2. SYNOPSIS

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Name of Finished Product: S95005 or TAS-102 **Name of Active Ingredients:** Trifluridine (FTD) and tipiracil hydrochloride (TPI)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: An open-label, randomised, phase III study comparing trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory metastatic colorectal cancer (SUNLIGHT study) Protocol No.: CL3-95005-007 EudraCT No.: 2020-001976-14 ClinicalTrials.gov: NCT04737187 Investigational New Drug No: 57674 Universal Trial Number: Not applicable The description of the study protocol given hereafter includes the modifications of one global amendment to the protocol.		
International Coordinator [redacted]		
Study countries: A total of 492 patients were randomised in 13 countries as follows: Spain (115 patients), Russian federation (77 patients), Brazil (63 patients), Hungary (47 patients), Italy (39 patients), Poland (34 patients), France (28 patients), Ukraine (21 patients), Denmark (20 patients), United States of America (16 patients), Austria (15 patients), Germany (10 patients), Belgium (7 patients).		
Publication (reference): Not applicable		
Study period: Initiation date: 25 November 2020 (first visit of first patient) Last randomised patient date: 18 February 2022 Clinical cut-off date: 05 July 2022 Primary completion date: 19 July 2022 (occurrence of 331st death)		**Phase of development of the study:** Phase III
Objectives: **Primary**: To demonstrate the superiority of trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab (Bev) over FTD/TPI monotherapy in terms of Overall Survival (OS) in patients with refractory metastatic colorectal cancer (mCRC). **Secondary**: To estimate the effect of FTD/TPI in combination with Bev *vs* FTD/TPI monotherapy in terms of: - Progression-free survival (PFS). - Overall response rate (ORR). - Disease control rate (DCR) in patients with refractory mCRC. - To compare the safety and tolerability - Impact on quality of life (QoL).		

Methodology:
This was a multinational, open-label, controlled two-arm, randomised phase III comparison study evaluating the efficacy and safety of FTD/TPI in combination with Bev *versus* FTD/TPI monotherapy in patients with refractory mCRC.
Patients were randomly assigned in a (1:1) ratio to receive FTD/TPI plus Bev (experimental arm) or FTD/TPI as monotherapy (control arm). The stratification factors were:

- Geographic region (North America, European Union, Rest of the World).
- Time since first metastasis diagnosis (< 18 months, ≥ 18 months).
- RAS status (wild type, mutant).

This main clinical study report (CSR) describes the results of the primary OS analysis and those of other clinical data. The cut-off dates were 05 July 2022 for clinical data and 19 July 2022 (occurrence of 331st death) for survival data only.

This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 490 patients (245 patients per each group).
Randomised: 492 patients in total, 246 patients in each group.
Number of events (death for any cause) required for the primary analysis: 331 events.

Diagnosis and main criteria for inclusion:

- Male or female participant aged ≥18 years at the time of informed consent signature.
- Had histologically confirmed unresectable adenocarcinoma of the colon or rectum.
- RAS status had been previously determined (mutant or wild type) based on local assessment of tumour biopsy.
- Had received a maximum of 2 prior chemotherapy regimens for the treatment of advanced CRC and had demonstrated progressive disease or intolerance to their last regimen:
  - Prior treatment regimens for the treatment of advanced CRC had included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody and/or an anti-epidermal growth factor receptor (EGFR) monoclonal antibody for RAS wild type patients.
  - Adjuvant/neoadjuvant chemotherapy could count as one prior regimen of chemotherapy for advanced CRC if the patient had recurrence during or within 6 months of completion of the adjuvant/neoadjuvant chemotherapy.
- Had measurable or non-measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.
- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1.
- Adequate organ function based on laboratory values.

Of note: prior anti-VEGF monoclonal antibody was optional except in France, where it was mandated.

Test drug: FTD/TPI + Bevacizumab
FTD/TPI (35 mg/m²/dose) was administered orally twice a day (BID), within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest; with bevacizumab (5 mg/kg, intravenous [IV]) administered every 2 weeks (Day 1 and Day 15). This treatment cycle was repeated every 4 weeks.

Batch numbers:

- FTD/TPI 15 mg: L0076619, L0077610, L0077872, L0079004, L0074189, L0079694.
- FTD/TPI 20 mg: L0077609, L0077871, L0079695, L0076844, L0075555, L0079007, L0075350.
- Bevacizumab 4 mL:
  Outside USA: L0077195, L0077616, L0077795, L0077794, L0077993, L0078378, L0078381, L0078666, L0078665; in USA: 3363536, 3363733, 3492534.
- Bevacizumab 16 mL:
  Outside USA: L0077618, L0077797, L0077796, L0077994, L0077995, L0078380, L0078379, L0078664, L0078753, L0078663; in USA: 3363543, 3363544, 3475017.

