Synopsis

Name of active ingredient: Trifluridine/tipiracil
Title of study: Prospective, multicenter, open-label phase IV trial of trifluridine/tipiracil to evaluate the health-related quality of life in patients with metastatic colorectal cancer **Protocol code:** Tallisur **EudraCT no.:** 2017-000292-83
Number of study center(s): 44 study centres in Germany
Studied period: **Date first patient registered:** 22 September 2017 **Date last patient completed:** 24 December 2020
Phase of development: IV
Background and rationale for the study: In Germany, 60,580 new cases of colorectal cancer were diagnosed in 2013, 33,370 of which in men. The 5-year survival rates in patients with metastatic colorectal cancer (mCRC), representing Stage IV CRC, reached only about 15%. Although the outcome of patients with mCRC had already improved with median survival reaching more than 30 months in clinical trials, more treatment options were needed for patients with disease progression after fluoropyrimidine (5-FU), irinotecan, oxaliplatin, applicable anti-VEGF agents and anti-EGFR agents or those unable to tolerate these agents. FTD/TPI (Lonsurf®) was authorized in the EEA in April 2016 for treatment of patients of these patients. Quality of life is very important in an end-of-life situation for patients with severe tumour disease that has already been treated and thus only limited further treatment options. Health-related quality of life (HR-QoL) is used to describe the impact of treatment on the patient's functioning regarding physical health (including disease-related morbidity), social, emotional, cognitive and role aspects. Facing the limited prolongation of overall survival under treatment with FTD/TPI (7.2 months compared to 5.2 months with placebo), HR-QoL in this end-of-life situation is even more important. Changes of HR-QoL during and after treatment with FTD/TPI had not previously been investigated in clinical trials in patients with mCRC. Thus, this trial was designed to investigate the HR-QoL in patients treated with FTD/TPI and those who were treated with BSC while being suitable for treatment with FTD/TPI according to the SmPC. It had to be the explicit and informed choice of the patient to limit the treatment to BSC. This design of a controlled trial with BSC as appropriate comparative treatment had been chosen according to advice by the German Federal Joint Committee (GB-A). The planned trial was performed in the approved patient population to analyze HR-QoL as practice-related care research, taking into account common treatment practice in oncology in Germany. Quality of life was assessed by means of the EORTC QLQ-C30. Additionally, the EQ-5D-5L

questionnaire was used as an instrument for evaluation of HR-QoL. The trial design also took into account the G-BA's request for further patient-relevant data with regard to HR-QoL, disease-related morbidity, and progression vs. FTD/TPI-associated adverse reactions as discussed with the G-BA.

Objectives:

Primary objective

To evaluate the effect of treatment with FTD/TPI on HR-QoL as measured by EORTC QLQ-C30 global health status / quality of life scale (QL2)

Secondary objectives

- To assess HR-QoL measured with EORTC QLQ-C30 (all scales and items) and EQ-5D-5L questionnaires under FTD/TPI and BSC
- To evaluate time-to-event measures under treatment with FTD/TPI and in those only observed and given BSC
- To evaluate safety of treatment with FTD/TPI

