FINAL QUALITY OF LIFE RESULTS OF THE NON-INTERVENTIONAL STUDY TACTIC

TRIFLURIDINE/TIPIRACIL IN PATIENTS WITH METASTATIC COLORECTAL CANCER IN CLINICAL ROUTINE IN GERMANY

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INTRODUCTION

Trifluridine/tipiracil (FTD/TPI; Lonsurf®), an oral nucleoside antitumor agent, is indicated as monotherapy for treatment of adult patients with metastatic colorectal cancer (mCRC), who had been previously treated with or who are not considered candidates for other available therapies.[1]

In the pivotal RECOURSE trial, FTD/TPI demonstrated a significant improvement in overall and progression-free survival (OS, PFS) compared to placebo in patients with refractory and heavily pretreated (≥2 prior chemotherapy regimens) mCRC.[2,3] While time to deterioration (TTD) of ECOG performance status (PS) from 0/1 to ≥ 2 was significantly longer in patients treated with FTD/TPI, quality of life (QoL) was not formally assessed in the RECOURSE trial. To address the effect of FTD/TPI on QoL, the TACTIC study was designed to assess patient-reported outcomes (PROs) on QoL in German patients.

CONCLUSION

TACTIC is the largest German trial in a real-world setting investigating the effect of FTD/TPI treatment on mCRC patients. In addition to a manageable and well-known toxicity profile, OS and TTD of ECOG PS was comparable with the results of the phase III RECOURSE trial. Complementing the pivotal trial, administration of FTD/TPI was associated with maintained patient-reported QoL, a paramount attribute of therapies for patients with late-stage cancer.

METHODS

In the prospective, multicenter, non-interventional study TACTIC, 307 patients were treated with FTD/TPI at 52 German sites between 06/2018 and 08/2021. Effectiveness and QoL were evaluated in patients treated with at least one dose of FTD/TPI according to SmPC (35 mg/m² twice a day on days 1 to 5 and 8 to 12 of each 28-day cycle).

PROs on QoL were assessed using the validated questionnaires EQ-5D-5L and PRO-CTCAE. For each individual patient, questionnaires were evaluated at baseline, at each treatment cycle and after months 1, 3, 5, 7, 9 and 11 of the follow-up period for a maximum duration of one year after the first intake of FTD/TPI. Scores for scales, subscales and single items were calculated according to the respective manual[4] or validation paper[5].

OS was defined as the primary endpoint. Secondary endpoints included PFS, QoL and safety. Time-to-event endpoints were estimated by the Kaplan-Meier method. In the OS analysis, patients with no documented date of death were censored at the date of last contact. In the PFS analysis, patients with neither progression nor documented date of death or patients having started a new therapy before progression were censored at the date of last contact or at the start date of a subsequent antineoplastic therapy, whatever came first, respectively. TTD of ECOG PS was defined as the time from the first intake of FTD/TPI to date of first deterioration from a baseline value of 0/1 to ≥2. Patients with no event were censored at the date of last contact.

As for safety, an AE was classified as a treatment-emergent AE (TEAE), if it had emerged or worsened in the on-treatment period defined as the time from the day of first dose to the day of last dose of study medication. Only AEs classified as TEAEs were included in the analysis. Severity of AEs were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

RESULTS

The total evaluable population for effectiveness analysis compromised 300 patients with a median age of 67.7 years and 58.0% male patients. 81.0% of patients had an ECOG PS of 0/1 at baseline. 79.0% of patients had ≥2 prior treatment lines. Patient characteristics are detailed further in **Table 1**.

In total, a median OS of 7.4 months (95% CI: 6.4-8.6) and a median PFS of 2.9 months (95% CI: 2.8-3.3) was reached. The mean (±SD) duration of FTD/TPI treatment was 14.8±14.4 weeks (median 9.6 weeks, range 0 to 93.4 weeks).

In TACTIC, the median TTD from a ECOG PS baseline value of 0/1 to a value ≥2 was 5.4 months (95%CI: 4.2-6.1) and similar to the RECOURSE trial in which the median time to an ECOG PS of ≥2 was 5.7 months in FTD/TPI treated patients versus 4.0 months in the placebo group[2] (see **Table 2**).

Patient-reported QoL as assessed by EQ-5D-5L visual analogue scale (VAS) was maintained throughout FTD/TPI treatment (**Figure 1**). Median TTD of the VAS score was 3.3 months (95% CI: 2.8-4.3).