Comparator: FTD/TPI
FTD/TPI (35 mg/m²/dose) was administered orally BID, within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest. This treatment cycle was repeated every 4 weeks.

Batch numbers: see above

Duration of treatment:
Active treatment period:
Patients were treated until they met a discontinuation criterion. Patients were on treatment as long as they continued FTD/TPI. Bevacizumab monotherapy was not allowed.

Follow-up period:
After the withdrawal visit, all treated patients were followed every 8 weeks:

- For tumour assessment (unless patient had discontinued study treatments for radiologic disease progression or withdrawal of consent) until radiologic progression regardless of initiation of a new anticancer therapy.
- For survival status until death or until end of the study was reached (whichever occurred first).

Criteria for evaluation:
Efficacy measurements:
Tumour evaluations were performed based on investigator assessment as per RECIST 1.1 at baseline and then every 2 cycles from Cycle 1 Day 1 (C1D1) until radiologic progression or end of study.
Safety measurements:
Standard safety monitoring was performed including physical examination, vital signs, ECOG PS, 12-lead ECG, adverse events and clinical laboratory evaluations. Adverse events (AEs) were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
Other measurements:
Quality of life assessments were performed at baseline, at each cycle and at withdrawal visit using EORTC QLQ-C30 and EQ-5D-5L questionnaires.

Statistical methods:
Sample size determination:
A maximum of 331 events (deaths for any cause) were required for the primary analysis to detect a hazard ratio of 0.70 with 90% power using a log-rank test at one-sided cumulative 2.5% level of significance. Based on the data from the RECOURSE study (Mayer, 2015), the median duration of OS in the control group was expected to be around 7.1 months. A hazard ratio (HR) of 0.70 translates into a 3-month increase of the median OS in the experimental arm (10.1 months) compared to the control arm. Based on the assumption that enrolment would have continued for approximately 12 months and that about 5% per year of the patients would have dropped out, a total of 490 patients randomized in a 1:1 ratio was needed to observe the 331st OS event approximately 9 months after the last patient randomisation.

Analysis Set:

- Full Analysis Set (FAS): based on the intention-to-treat principle, all patients to whom a therapeutic unit was randomly assigned using Interactive Web Response System (IWRS). Patients were analysed in the arm they were assigned by randomisation.
- Safety Set (SS): all patients having taken at least one dose of FTD/TPI.

Efficacy analysis:

Efficacy analyses were carried out in the FAS.

Primary estimand based on OS

The primary estimand of interest was defined to assess the effect of the randomised treatments on the survival duration in all patients regardless of whether or not intercurrent events had occurred (treatment policy strategy).

OS was defined as the time elapsed between the date of randomisation and the date of death due to any cause. For patients without documentation of death, the OS was censored at the last contact date the patient was known to be alive.

- Primary analysis: the distribution of OS was compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (strata based on IWRS data). The HR of OS with its 95% confidence interval (CI) was estimated with a stratified Cox proportional hazard (CPH) model using stratification factors based on IWRS data. OS for each arm was summarised using Kaplan Meier curves and further characterised in terms of median and survival probabilities at 6, 12 and 18 months along with the corresponding 2-sided 95% CI for the estimates.
- Sensitivity analyses were performed to address the impact of stratification and of excluding patients not fulfilling pre-defined medical and therapeutic criteria and to assess the restricted mean survival time (RMST).
- Analyses by predefined subgroups were performed.
- An additional estimand based on OS was defined to assess the effect of the randomised treatments on the survival time in all patients before patients receive further anticancer therapy or treatment switch.

Secondary estimands based on PFS, ORR and DCR

An important secondary estimand of interest was the effect of the randomised treatments on PFS in all patients regardless of whether or not intercurrent events occurred (treatment policy strategy).

PFS was based on the investigator's judgment and was defined as the time elapsed between the randomisation and the date of radiologic tumour progression according to RECIST version 1.1 or death from any cause. A hierarchical testing strategy was used *i.e.* PFS was to be statistically evaluated and interpreted only if the primary estimand OS was significantly different between the 2 treatment groups. Primary analyses of PFS were similar as those for OS (see above). Sensitivity analyses were performed including clinical progression and further anticancer therapies as PFS events, using unstratified log-rank test and censoring further anticancer therapies and patients missing 2 consecutive tumour assessments.

Other secondary estimands of interest were the effect of the randomised treatments on response in all patients before modification of randomised treatment (while on treatment strategy): ORR [Complete Response (CR) + Partial Response (PR)] and DCR [CR + PR + Stable Disease] based on the investigator's assessment of tumour response were compared between the two treatment groups.

Time to worsening of ECOG PS to ≥ 2 was analysed using Kaplan-Meier curves and compared between treatment groups with a stratified log-rank test (strata based on IWRS data).

Quality of Life analysis: change from baseline and Time Until Definitive Deterioration (TUDD) ≥ 10 points in global health status and sub-scale scores for the QLQ-C30; change from baseline in VAS and health utility index for the EQ-5D-5L. QoL analyses were carried out in the FAS.