Methodology: This was a prospective multicenter, open-label, interventional phase IV trial without randomisation or blinding. The study was conducted in two groups of patients: patients who received treatment with FTD/TPI according to the SmPC for Lonsurf® (Group A) and patients who, while being suitable for treatment with FTD/TPI (Group B) according to the SmPC, received BSC and were closely observed. It had to be the explicit and informed choice of the patient to remain without any active anti-tumour treatment and to limit the treatment to BSC.
The FTD/TPI dosage was calculated according to the body surface area (BSA). FTD/TPI was administered orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as a benefit was observed or until unacceptable toxicity occurred. The starting dose was 35 mg/m^2 BSA/dose given twice daily; the dosage was, however, not allowed to exceed 80 mg per dose.
Patient-reported HR-QoL was analysed in patients with mCRC suitable for treatment with FTD/TPI using EORTC QLQ-C30 and EQ-5D-5L questionnaires on Day 1 of every treatment/close observation cycle or within 2 days before the start of the cycle, at the end of treatment/close observation visit, after every month from Month 1–6 of the follow up (FU) and after Month 9 and 12 of follow up for a maximum duration of one year after the start of treatment/close observation for the individual patient. (With Amendment 4, protocol version 6.0, dated 29 April 2019 and approved on 25 May 2019, an exception regarding patients who received FTD/TPI treatment for more than 1 year (Group A) was introduced; questionnaires were scheduled for the duration of treatment, at the end of treatment visit and at month 1 of the follow up.)
Furthermore, efficacy parameters (OS, PFS, exploratory analysis of ORR, TTP) and safety parameters (type, incidence and severity of FTD/TPI-related adverse reactions; tumour-related symptoms and adverse events; treatment duration/exposure to FTD/TPI [treatment duration/exposure to FTD/TPI only in Group A]; ECOG PS) were measured. Groups A and B were analysed separately. Patients in Group A were furthermore analysed separately depending on whether they received treatment ≥2 cycles or discontinued treatment permanently earlier (<2 cycles treatment duration).

Number of patients:
Planned: 195 patients
Enrolled: 202 patients

Diagnosis and main criteria for inclusion and exclusion:
Adult patients with histologically or cytologically confirmed UICC stage IV carcinoma of the colon or rectum with metastasis (metastatic colorectal cancer, mCRC), at least one measurable or non-measurable lesion as defined by RECIST version 1.1, adequate organ function and any ECOG performance status, who had been previously treated with or had not been considered candidates for available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents and anti-EGFR agents.

The major exclusion criteria included previous treatment with FTD/TPI, concurrently active malignancies other than mCRC, intestinal obstruction and any other severe concomitant disease or disorder, which could have influenced the safety of the patient during the clinical study.

Test product, dose and mode of administration, batch number(s):
FTD/TPI was given as film-coated tablets Lonsurf® 15 mg/6.14 mg (containing 15 mg FTD and 6.14 mg TPI) and/or Lonsurf® 20 mg/8.19 mg (containing 20 mg FTD and 8.19 mg TPI) according to the body surface area (BSA). FTD/TPI (starting dose 35 mg/m^2 BSA/dose) was administered orally twice daily (BID) on Days 1 to 5 and Days 8 to 12 of each 28-day cycle. The dosage was not allowed to exceed 80 mg per dose. FTD/TPI was prescribed; batch numbers were thus not listed.

Duration of treatment:
FTD/TPI was given in 28-day cycles for as long as benefit was observed or until unacceptable toxicity occurred.

Reference therapy, dose and mode of administration, batch number(s):
Placebos or active comparators were not used.

Endpoints:

Primary endpoint

Rate of responders with continued unchanged or improved HR-QoL.

Response was calculated as the mean of the score of the EORTC QLQ-C30 global health status/quality of life scale (QL2) at all scheduled time points of HR-QoL analysis in the time interval from two days before start of Cycle 2 until the end of treatment/end of close observation compared to the baseline score of the global health status/quality of life (QL2) scale.

Response was defined as improvement (≥10 scores) or stabilization (>-10 and <10 scores) compared to the baseline score.

The rate of responders was defined as the proportion of patients with response, i.e. improvement (≥10 scores) or stabilization (>-10 and <10 scores) of the EORTC QLQ-C30 global health status/ quality of life (QL2) score compared to the baseline score.

Secondary endpoints

Quality-of-life

- Rate of responders in the HR-QoL analysis (measured by the EORTC QLQ-C30 global health status/QoL (QL2) scale) at every scheduled time point for EORTC QLQ-C30 separately in the time interval from two days before start of Cycle 2 until end of treatment/end of close observation at every time point compared to the baseline score of the global health status/QoL (QL2) scale.
- Response was defined as improvement (≥10 scores) or stabilization (>-10 and <10 scores) compared to the baseline score.
- HR-QoL analysis measured by the EORTC QLQ-C30 questionnaire (all scales/single items; all time points from baseline until end of follow up)
- HR-QoL analysis measured by the questionnaire EQ-5D-5L descriptive system (all time points from baseline until end of follow up)
- Scores of the EQ VAS as a measure of overall self-rated health compared to baseline EQ VAS score (all time points until end of follow up)
- Time to HR-QoL deterioration measured by EORTC QLQ-C30 global health status/QoL (QL2) scale (deterioration defined as a first change of score to <-10 compared to baseline score)
- Time to HR-QoL deterioration measured by EQ VAS score (deterioration compared to baseline EQ VAS score; deterioration defined as first numerical change in VAS of at least -10 scores compared to baseline)

