4)	3 (2.9)	3 (1.9)	4 (4.8)	1 (2.9)	4 (3.2)	4 (2.4)
ECOG PS, n (%)								
0	55 (50.0)	20 (43.5)	56 (47.9)	77 (44.8)	45 (51.1)	16 (45.7)	66 (47.5)	81 (44.3)
1	55 (50.0)	26 (56.5)	61 (52.1)	94 (54.7)	43 (48.9)	19 (54.3)	73 (52.5)	101 (55.2)
2	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Time since first metastasis, n (%)								
<18 months	45 (40.9)	14 (30.4)	50 (42.7)	80 (46.5)	37 (42.1)	12 (34.3)	58 (41.7)	82 (44.8)
≥ 18 months	65 (59.1)	32 (69.6)	67 (57.3)	92 (53.5)	51 (58.0)	23 (65.7)	81 (58.3)	101 (55.2)
Liver metastasis, n (%)	81 (73.6)	26 (56.5)	100 (85.5)	146 (84.9)	68 (77.3)	20 (57.1)	113 (81.3)	152 (83.1)
Number of metastatic sites, n (%)								
1–2	74 (67.3)	28 (60.9)	70 (59.8)	100 (58.1)	55 (62.5)	22 (62.9)	89 (64.0)	106 (57.9)
≥ 3	36 (32.7)	18 (39.1)	47 (40.2)	72 (41.9)	33 (37.5)	13 (37.1)	50 (36.0)	77 (42.1)
Location of primary disease, n (%)								
Right	25 (22.7)	12 (26.1)	34 (29.1)	54 (31.4)	19 (21.6)	8 (22.9)	40 (28.8)	58 (31.7)
Left	85 (77.3)	34 (73.9)	83 (70.9)	118 (68.6)	69 (78.4)	27 (77.1)	99 (71.2)	125 (68.3)
Prior surgical resection, n (%)	84 (76.4)	40 (87.0)	63 (53.9)	119 (69.2)	66 (75.0)	30 (85.7)	81 (58.3)	129 (70.5)
Prior bev, n (%)								
Yes	64 (58.2)	32 (69.6)	97 (82.9)	122 (70.9)	50 (56.8)	23 (65.7)	111 (79.9)	131 (71.6)
Prior anti-cancer agents, n (%)								
Fluoropyrimidine	110 (100.0)	46 (100.0)	117 (100.0)	172 (100.0)	88 (100.0)	35 (100.0)	139 (100.0)	183 (100.0)
Irinotecan	110 (100.0)	46 (100.0)	117 (100.0)	171 (99.4)	88 (100.0)	35 (100.0)	139 (100.0)	182 (99.5)
Oxaliplatin	107 (97.3)	45 (97.8)	117 (100.0)	170 (98.9)	87 (98.9)	35 (100.0)	137 (98.6)	180 (98.4)

Bev, bevacizumab. CI, confidence interval. ECOG PS, Eastern Cooperative Oncology Group performance status. ETS, early tumor shrinkage. FTD/TPI, trifluridine/tipiracil. HR, hazard ratio. OS, overall survival. PFS, progression-free survival. SD, standard deviation. TS, tumor shrinkage.

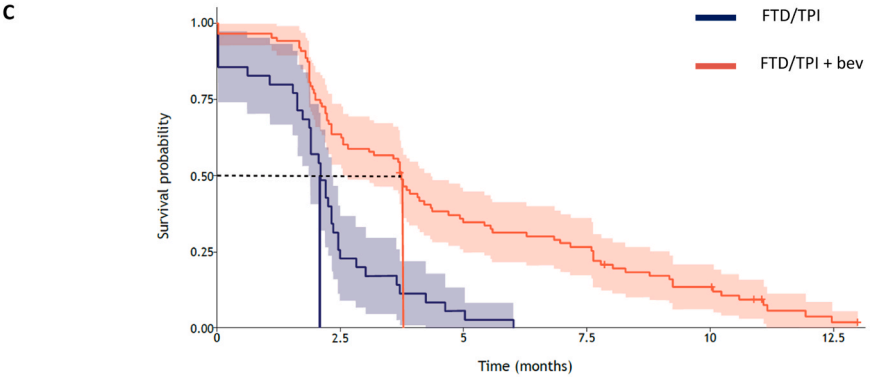




Number at risk

FTD/TPI	46	15	5	3	1	0
FTD/TPI + bev	110	67	35	25	11	1

	FTD/TPI + bev (N = 110)	FTD/TPI (N = 46)
Median (95 % CI), months	3.7 (2.6, 4.1)	2.2 (1.9, 2.5)
HR (95 % CI)	0.55 (0.38, 0.78)	