Safety analysis: descriptive statistics were provided based on the SS. Analysis of AEs was carried out for emergent AEs (EAEs) during the treatment period. Analyses were performed in predefined subgroups based on baseline characteristics: ECOG PS (0, ≥ 1), age (< 65, ≥ 65 years), sex, creatinine clearance (< 60, ≥ 60 mL/min).

Interim analysis: considering the anticipated rapid enrolment and event accumulation in this population, no interim analysis for efficacy or futility was conducted.

SUMMARY - CONCLUSIONS

A total of 659 patients provided consent and were screened. Among them, 167 (25.3%) were not included due to eligibility criteria not met (24.3%) or withdrawal of consent (1.1%).

DISPOSITION OF RANDOMISED PATIENTS AND ANALYSIS SETS

Table 1 - Disposition of randomised patients (as of clinical data cut-off 05 July 2022) and Analysis Sets

Patient Status		FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)	All (N = 492)
Included / Randomised	n	246	246	492
CONTINUING ON STUDY TREATMENT	n (%)	32 (13.01)	4 (1.63)	36 (7.32)
WITHDRAWN ON TREATMENT DUE TO	n (%)	214 (86.99)	242 (98.37)	456 (92.68)
Adverse event	n (%)	16 (6.50)	16 (6.50)	32 (6.50)
Radiological progressive disease	n (%)	145 (58.94)	146 (59.35)	291 (59.15)
Clinical progressive disease	n (%)	20 (8.13)	20 (8.13)	40 (8.13)
Radiological and clinical progressive disease	n (%)	26 (10.57)	52 (21.14)	78 (15.85)
Non-medical reason	n (%)	5 (2.03)	8 (3.25)	13 (2.64)
Consent withdrawal from study treatment period only	n (%)	3 (1.22)	4 (1.63)	7 (1.42)
Consent withdrawal from study treatment period and FU period	n (%)	2 (0.81)	4 (1.63)	6 (1.22)
Other, physician decision	n (%)	2 (0.81)	-	2 (0.41)
WITHDRAWAL ON TREATMENT RELATED TO COVID-19 PANDEMIC	n (%)	3 (1.22)	3 (1.22)	6 (1.22)
WITHDRAWN ON FOLLOW-UP PERIOD DUE TO	n	145	169	314
Consent withdrawal	n (%)	2 (1.38)	2 (1.18)	4 (1.27)
Lost to follow-up	n (%)	1 (0.69)	1 (0.59)	2 (0.64)
Death*	n (%)	142 (97.93)	166 (98.22)	308 (98.09)
REASON OF DEATH ON FOLLOW-UP PERIOD	n	142	166	308
Progressive disease	n (%)	133 (93.66)	154 (92.77)	287 (93.18)
Other	n (%)	9 (6.34)	12 (7.23)	21 (6.82)
WITHDRAWAL ON FOLLOW-UP RELATED TO COVID-19 PANDEMIC	n (%)	-	1 (0.59)	1 (0.32)

N: number of patients by treatment group; n: number of patients; percentages are based on n; FU: follow-up
** deaths as reported by the investigator based on the eCRF page Status of the patient at follow-up', which aligned with the follow-up definition used in the protocol. Analyses presented in the safety results are based on the follow-up period definition in the statistical analysis plan.*

Analysis sets		FTD/TPI + Bev	FTD/TPI	All
Full Analysis Set	n (%)	246 (50.0)	246 (50.0)	492 (100)
Safety Set	n (%)	246 (50.0)	246 (50.0)	492 (100)

Percentages are based on number of all patients for each analysis set

BASELINE CHARACTERISTICS

In the FAS, demographic and other baseline characteristics showed that randomised patients reflected the target population. The mean ± SD (median) age was 61.7 ± 11.1 (63.0) years with 44.1% of patients ≥ 65 years and 11.8% of patients ≥ 75 years. Overall, 52.0% of patients were male and 95.2% were white. Demographic characteristics were generally well balanced between the two treatment groups with a slight difference with regards to sex and age. Regional distribution of patients included 315 (64.0%) patients from European Union (Austria, Belgium, Denmark, France, Germany, Hungary, Italy, Poland, Spain), 161 (32.7%) patients from Brazil, Russia and Ukraine, and 16 (3.3%) patients from North America (USA).

At baseline, all patients had unresectable advanced/metastatic adenocarcinoma of CRC. No relevant between-group difference was observed for the hereafter baseline characteristics. The primary tumour site was the left colon (including rectum) for 71.8% of patients and right colon for 28.2% of patients. The mean (median) disease duration from initial CRC diagnosis was 2.5 ± 1.8 (2.0) years and mean (median) time since first metastasis diagnosis was 23.4 ± 14.4 (21.1) months.