- Disease-specific symptoms of the mCRC measured by the respective subdomains of the EORTC QLQ C30 symptom scales (fatigue, nausea and vomiting, appetite loss, pain, dyspnoea, constipation, diarrhoea)
- HR-QoL analysis measured by the EORTC QLQ-C30 questionnaire (all scales/single items; all time points from baseline until follow up, analysis of response) for the following comparisons (if applicable):
  - During treatment/close observation vs. after treatment/close observation
  - Treatment with FTD/TPI vs. close observation with BSC
  - During treatment/close observation (patients with ≥2 cycles) vs. during treatment/close observation (patients with <2 cycles and early progression in Cycle 1).
- HR-QoL analysis measured by the questionnaire EQ-5D-5L and the EQ VAS (all time points from baseline to follow up) for the following comparisons (if applicable):
  - During treatment/close observation vs. after treatment/close observation
  - Treatment with FTD/TPI vs. close observation with BSC
  - During treatment/close observation (patients with ≥2 cycles) vs. during treatment/close observation (patients with <2 cycles and early progression in Cycle 1).

<u>Efficacy</u>

- PFS (clinical or radiological progression)
- OS (calculated from start of treatment/close observation on study)
- Exploratory analysis of objective response rate (ORR)

<u>Safety</u>

- Type, incidence, and severity of FTD/TPI-related adverse reactions (severity evaluated according to common terminology criteria for adverse events [CTCAE; version 4])
- Tumour-related symptoms and adverse events
- Treatment duration/exposure to FTD/TPI (only Group A).

Statistical methods:

The primary endpoint (rate of responders with regard to the EORTC QLQ-C30 global health status/QoL (QL2) scale) was analysed based on Group A (patients with ≥2 cycles FTD/TPI) and Group B (patients with ≥2 cycles close observation) using 95% confidence intervals (exact method). According to the statistical considerations, response rates of 45% ±10% (Group A) and 45% ±20% (Group B) were considered appropriate and the strategy considered successful if the lower boundary of the 2-sided 95% confidence interval was ≥35% for Group A and ≥25% for Group B.
HR-QoL was scored according to the algorithm described in the respective scoring manual. HR-QoL was analysed stratified by visit and Group A (treatment with FTD/TPI ≥2 cycles and <2 cycles separately), and Group B (BSC). Absolute and relative changes of HR-QoL scores from baseline were summarised stratified by group and by time point. A frequency table demonstrated change categories of scores, decrease by at least 10 scores, increase by at least 10 scores and no substantial (i.e., minimally clinically meaningful) change. Change categories of scores in % were analysed in the same way.
Time-to-event data were analysed according to the Kaplan-Meier analysis (product-limit method) and presented graphically (one graphic for each group). Patients who had not reached the endpoint by the time of the analyses were censored with the last date at which it was known that they had been event-free if not stated otherwise.
Groups or subgroups were not compared if not stated otherwise.

Summary of results and conclusions:

Disposition of patients and analysis sets

A total of 202 patients were enrolled in this clinical study. 195 of the enrolled patients entered the treatment/close observation period; these included patients who received at least one FTD/TPI treatment (186 patients, Group A) or started BSC and close observation (9 patients, Group B). Patient disposition information and analysis sets are given in Table 1 and Table 2.