Number at risk

FTD/TPI	35	8	2	0	0	0
FTD/TPI + bev	88	56	30	23	11	1

	FTD/TPI + bev (N = 88)	FTD/TPI (N = 35)
Median (95 % CI), months	3.8 (2.7, 4.3)	2.1 (1.9, 2.4)
HR (95 % CI)	0.34 (0.22, 0.53)	

Fig. 2. Depth of response and tumor shrinkage according to treatment group for individual patients in the TUMEV (A), duration of response in patients receiving FTD/TPI + bevacizumab and FTD/TPI in the TUMEV with tumor shrinkage (B), and with early tumor shrinkage (C). Bev, bevacizumab. BOR, best overall response. CI, confidence interval. FTD/TPI, trifluridine/tipiracil. HR, hazard ratio. NE, non-evaluable. PD, progressive disease. PR, partial response. SD, stable disease. TS, tumor shrinkage. TUMEV, tumor evaluable population.

3.2. Association between survival, early tumor shrinkage and depth of response

In the TUMEV, median OS was longer in patients with ETS compared to patients without ETS (HR: 0.43 [95 % CI: 0.32, 0.57], P < 0.0001; Figure 3A). In both treatment groups, median OS was prolonged in patients achieving ETS compared to those not achieving ETS (HR: 0.39 [95 % CI: 0.27, 0.58], P < 0.0001 for the FTD/TPI + bevacizumab treatment group and HR: 0.61 [95 % CI: 0.40, 0.95], P = 0.026 for the FTD/TPI group; Figures 3B and 3C and Supplementary Figure 1A). Median OS was longer in the FTD/TPI + bevacizumab treatment group than in the FTD/TPI treatment group, regardless of whether ETS was achieved (HR: 0.75 [95 % 0.58, 0.97], P = 0.030 for the subgroup without ETS and HR: 0.48 [0.28, 0.80], P = 0.005 for the subgroup with ETS; Supplementary Figure 1B).

A multivariate Cox proportional hazard regression analysis, adjusted for known prognostic factors, showed that the OS and PFS benefit in the FTD/TPI + bevacizumab group compared to the FTD/TPI group was maintained with and without ETS (Table 2). A Cox proportional hazard analysis confirmed that DpR and ETS were likely associated with both OS and PFS in the FTD/TPI + bevacizumab treatment group and the FTD/TPI treatment group (Supplementary Table 2).

3.3. Association between QoL deterioration and early tumor shrinkage

In patients receiving FTD/TPI + bevacizumab, GHS was maintained for longer in patients that achieved ETS compared to those without ETS (6.1 vs 4.4 months; P = 0.031; Supplementary Figures 2A and 3). Similarly, in patients receiving FTD/TPI, GHS was maintained for longer in patients with ETS compared to those without ETS (4.7 vs 3.2 months; P = 0.16; Supplementary Figures 2B and 3).

4. Discussion

In this *post hoc* analysis of SUNLIGHT, a higher proportion of TS and ETS and a greater magnitude of DpR was observed in patients receiving FTD/TPI + bevacizumab, than in patients receiving FTD/TPI. Additionally, the DTS was prolonged in the FTD/TPI + bevacizumab treatment group compared with the FTD/TPI group, in patients achieving TS and in patients achieving ETS. Therefore, this analysis suggests that the previously observed survival benefit of treatment with FTD/TPI + bevacizumab compared to FTD/TPI in SUNLIGHT is accompanied by improvement of the more refined metrics of tumor response (ETS and DpR).

Although, ORR based on RECIST was modest when compared to the improved PFS and OS magnitude demonstrated in SUNLIGHT [1], this additional analysis showed improved response to FTD/TPI + bevacizumab compared to FTD/TPI outside of the confines of the RECIST classifications (i.e., TS of ≥30 %) [2]. The response to FTD/TPI + bevacizumab measured by ETS was likely associated with prolonged OS, which suggests that ETS in response to treatment may be associated with a survival benefit, despite not being a part of the RECIST classifications.