Patients received a mean (median) of 2.2 ± 0.6 (2.0) prior regimens of anticancer systemic treatment, whatever the intent (*i.e.* neoadjuvant, adjuvant, metastatic). A total of 92.1% of patients received 2 previous chemotherapy regimens for advanced CRC, 5.3% received 1 previous treatment regimen as per protocol. The percentage of patients who received more than 2 prior regimens for advanced CRC was 2.6%. Prior chemotherapy for advanced CRC had to include a fluoropyrimidine, irinotecan, oxaliplatin for all patients, plus an EGFR monoclonal antibody for RAS wild-type patients only. All patients received prior fluoropyrimidine, 99.8% and 98.4% received irinotecan and oxaliplatin respectively (but 100% of patients have been exposed to irinotecan and oxaliplatin during their disease, *i.e.* neoadjuvant, adjuvant or metastatic), and 93.7% of RAS wild-type patients received prior anti-EGFR monoclonal antibody. An anti-VEGF monoclonal antibody was optional (except in France, where it was mandatory) and 72.0% of patients received it.

The treatment groups were well balanced with respect to RAS and BRAF status (wild-type or mutant) and MSI/MMR status (high or stable / deficient or proficient).

ECOG PS was rated 0 for 45.7% of patients and 1 for 54.1% of patients. One patient had an ECOG PS rated 2 at baseline prior to treatment while it was rated 1 at inclusion.

EXTENT OF EXPOSURE

As of the clinical data cut-off, the mean (median) treatment duration was longer in the FTD/TPI + Bev group than in the FTD/TPI group: 6.1 ± 4.3 (5.0) *vs* 3.4 ± 2.5 (2.1) months. The mean (median) relative dose intensity (RDI) for FTD/TPI was similar in the two groups: 85.0 ± 13.2 (88.3%) *vs* 87.2 ± 14.2 (90.4%). A majority of patients had at least one administration postponed (*i.e.* cycle initiation was delayed) in both groups with higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 69.5% *vs* 53.2%. The percentage of patients with at least one unplanned intra-cycle treatment interruption was low in the two groups: 5.3% *vs* 2.8%. The percentage of patients who had at least one FTD/TPI dose reduction was similar in the two groups: 16.3% in the FTD/TPI + Bev group and 12.2%. in FTD/TPI group. In the FTD/TPI + Bev group, the mean (median) RDI for bevacizumab was 86.9 ± 27.3 (87.6%). The mean (median) number of bevacizumab infusions was 11.0 ± 7.9 (8.0) with full dose of bevacizumab administered at each infusion. The percentage of patients with at least one bevacizumab missed intake was 38.2% (median number of cycles with missed intake was 1.0).

EFFICACY RESULTS

- **Primary efficacy estimand based on Overall Survival**
  - ***Primary OS analysis***

The median follow-up duration was 14.1 months. In the FAS, as of the survival data cut-off, the addition of bevacizumab to FTD/TPI resulted in a statistically and clinically significant superiority in OS compared to FTD/TPI monotherapy (one-sided $p < 0.001$, stratified log-rank test) with an estimated HR of 0.61 (95% CI: 0.49, 0.77) corresponding to 39% reduction in the risk of death. The median OS improved by 3.3 months with FTD/TPI + Bev *vs* FTD/TPI: 10.8 months (95% CI: 9.36, 11.83) *vs* 7.5 months (95% CI: 6.34, 8.57), respectively; see Table 2 hereafter.

Table 2 - Overall Survival in the FAS (N = 492)

		FTD/TPI + Bev (N = 246)	**FTD/TPI (N = 246)**
Number of censors	n	98	63
Alive	n (%)	98 (39.84)	63 (25.61)
Number of events	n	148	183
Death	n (%)	148 (60.16)	183 (74.39)
Survival (months)			
Median (months)[1]		10.78	7.46
95% confidence interval[2]		[9.36 ; 11.83]	[6.34 ; 8.57]
p-value[3]		< 0.001	
Survival probability			
Survival probability at 6 months[1]		0.77	0.61
95% confidence interval (4)		[0.72 ; 0.82]	[0.55 ; 0.67]
Survival probability at 12 months[1]		0.43	0.30
95% confidence interval[4]		[0.36 ; 0.49]	[0.24 ; 0.36]
Survival probability at 18 months[1]		0.28	0.15
95% confidence interval[4]		[0.19 ; 0.37]	[0.09 ; 0.22]
Hazard ratio* (relative to FTD/TPI monotherapy)		0.61	
95% confidence interval		[0.49 ; 0.77]	

Percentages are based on n
(1) Kaplan-Meier estimates
(2) Methodology of Brookmeyer and Crowley
(3) Stratified Log-Rank Test at one-sided 2.5% level of significance (IWRS stratification factors geographic region, time since first metastasis diagnosis, RAS status)
(4) Using log-log transformation methodology of Kalbfleisch and Prentice
** Stratified Cox proportional hazard model using IWRS stratification factors*

- ***Sensitivity OS analyses***

Sensitivity analyses using unstratified CPH model or excluding patients who did not fulfil relevant eligibility criteria showed HR of 0.62 (95% CI: 0.50, 0.77) and 0.59 (95% CI: 0.47, 0.74), respectively.