Table 1: Patient disposition of included patients

Disposition of patients	Group A (FTD/TPI) N=190		Group B (BSC) N=12		All N=202	
	n (%)		n (%)		n (%)	
Enrolled	190		12		202	
Not entering treatment/close observation period	4		3		7	
Entering treatment/close observation period/included (≥1 treatment/start of BSC)	186	(100.0)	9	(100.0)	195	(100.0)
End of treatment						
Disease progression (acc. to RECIST 1.1)	95	(51.1)	1	(11.1)	96	(49.2)
Diesease progression (clinical)	23	(12.4)	-	-	23	(11.8)
Adverse events (excl. death; treatment-related)	7	(3.8)	-	-	7	(3.6)
Adverse events (excl. deaths; not treatment-related)	18	(9.7)	1	(11.1)	19	(9.7)
Death	10	(5.4)	3	(33.3)	13	(6.7)
Patient refused further treatment	8	(4.3)	-	-	8	(4.1)
Withdrawal of consent	4	(2.2)	1	(11.1)	5	(2.6)
Physician's decision	6	(3.2)	-	-	6	(3.1)
Loss of contact	2	(1.1)	1	(11.1)	3	(1.5)
Start of further anti-tumour therapy	-	-	2	(22.2)	2	(1.0)
Protocol violation	2	(1.1)	-	-	2	(1.0)
Patient non-compliance	1	(0.5)	-	-	1	(0.5)
Other	10	(5.4)	-	-	10	(5.1)

Table 2: Analysis sets

Analysis sets	Group A (FTD/TPI) N=186		Group B (BSC) N=9		All N=195	
	n (%)		n (%)		n (%)	
Full analysis set / Safety set	186	(100.0)	9	(100.0)	195	(100.0)
FAS-C30	123	(100.0)	6	(100.0)	129	(100.0)
FAS-C30 evaluable for primary endpoint	106	(86.2)	6	(100.0)	112	(86.8)
FAS-EQ	122	(100.0)	6	(100.0)	128	(100.0)
Per protocol set	165	(100.0)	6	(100.0)	171	(100.0)

Demography and baseline characteristics

The majority of all patients were men (62.6%) and Caucasian (99.0%). The median age was 67.0 years (range: 40–88 years); the proportions of patients of ≥65 years of age was higher in Group B (77.8%) than in Group A (60.2%). Most patients had an ECOG performance status (PS) of 1 (50.3%). However, the proportion of patients with a higher ECOG PS was larger in Group B than in Group A. Almost all patients (96.9%) had past illnesses and ongoing pre-existing conditions recorded that were consistent with the usual health condition of the elderly (including hypertension and diabetes mellitus) and the underlying disease.

All patients had a UICC stage IV carcinoma of the colon or rectum with metastasis. Metastatic disease had in the majority of patients been diagnosed within 6 months after the first diagnosis (106 patients, 54.4%). 164 of all patients (84.1%) had a previous surgery of the primary tumour and 89 patients a surgery of one or more metastases (45.6%). 56 of all patients (28.7%) had previously

received radiation therapy. All patients of the FAS had previously received systematic anti-CRC therapies. 195 patients (100.0%) had previously received fluoropyrimidine; for most of the patients, therapies included oxaliplatin (93.3%), irinotecan (90.8%), and / or bevacizumab (81.0%). The majority of patients (161 patients, 83.0%) had previously received at least two therapy lines for the treatment of the mCRC.

Extent of exposure:
186 patients of the 202 enrolled patients were treated with FTD/TPI. These patients received treatment for a mean (±SD) treatment duration of 102.1 ±119.1 days (median: 68 days, range: 1.0–719.0 days) in a mean (±SD) number of 3.9 ±3.8 cycles (median: 3.0 cycles, range: 1.0–23.0 cycles). The mean (±SD) cumulative FTD/TPI dose administered was 617.2 ±112.2 mg/m^2 (median: 657.4 mg/m^2, range: 32.5–743.9 mg/m^2). The mean (±SD) FTD/TPI dose intensity was 90.8 ±16.5% (median: 98.1%, range: 4.7–110.0%).