This was also reflected in all 5 dimensions assessed (anxiety/depression, problems with mobility, pain/discomfort, problems with self-care, and problems with usual activities) for which the relative frequency at baseline and over time are depicted in **Figure 2**.

No clinically relevant difference from baseline (i.e., no change in the median score by at least 10 points) was observed over time during FTD/TPI treatment in all cluster scores of the PRO CTCAE questionnaire: anxiety and sadness, appetite loss, constipation, diarrhea, dyspnea, fatigue, insomnia, mental concentration, mucositis and xerostomia, nausea, vomiting, numbness and tingling, pain (data not shown).

In the safety population (n=307 patients), 47.6% of patients were reported with an AE grade ≥3. The documented AEs are detailed further in **Table 3**.

Subsequent antineoplastic therapy was reported in 45.7% of patients; the most frequently used regimens were FOLFOX (5.0%), regorafenib (3.0%), capecitabine (2.7%), and FOLFOX + bevacizumab (2.3%).

Table 1

	Total population (n=300)
Age (years)	
Median (min – max)	67.7 (33.4-90.5)
Sex	
Male	174 (58.0%)
ECOG	
0	72 (24.0%)
1	171 (57.0%)
≥2	51 (17.0%)
Missing	6 (2.0%)
Number of prior palliative treatment lines	
0	2 (0.7%)
1	61 (20.3%)
2	130 (43.3%)
≥3	107 (35.7%)
Substances of prior anti-neoplastic therapies	
Fluoropyrimidine-based	294 (98.0%)
Irinotecan-based	268 (89.3%)
Bevacizumab	226 (75.3%)
Anti-VEGF	59 (19.7%)
Oxaliplatin-based	225 (75.0%)
Anti-EGFR	101 (33.7%)
Other	10 (3.3%)
Regorafenib*	1 (0.3%)

* Regorafenib has been withdrawn from the German market.

Table 1: Patient and disease characteristics (N=300)

Table 2

	RECOURSE[2]	TACTIC
Baseline ECOG PS	≤1 (n = 534)	≤1 (n = 243)
Median TTD of ECOG PS (months (95% CI))	5.7	5.4 (4.2-6.1)

Table 2: TTD of ECOG PS of 0/1 to ≥2

Time to deterioration of ECOG PS for patients with a baseline of 0/1, which was defined as the time from the first intake of FTD/TPI to date of first deterioration to a value ≥2. TTD = Time To Deterioration

Figure 1

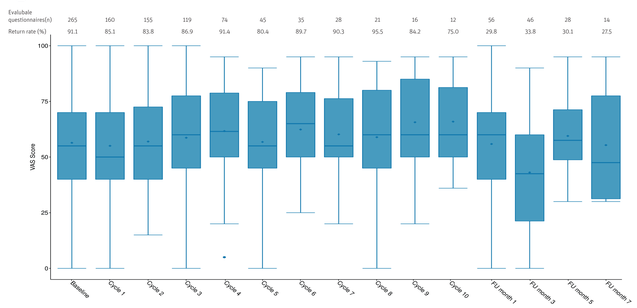

Figure 1: EQ-5D-5L VAS score

The EQ-5D-5L visual analogue scale (VAS) score and questionnaire return rates (number of evaluable questionnaires/handed out questionnaires) are depicted at baseline and during FTD/TPI treatment and follow-up. Only timepoints with more than 10 evaluable questionnaires (i.e., at least one questionnaire item was answered at respective time point) are shown. Higher scores indicate a better quality of life. Box: lower to upper quartile; horizontal line inside box: median; diamond inside box: mean; whisker: minimum/maximum value within lower quartile minus 1.5x interquartile range / upper quartile plus 1.5x interquartile range, respectively; n: number of evaluable questionnaires

Table 3

	Any grade		Grade ≥3	
	Cases	n (%)	Cases	n (%)
Any	1000	238 (77.5%)	291	146 (47.6)
Anemia	81	63 (20.5)	27	25 (8.1)
Leukopenia	110	57 (18.6)	32	23 (7.5)
Neutropenia	101	52 (16.9)	60	40 (13.0)
Nausea	50	40 (13.0)	3	3 (1.0)
Diarrhea	42	36 (11.7)	1	1 (0.3)
Fatigue	39	36 (11.7)	3	3 (1.0)
Vomiting	29	23 (7.5)	1	1 (0.3)
Decreased appetite	19	18 (5.9)	0	0
Thrombo-cytopenia	21	17 (5.5)	3	3 (1.0)

Table 3: Most frequent treatment-emergent AEs (N=307)