- ***OS analyses by subgroup***

The HRs were consistently in favour of the FTD/TPI + Bev treatment group in all of the 15 subgroups examined, including the stratification factors subgroups, and ranging from 0.33 to 0.85.

- ***Additional estimand based on OS***

Taking into account deaths occurring before any further anticancer therapy, HR was 0.40 (95% CI: 0.30, 0.55) and median OS of 14.5 months in the FTD/TPI + Bev group (95% CI: 10.41, upper bound not calculated) *vs* 7.8 months in the FTD/TPI group (95% CI: 6.21, 8.77), consistent with the primary OS analysis.

- **Secondary efficacy estimands**

- ***Key secondary endpoint: Progression-Free Survival***

In the FAS, the FTD/TPI + Bev group demonstrated a statistically significant improvement in PFS compared to the FTD/TPI group (one-sided $p < 0.001$, stratified log-rank test) with a 56% reduction in the risk of disease progression or death (HR of 0.44; 95% CI: 0.36, 0.54). The median PFS improved by 3.2 months with FTD/TPI + Bev *vs* FTD/TPI: 5.6 months (95% CI: 4.50, 5.88) *vs* 2.4 months (95% CI: 2.07, 3.22). Results of sensitivity analyses were consistent with that of the primary PFS analysis.

- ***Overall response rate, disease control rate***

The ORR was 6.1% in the FTD/TPI + Bev group (15 patients, all with PR) *vs* 1.2% in the FTD/TPI group (1 patient with CR, 2 patients with PR). The between-group difference in ORR was 4.9% (95% CI: 1.59, 8.17; $p = 0.007$).

The DCR was 69.5% in the FTD/TPI + Bev group (63.4% of patients with stable disease) and 41.9% in the FTD/TPI group (40.7% of patients with stable disease) with a between-group difference of 27.6% (95% CI:19.21, 36.07; $p < 0.001$).

- **Time to worsening of ECOG PS**

In the FAS, the FTD/TPI + Bev group showed a statistically significant improvement in time to worsening of ECOG PS to ≥ 2 compared to the FTD/TPI group ($p < 0.001$, stratified log-rank test). The median time to worsening of ECOG PS to ≥ 2 was 9.3 months (95% CI: 8.34, 10.61) *vs* 6.3 months (95% CI: 5.55, 7.23), respectively.

- **Quality of life**

In the FAS, QLQ-C30 analyses showed no clinically relevant mean change from baseline for global health status (GHS) in either group, as well as for almost all functioning and symptom/single items. At the treatment withdrawal visit, the proportion of patients who worsened < 10 points from baseline in GHS was similar in the two groups: 61.2% in the FTD/TPI + Bev group and 57.3% in the FTD/TPI group. The percentage of patients with definitive GHS deterioration was lower in the FTD/TPI + Bev group than in FTD/TPI group: 48.8% *vs* 57.3%. The TUDD for GHS was statistically longer in the FTD/TPI + Bev group than in the FTD/TPI group ($p < 0.001$, stratified log rank test) with median value of 8.5 *vs* 4.7 months.

EQ-5D-5L utility score and VAS did not show relevant changes from baseline in either group.

SAFETY RESULTS

- **Emergent adverse events**

The main results of adverse events in the Safety Set are summarised in Table 3.

Table 3 - Overall summary for emergent adverse events in the Safety Set (N = 492) as of clinical data cut-off 05 July 2022

		FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)
Patients having reported at least one:			
EAE	n (%)	241 (98.0)	241 (98.0)
Treatment-related[1] EAE	n (%)	223 (90.7)	200 (81.3)
Severe (Grade ≥ 3) EAE	n (%)	178 (72.4)	171 (69.5)
Severe treatment-related[1] EAE	n (%)	145 (58.9)	112 (45.5)
Serious EAE (including death) (SEAE)	n (%)	61 (24.8)	77 (31.3)
Serious treatment-related[1] EAE	n (%)	13 (5.3)	20 (8.1)
EAE leading to FTD/TPI withdrawal	n (%)	31 (12.6)	31 (12.6)
Treatment-related EAE leading to FTD/TPI withdrawal[2]	n (%)	6 (2.4)	5 (2.0)
Severe EAE leading to FTD/TPI withdrawal[2]	n (%)	22 (8.9)	20 (8.1)
Serious EAE leading to FTD/TPI withdrawal[2]	n (%)	20 (8.1)	17 (6.9)
EAE leading to FTD/TPI treatment delayed	n (%)	167 (67.9)	147 (59.8)
EAE leading to FTD/TPI dose reduction	n (%)	18 (7.3)	20 (8.1)
EAE leading to FTD/TPI treatment delayed and dose reduction	n (%)	31 (12.6)	11 (4.5)
EAE leading to FTD/TPI temporary interruption	n (%)	27 (11.0)	21 (8.5)
EAE leading to bevacizumab withdrawal	n (%)	36 (14.6)	NA
EAE leading to bevacizumab treatment delayed	n (%)	172 (69.9)	NA
EAE leading to bevacizumab temporary interruption	n (%)	64 (26.0)	NA
Patients who died during the study[3]			
During treatment period	n (%)	13 (5.3)	24 (9.8)
During the follow-up period	n (%)	133 (54.1)	153 (62.2)
Treatment-related[1] EAE leading to death	n (%)	-	-