Quality-of-life results
The primary endpoint was the rate of responders with regard to the EORTC QLQ-C30 global health status/QoL (QL2) scale defined as the proportion of patients with improvement (≥10 scores) or stabilization (>-10 and <10 scores) of the EORTC QLQ C30 global health status/QoL (QL2) score compared to the baseline score. All patients evaluable for the primary endpoint had received at least two cycles of FTD/TPI treatment with FTD/TPI given on at least 5 days in Cycle 2, filled in a baseline EORTC QLQ-C30 questionnaire and at least one additional EORTC QLQ-C30 questionnaire after Cycle 1. The rate of responders in the population evaluable for the primary endpoint was 58.5% for FTD/TPI-treated patients (Group A); 95% CI: 48.6–68.0) and 50.0% for patients receiving BSC (Group B; 95% CI: 11.8–88.2). According to the statistical considerations, response rates of 45% ±10% (Group A) and 45% ±20% (Group B) were considered appropriate and the strategy considered successful if the lower boundary of the 2-sided 95% confidence interval was ≥35% for Group A and ≥25% for Group B. Therefore, response was achieved for Group A but not for Group B as the lower boundary for the respective confidence interval in Group B was <25%. However, the results for Group B have to be considered with caution due to the small sample size of less than the planned 24 patients.

Results from the HRQoL analysis indicate only a slight worsening of the quality of life during FTD/TPI treatment; for most of the mean scores for the global health status/QoL, functioning and symptom scales/items, only slight deteriorations of less than 10 points compared to baseline for patients in Group A during FTD/TPI treatment. Results after discontinuation of treatment indicate a further slight worsening; compared to values under treatment, a deterioration of the mean scores by more than 10 points compared to the baseline scores was observed.

The estimated median time to deterioration of the EORTC QLQ-C30 global health status/QoL (QL2) score was 121 days (95% CI: 84.0–172.0) for FTD/TPI-treated patients (Group A) and 104 days (95% CI: 60.0– -) for patients receiving BSC (Group B). Similarly, the estimated median time to deterioration of the EQ VAS was 113 days (95% CI: 85.0–140.0) for FTD/TPI-treated patients (Group A) and 104 days (95% CI: 60.0– -) for patients receiving BSC (Group B).

Efficacy results
Patients receiving FTD/TPI (Group A of the FAS) had a median OS of 6.9 months (95% CI: 6.1–8.3), PFS of 2.5 months (95% CI: 2.1–2.9) and a median TTP of 2.5 months (95% CI: 2.1–3.1). The ORR was 2.2% for FTD/TPI-treated patients with PR as BOR. Patients receiving BSC (Group B of the FAS) had a median OS of 4.7 months (95% CI: 3.6–11.6), a median PFS of 3.7 months (95% CI: 2.2–4.7) and a median TTP of 2.2 months (95% CI: 0.8–2.3). No patient receiving BSC had an objective response or stable disease; however, it has to be noted that there was no mandatory interval for tumour assessment by means of imaging procedures for patients in Group B.

Details on efficacy parameters are given in Table 3.

Table 3: Efficacy parameters (FAS)

Efficacy parameter	Group A (FTI/TPI)			Group B (BSC) N=9	All N=195
	<2 cycles N=27	≥2 cycles N=159	All Group A N=186		
PFS, months [median (95% CI)]	1.4 (1.1–1.7)	2.8 (2.2–3.3)	2.5 (2.1–2.9)	3.7 (2.2–4.7)	2.5 (2.2–3.1)
OS, months [median (95% CI)]	2.7 (2.4–4.7)	7.7 (6.6–11.1)	6.9 (6.1–8.3)	4.7 (3.6–11.6)	6.8 (6.0–8.2)
TTP, months [median (95% CI)]	1.4 (1.2–1.7)	2.8 (2.2–3.4)	2.5 (2.1–3.1)	2.2 (0.8–2.3)	2.5 (2.1–2.9)
ORR [n (%) (95% CI)]	0 (0.0) (0.0–12.8)	4 (2.5) (0.7–6.3)	4 (2.2) (0.6–5.4)	0 (0.0) (- –33.6)	4 (2.1) (0.6–5.2)