The use of ETS as a clinical endpoint has been widely investigated. Previous studies have shown that while ETS is a good prognostic factor, it may not be appropriate to use ETS as a surrogate marker for predicting treatment efficacy in mCRC [12]. However, in this analysis of patients in the third-line treatment setting, there was likely an association between OS and ETS, irrespective of treatment group, which is consistent with results of a previous meta-analysis of mCRC after first-line treatment [13]. While the use of ETS as an endpoint for clinical trials needs further exploration, its use in clinical practice could be beneficial. ETS may be a helpful addition to existing outcome measures as it may provide an earlier indication, from first tumor assessment, of potential future response [14]. In turn, this could optimize the management of patients with mCRC and aid clinical decision-making.

Furthermore, this analysis demonstrated an association between ETS and prolonged time to GHS deterioration in both treatment groups, with a greater association in the FTD/TPI + bevacizumab treatment arm. This is of importance as some patients with advanced cancer report QoL to be as important as survival outcomes [15]. So, patients receiving FTD/TPI + bevacizumab that experience ETS are more likely to have an additional benefit of prolonged QoL.

DpR has been shown to be a valid surrogate endpoint for survival in mCRC patients receiving first-line cetuximab, panitumumab or bevacizumab-based chemotherapy and second-line cetuximab-based chemotherapy [16–19]. DpR has also been shown to be associated with OS and PFS in mCRC patients receiving first-line 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) + bevacizumab [6]. In this analysis, DpR was likely associated with both OS and PFS, and a greater magnitude of DpR was observed in patients treated with FTD/TPI + bevacizumab compared to those treated with FTD/TPI. Further work is needed to investigate the reliability of DpR as a predictor for overall response to treatment with FTD/TPI + bevacizumab.

A limitation of this analysis was that there was no central review of images from tumor assessments. There could be irregularities in the clinical examination of images between individual investigators, potentially introducing a level of bias. This was an unplanned *post hoc* analysis of SUNLIGHT and therefore conclusions should be taken with caution and used as the basis for hypothesis testing in future clinical trials investigating the use of FTD/TPI + bevacizumab. Another limitation of this study is the selected and small sample size for some analyses, particularly when investigating the association between OS and ETS. Future clinical trials with larger tumor evaluable populations should investigate the association between ETS and OS in patients treated with FTD/TPI + bevacizumab and put that in the perspective of common RECIST results.

5. Conclusion

In conclusion, this analysis of the SUNLIGHT trial showed that a higher proportion of patients receiving FTD/TPI + bevacizumab experienced TS and ETS, improved DpR and prolonged DTS than patients receiving FTD/TPI. ETS is associated with OS and deserves further evaluation in future prospective trials.

CRediT authorship contribution statement

Nadia Amellal: Writing – review & editing, Conceptualization. **Gerald W. Prager:** Writing – review & editing, Investigation, Conceptualization. **Julien Taieb:** Writing – review & editing, Investigation, Conceptualization. **Valentine Barboux:** Writing – review & editing, Formal analysis. **Lucas Roby:** Writing – review & editing, Writing – original draft. **Cristina Gravalos:** Writing – review & editing, Investigation. **Arinilda Campos Bragagnoli:** Writing – review & editing, Investigation. **Eric Van Cutsem:** Writing – review & editing, Investigation. **Elena Elez:** Writing – review & editing, Investigation. **Fortunato Ciardiello:** Writing – review & editing, Investigation. **Dominik P Modest:** Writing – review & editing, Investigation, Conceptualization. **Marwan Fakih:** Writing – review & editing, Investigation.

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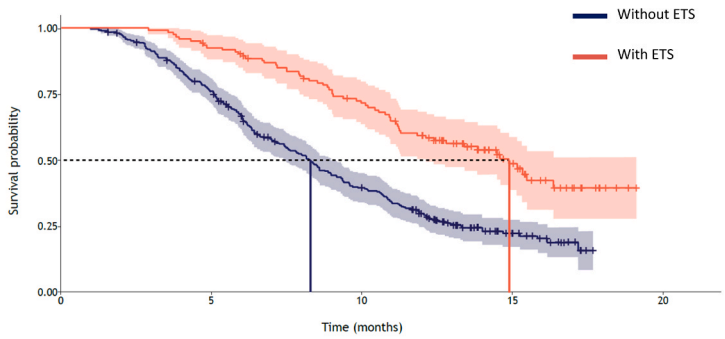
Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Julien Taieb: Reports personal fees for speaker bureau and/or advisory role from Merck KGaA, Sanofi, Roche Genentech, MSD, BMS, Novartis, Astellas, Takeda, Ono Pharmaceutical, Boehringer-Ingelheim, Pierre