NA not applicable

1. In the FTD/TPI + Bev group, EAEs related to the combination i.e. related to FTD/TPI and/or bevacizumab

2. FTD/TPI withdrawal corresponded to treatment withdrawal as bevacizumab monotherapy was not allowed.

3. As of the clinical cut-off, a total of 323 deaths were reported and used for safety analysis. As of the survival cut-off, a total of 331 deaths were reported and used for the OS analysis.

Almost all patients experienced at least one EAE: 98% in both groups. The most frequently reported SOCs (≥ 50% in either group) were Blood and lymphatic system disorders (74.0% in the FTD/TPI + Bev group and 69.1% in the FTD/TPI group) and Gastrointestinal disorders (63.4% and 53.7%, respectively) with similar frequency in the two groups (between-group difference ≤ 10%). Among other SOCs, the frequencies were similar in the two groups, except for Investigations at > 10% higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 39.8% *vs* 29.7%.

The ***most frequent EAEs*** (> 20% in either group) were neutropenia (62.2% in the FTD/TPI + Bev group *vs* 51.2% in the FTD/TPI group), nausea (37.0% *vs* 27.2%), anaemia (28.9% *vs* 31.7%), asthenia (24.4% *vs* 22.4%), fatigue (21.5% *vs* 16.3%), diarrhoea (20.7% *vs* 18.7%) and decreased appetite (20.3% *vs* 15.4%). Among those EAEs, neutropenia, nausea and fatigue occurred at > 5% higher frequency in FTD/TPI + Bev group than in FTD/TPI group. Other EAEs occurring at higher frequency in the FTD/TPI + Bev group were thrombocytopenia (17.1 *vs* 11.4%), neutrophil count decreased (13.8% *vs* 6.9%), stomatitis (11.0% *vs* 3.7%), hypertension (10.2% *vs* 2.0%) and platelet count decreased (8.9% *vs* 2.0%).

The percentage of patients who experienced ***severe (Grade ≥ 3) EAEs*** was similar in the FTD/TPI + Bev group and the FTD/TPI group: 72.4% *vs* 69.5%. The most frequent (> 10 % in either group) severe EAEs were neutropenia, which occurred at higher frequency in the FTD/TPI + Bev group (43.1% *vs* 32.1% in the FTD/TPI group) and anaemia, which occurred at lower frequency in the FTD/TPI + Bev group (6.1% *vs* 11.0% in the FTD/TPI group).

The percentage of patients who experienced ***treatment-related EAEs*** was higher in the FTD/TPI + Bev group than in the FTD/TPI group: 90.7% *vs* 81.3%. The most frequent (> 20 % in either group) treatment-related EAEs were neutropenia, nausea and anaemia. Among those EAEs, neutropenia and nausea occurred at > 5% higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group (neutropenia: 60.2% *vs* 48.4%; nausea: 33.3% *vs* 20.7%) and anaemia occurred with similar frequency in the two treatment groups (23.6% *vs* 25.2%). Other treatment-related EAEs occurring at higher frequency in the FTD/TPI + Bev group were thrombocytopenia (15.4% *vs* 8.9%), vomiting (16.7% *vs* 11.0%), neutrophil count decreased (13.8% *vs* 6.9%), stomatitis (10.6% *vs* 3.7%), platelet count decreased (8.9% *vs* 1.6%) and hypertension (7.3% *vs* none). ***Severe treatment-related EAEs*** were reported with higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 58.9% *vs* 45.5%. Among those, the most frequent (> 5% in either group) severe treatment-related EAEs were neutropenia and neutrophil count decreased with higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group (41.5% *vs* 29.3% and 8.9% *vs* 5.3%, respectively), and anaemia with lower frequency in the FTD/TPI + Bev group (4.9% *vs* 8.1%). Among other severe treatment-related EAEs, hypertension occurred at higher frequency in the FTD/TPI + Bev group (4.1% *vs* none).