Safety results:
At least one TEAE was recorded for 179 of the 186 FTD/TPI-treated patients (96.2%, Group A) and 7 of the 9 patients receiving BSC (77.8%, Group B). The most frequently reported TEAEs occurring in ≥10% of the FTD/TPI-treated patients (Group A) were neutropenia, anaemia, nausea, fatigue, diarrhoea, leukopenia, decreased appetite, vomiting, constipation, neoplasm progression, dyspnea, and oedema. The most frequently reported TEAEs with a suspected causal relationship to FTD/TPI occurring in ≥10% of the FTD/TPI-treated patients (Group A) were neutropenia, anaemia, leukopenia, nausea, fatigue, diarrhoea, and vomiting.
125 FTD/TPI-treated patients (67.2%, Group A) and 6 patients receiving BSC (66.7%, Group B) had TEAEs of Grade ≥3. TEAEs of Grade ≥3 occurring in ≥10% of the FTD/TPI-treated patients (Group A) were neutropenia and leukopenia.
TESAEs were reported for 83 patients (44.6%) treated with FTD/TPI (Group A) and for 5 patients (55.6%) who received BSC (Group B). 18 of the FTD/TPI-treated patients (9.7%, Group A) had TESAEs with a suspected relationship to FTD/TPI treatment, and 55 (29.6%) had TESAEs that were not considered related to FTD/TPI treatment but to tumour progression. The most common TESAEs with a suspected relationship to FTD/TPI treatment were anaemia, acute kidney injury, diarrhoea and neutropenia, each occurring in only 2 to 4 patients.
26 patients had TEAEs that resulted in death (25 patients, 13.4%, Group A; 1 patient, 11.1%, Group B), none of which had a suspected relationship to FTD/TPI treatment; 24 deaths were considered related to tumour progression.
53 patients discontinued study treatment due to a TEAE (28.5%, Group A). For most of those patients (40 patients, 21.5%), tumour progression was considered the cause of the TEAE, while a relationship to study treatment was suspected in 16 patients (8.6%). The most common TEAEs leading to discontinuation of study treatment in patients treated with FTD/TPI (Group A, incidence ≥3 patients) were neoplasm progression, fatigue, cholestasis, vomiting anaemia, acute kidney injury, ascites, cholangitis, general physical health deterioration, nausea, and pneumonia.

The time to deterioration of the ECOG PS was defined as the duration to worsening of the ECOG PS by ≥2 grades compared to baseline or to death from any cause. 156 patients had a deteriorated ECOG PS (149 patients, Group A; 7 patients, Group B). The calculated median time to deterioration of the ECOG PS was 6.4 months (95% CI: 5.8–7.4) for patients treated with FTD/TPI (Group A) and 3.7 months (95% CI: 3.0–5.0) for patients receiving BSC (Group B).

Conclusions:
The results of this phase IV clinical study support the following conclusions:

- Adult patients with stage IV carcinoma of the colon or rectum with metastases who have previously been treated with or are not considered candidates for available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents can largely maintain their health-related quality of life while on FTD/TPI therapy.

- The safety profile of FTD/TPI-treated patients observed in this clinical study is largely consistent with the safety profile established for FTD/TPI to date with neutropenia, anaemia, leukopenia, nausea, fatigue, diarrhoea, and vomiting as the most frequently (incidence ≥10%) observed treatment-emergent adverse events with a suspected causal relationship to FTD/TPI.
- Furthermore, the safety data of the present clinical study suggest that adverse events related to FTD/TPI may be less often serious, may lead to fewer deaths and less often to discontinuation of FTD/TPI treatment than adverse events related to tumour progression.
- The efficacy results observed in this clinical study for FTD/TPI-treated patients are generally consistent with previously published data from the RECOURSE clinical study (NCT01607959).
- Although possible differences between groups have to be considered with caution since Group A and Group B were separately analysed and the results summarised descriptively, the data suggest that health-related quality of life was at least equivalent in patients treated with FTD/TPI to HR-QoL in those receiving BSC. Moreover, the data suggest advantages for FTD/TPI over BSC regarding efficacy, and no relevant safety differences.
- Based on the HR-QoL results and the acceptable safety profile confirmed in this clinical study, the oral intake of FTD/TPI, which can conveniently be done at home, is a treatment option for patients with final stage mCRC.

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