Figure 2

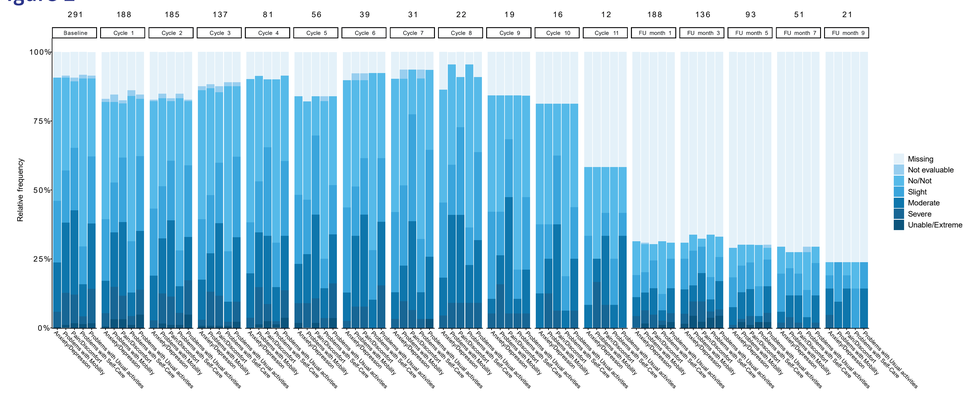

Figure 2: Relative frequency at baseline and over time

The relative frequency of answers given to the EQ-5D-5L dimensions problems with mobility, problems with self-care, problems with usual activities, pain/discomfort and anxiety/depression are depicted for each time point during which at least 10 questionnaires were handed out. When interpreting these results, patients who benefited most from therapy are overrepresented and only patients alive at the respective time point were able to be analyzed (Survivor bias). N: number of handed-out questionnaires at the respective time point.

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Conflicts of interest

Schwaner I: Consultancy for Abbvie, AstraZeneca, Beigene, Janssen, Novartis, Roche; Honoraria from AbbVie, Amgen, AstraZeneca, Beigene, Celgene, Incyte, Janssen, Novartis, Roche, Servier. Travel funds from Servier. **Kröning H**: Consultancy for Servier. **Decker T**: Consultancy for Novartis; Executive board iOMEDICO. **Sauer A**: Honoraria from Novartis, Janssen, Pfizer, Servier, Amgen. **Bruch HR**: Consultancy for cpu. **Nusch A**: Honoraria from Roche, Novartis, AstraZeneca. **Welslau M**: Consultancy for AMGEN, Bristol-Myers Squibb, Celgene, GILEAD, HEXAL, Janssen, Lilly, medac, NOVARTIS, Roche, SANOFI; Honoraria from AMGEN, astellas, AstraZeneca, Celgene, GILEAD, HEXAL, Janssen, Lilly, NOVARTIS, Roche, SANOFI. **Harich HD**: Shareholder of iOMEDICO. **Uhlig J**: Consultancy for Roche, Amgen, Servier, MSD, Bristol-Myers Squibb, Sanofi, Merck, Celgene, Novartis, Janssen-Cilag, Boehringer-Ingelheim und Bayer, Biogene. **Hartmann F**: Employee of Servier Deutschland GmbH. **Reisländer T**: Employee of Servier Deutschland GmbH. **de Buhr R**: Employee of iOMEDICO. Travel funds from Servier. **Marschner N**: CEO of iOMEDICO; Consultancy for AstraZeneca, Bayer, Beigene, BMS, Clovis, Daiichi-Sankyo, Deloitte, Eusapharm, EISAI, GSK, IPSEN, J&J, Lilly, MSD, Mylan, Novartis, Oncopeptides, Onkovis, Pfizer, Pierre Fabre, Roche, Sanofi, Seagen, Servier. Share holder of iOMEDICO. Research funding from AbbVie, Amgen, AstraZeneca, Bayer, Beigene, BMS, Clovis, Daiichi-Sankyo, Deloitte, Eusapharm, EISAI, Gilead, GSK, IPSEN, J&J, Lilly, Morphosys, MSD, Mylan, Novartis, Oncopeptides, Onkovis, Pfizer, Pierre Fabre, Roche, Sanofi, Seagen, Servier. **Frank M, Hogrefe C, Potthoff K**: Employee of iOMEDICO. **Göhler T, Grundeis M, Kojouharoff G, Lipke J, Semsek D, Moorahrend E, Liersch R, Vehling-Kaiser U, Grunewald R, Stephany M**: No conflicts of interest.

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