EAEs leading to treatment withdrawal were reported with same frequency in both groups (12.6%) and those that occurred in more than 1 (0.4%) patient were asthenia (3.3% *vs* 0.4%), fatigue, jaundice, decreased appetite, biliary dilatation, blood bilirubin increased, pain, anaemia, intestinal obstruction, malignant neoplasm progression and metastases to central nervous system, each at frequency ≤ 0.8% in either group. Treatment-related EAEs leading to treatment withdrawal were reported in 2.4% in the FTD/TPI + Bev group *vs* 2.0% in the FTD/TPI group, those occurring in more than 1 (0.4%) patient were anaemia (0.4% *vs* 0.8%) and fatigue (none *vs* 0.8%).
In the FTD/TPI + Bev group, 14.6% of patients experienced at least one ***EAE leading to bevacizumab withdrawal***. These EAEs that occurred in more than 1 (0.4%) patient were asthenia (3.3%), pain, biliary dilatation, jaundice, blood bilirubin increased, decreased appetite, proteinuria and pulmonary embolism (0.8% each).

EAEs leading to FTD/TPI treatment delayed were reported at higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 67.9% *vs* 59.8%. The most common of these EAEs were neutropenia (48.0% *vs* 41.5%) and neutrophil count decreased (11.8% *vs* 5.7%). ***EAEs leading to FTD/TPI dose reduction*** were reported with similar frequency in the two groups: 7.3% *vs* 8.1%. The most common of these EAEs was neutropenia (3.7% *vs* 2.4%). ***EAEs leading to FTD/TPI treatment delayed and dose reduction*** were reported at higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 12.6% *vs* 4.5%. The most common of these EAEs was neutropenia (9.3% *vs* 2.4%).
In the FTD/TPI + Bev group, 69.9% of patients experienced at least one ***EAE leading to bevacizumab treatment delayed***. The most common of these EAEs were neutropenia (49.6%), neutrophil count decreased (11.8%), COVID-19 (3.3%) and thrombocytopenia (2.8%).

Regarding EAE subgroups analysis, a difference of ≥ 10% between the subgroups was observed in the FTD/TPI + Bev group for serious EAEs which were more frequent for patients ≥ 65 years *vs* < 65 years: 31.0% *vs* 20.5%. Among the most frequent EAEs in the overall study population, severe neutropenia was more frequent in patients ≥ 65 *vs* < 65 years in both treatment groups (51.0% *vs* 37.7%, respectively, in FTD/TPI + Bev group; 40.2% and 24.8%, respectively, in FTD/TPI group); nausea was more frequent for females *vs* males (45.2% *vs* 28.7%, respectively) in the FTD/TPI + Bev group.

The percentage of patients who experienced ***serious EAEs*** was lower in the FTD/TPI + Bev group than in the FTD/TPI group: 24.8% *vs* 31.3%. The most frequent SEAEs (≥ 2%) were intestinal obstruction (2.8% *vs* 2.0%), malignant neoplasm progression (2.4% *vs* 4.5%), COVID-19 (2.0% *vs* 2.4%), jaundice (0.8% *vs* 2.0%), anaemia (0.4% *vs* 3.3%), febrile neutropenia (0.4% *vs* 2.4%) and hepatic failure (none *vs* 2.0%). Treatment-related SEAEs were reported for 5.3% *vs* 8.1%, respectively; those occurring in more than 2 (0.8%) patients were febrile neutropenia and anaemia (0.4% *vs* 2.4% for each).

As of the survival cut-off, 331 ***deaths*** were reported and used for OS primary analysis. As of the clinical cut-off, a total of 323 patients had died: 59.4% of patients in the FTD/TPI + Bev group and 72.0% of patients in the FTD/TPI group. Among those, 37 patients died during the treatment period (5.3% and 9.8% of patients, respectively) and 286 patients died during the follow-up period (54.1% and 62.2% of patients, respectively). The percentage of patients who experienced at least one EAE leading to death was lower in the FTD/TPI + Bev group than in the FTD/TPI group: 5.3% *vs* 11.0%. Of note, fatal EAEs occurred during the treatment period, but the resulting death could have occurred during the follow-up period. Fatal EAEs reported in more than one patient were malignant neoplasm progression (6 patients, 2.4% *vs* 11 patients, 4.9%), hepatic failure (none *vs* 3 patients, 1.2%), septic shock (2 patients, 0.8% *vs* none), multiple organ dysfunction syndrome and cachexia (none *vs* 2 patients, 0.8%, for each). For most of patients who experienced fatal EAEs, death was related to disease progression: 3.3% in the FTD/TPI + Bev group *vs* 8.9% in the FTD/TPI group. None of the fatal EAEs were considered treatment-related in either group.
Out of the 286 patients who died during follow-up period, most of the deaths were attributed to progressive disease: 96.2% in the FTD/TPI + Bev group and 93.3% in the FTD/TPI group.