A

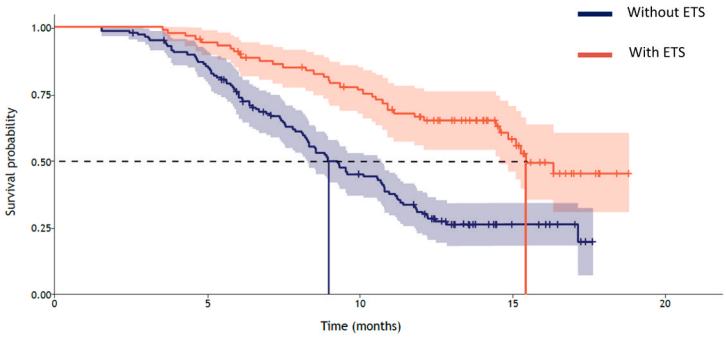


Number at risk

No ETS	322	241	115	25	0
With ETS	123	113	83	27	0

	With ETS (N = 123)	Without ETS (N = 322)
Median (95 % CI), months	14.9 (12.1, NA)	8.3 (7.4, 9.0)
HR (95 % CI)	0.43 (0.32, 0.57)	

B

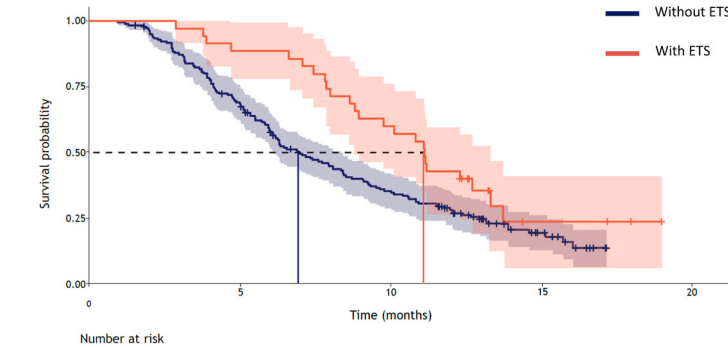


Number at risk

No ETS	139	117	55	12	0
With ETS	88	82	62	24	0

	With ETS (N = 88)	Without ETS (N = 139)
Median (95 % CI), months	15.5 (14.59, NA)	9.0 (8.3, 10.7)
HR (95 % CI)	0.39 (0.27, 0.58)	

C



Number at risk

No ETS	183	124	60	13	0
With ETS	35	31	21	3	0

	With ETS (N = 35)	Without ETS (N = 183)
Median (95 % CI), months	11.2 (8.9, 13.4)	7.0 (6.1, 8.5)
HR (95 % CI)	0.61 (0.40, 0.95)	

Fig. 3. Overall survival of patients with and without early tumor shrinkage in the TUMEV (A), in patients receiving FTD/TPI + bevacizumab (B) and in patients receiving FTD/TPI (C). Bev, bevacizumab. CI, confidence interval. ETS, early tumor shrinkage. FTD/TPI, trifluridine/tipiracil. HR, hazard ratio. NA, not applicable. TUMEV, tumor evaluable population.

Table 2
Association of ETS with OS and PFS in patients in the FTD/TPI + bevacizumab group versus patients in the FTD/TPI group.

		OS		PFS	
Level	Factor	HR [95 % CI]	P-value	HR [95 % CI]	P-value
FTD/TPI + bev versus FTD/TPI[a]	**With ETS**	0.48 [0.27, 0.85]	0.013	0.26 [0.16, 0.43]	< 0.0001
	Without ETS	0.73 [0.56, 0.95]	0.021	0.47 [0.37, 0.60]	< 0.0001

[a] HR calculated using a multivariate Cox proportional hazard regression model and corresponds to the treatment effect in each subgroup adjusted to all stratification factors (geographic region, time since diagnosis of first metastasis, RAS mutational status) and all significant prognostic factors (ECOG PS, location of primary disease, prior surgical resection, number of metastatic sites, neutrophil-to-lymphocyte ratio, prior bevacizumab). Bev, bevacizumab. CI, confidence interval. ETS, early tumor shrinkage. FTD/TPI, trifluridine/tipiracil. HR, hazard ratio. OS, overall survival. PFS, progression-free survival.

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Appendix A. Supporting information

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