- **Laboratory tests**

For the **biochemistry parameters**, treatment-emergent severe abnormalities in ≥ 5% of patients were observed for high bilirubin with identical incidence in the two groups (5.8%).
For the **haematological parameters,** treatment-emergent severe low neutrophils were observed with higher frequency in the FTD/TPI + Bev group (51.7% with 33.5% Grade 3 and 18.2% Grade 4) than in the FTD/TPI group (38.6% with 26.6% Grade 3 and 12.0% Grade 4). Those severe low neutrophils were observed at ≥ 10% higher frequency for patients ≥ 65 *vs* < 65 years in both treatment groups. Emergent severe low values were observed for leukocytes (21.1% in the FTD/TPI + Bev group *vs* 13.7% in the FTD/TPI group), lymphocytes (12.8% *vs* 12.0%), haemoglobin (5.4% *vs* 11.3%) and platelets (4.1% *vs* 0.8%). Those values were mostly rated Grade 3 and the between-group differences observed were ≤ 10%.

- **Other safety evaluation**

There were no relevant between-group differences in mean change for weight, blood pressures, heart rate and ECG parameters.

CONCLUSION

This was a multinational, randomised, open-label, controlled two-arm, phase III study comparing trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab (Bev) to FTD/TPI monotherapy in patients with refractory mCRC who had received a maximum of 2 prior chemotherapy regimens for advanced CRC and had demonstrated progressive disease or intolerance to their last regimen.

At survival data cut-off date, the primary analysis for the primary estimand based on overall survival (OS) was performed on 331 deaths among 492 randomised patients. The FTD/TPI + Bev group demonstrated a statistically and clinically significant superiority in OS compared to the FTD/TPI group (one-sided p < 0.001 stratified log-rank test), demonstrating a 39% reduction in the risk of death (HR of 0.61, 95% CI: 0.49, 0.77). The median OS improved by 3.3 months with FTD/TPI + Bev *vs* FTD/TPI (10.8 *vs* 7.5 months). The sensitivity analyses using unstratified Cox proportional hazard model or excluding patients who did not fulfil relevant eligibility criteria showed HR of 0.62 (95% CI: 0.50, 0.77) and 0.59 (95% CI: 0.47, 0.74), respectively. In all pre-specified subgroups, including the stratification factors, the OS HR was consistently in favour of the FTD/TPI + Bev group.

Regarding the key secondary efficacy estimand based on progression-free survival (PFS), the FTD/TPI + Bev group demonstrated a statistically significant improvement compared to the FTD/TPI group (one-sided p < 0.001, stratified log-rank test) with a 56% reduction in the risk of disease progression or death (HR of 0.44; 95% CI: 0.36, 0.54). The median PFS improved by 3.2 months with FTD/TPI + Bev *vs* FTD/TPI (5.6 *vs* 2.4 months). The overall response rate was 6.1% in the FTD/TPI + Bev group *vs* 1.2% in the FTD/TPI group with a between-group difference of 4.9% (p = 0.007). The disease control rate was 69.5% and 41.9%, respectively, with a between-group difference of 27.6% (p < 0.001).
The FTD/TPI + Bev group showed a statistically significant improvement in time to worsening of ECOG PS to ≥ 2 compared to the FTD/TPI group (p < 0.001, stratified log-rank test) with a median time to worsening of ECOG PS to ≥ 2 of 9.3 *vs* 6.3 months, respectively.
Quality of Life (QoL) was stable in the two groups with no clinically relevant change over the treatment period for global health status and most of other QoL items.

Treatment-related EAEs occurred at higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 90.7% *vs* 81.3%. Consistent with previous studies of FTD/TPI in monotherapy, the most common (> 20%) treatment-related EAEs observed with FTD/TPI in combination with bevacizumab were predominantly haematologic and gastrointestinal in nature: neutropenia, anaemia and, nausea. Severe treatment-related EAEs were reported at higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 58.9% *vs* 45.5%. Among those, the most frequent (> 5%) were neutropenia and neutrophil count decreased which occurred at higher frequency in the FTD/TPI + Bev group (41.5% *vs* 29.3% and 8.9% *vs* 5.3%, respectively). Although the FTD/TPI + Bev group had higher incidence of neutropenia, the incidence of febrile neutropenia was lower in this group *vs* FTD/TPI (0.4% *vs* 2.4%). Serious EAEs occurred at lower frequency in the FTD/TPI + Bev group than in the FTD/TPI group (24.8% *vs* 31.3%), with no relevant between-group difference for any of the serious EAEs.

This phase III study met its primary objective by demonstrating the superiority of the combination FTD/TPI with bevacizumab over FTD/TPI monotherapy in terms of OS in patients with refractory mCRC and showed that the safety profile of the combination FTD/TPI with bevacizumab was generally consistent with that of each drug toxicity profile except for an increased incidence of neutropenia events compared to FTD/TPI monotherapy.

Date of the report: 02 December 2022

Version of the report: Final Version