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Trifluridine/tipiracil (colorectal cancer) –

Addendum to Commission A20-35[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCRC	metastatic colorectal cancer
QLQ-C30	Quality of Life Questionnaire-Core 30
SAE	serious adverse event
VAS	visual analogue scale

1 Background

On 10 August 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-35 (Trifluridine/tipiracil – Benefit assessment according to §35a Social Code Book V) [1].

The randomized controlled trials TPU-TAS-102-301 (RECOURSE) and 10040090 (TERRA) were included for the benefit assessment of trifluridine/tipiracil in adult patients with metastatic colorectal cancer (MCRC) who have been previously treated with, or are not considered candidates for, available therapies.

In the dossier assessment, the subgroup characteristic "number of prior regimens" (2 versus ≥ 3) was considered as subgroup characteristic [1], as a statistically significant subgroup effect for overall survival was determined and a different added benefit for these 2 subgroups was derived in the addendum to the first assessment [2,3]. In Module 4 of the dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"), corresponding subgroup analyses were only available for the RECOURSE study [4]. This subgroup analysis was not available for the relevant subpopulation of the TERRA study. It was therefore not possible to conduct a meta-analytical summary of the results. Based on the results of the RECOURSE study, an effect modification was shown regarding the subgroup characteristic "number of prior regimens" (2 versus ≥ 3), and the overall conclusion on the added benefit was drawn separately for patients with 2 or ≥ 3 prior regimens.

In the framework of the commenting procedure, the company provided the subgroup analyses for overall survival by number of prior regimens (2, 3, ≥ 4) for the relevant subpopulation of the TERRA study [5]. It additionally presented a meta-analysis of the results on the subgroup characteristic "number of prior regimens" from the studies RECOURSE and TERRA.

In addition to the studies RECOURSE and TERRA, the company also included the non-randomized study IC4-95005-183-DEU (TALLISUR), which it conducted to fulfil the G-BA's condition of the limitation from the first assessment in 2016. In contrast to the studies RECOURSE and TERRA, the TALLISUR study also recorded patient-relevant outcomes on morbidity and health-related quality of life. The TALLISUR is unsuitable for the benefit assessment, however, and the results of this study were therefore not used for the benefit assessment of trifluridine/tipiracil.

The G-BA commissioned IQWiG with the assessment of the following additional data submitted by the company under consideration of the information provided in the dossier [1]:

- subgroup analysis on the characteristic "number of prior regimens" for overall survival of the relevant subpopulation of the TERRA study

- meta-analysis of the subgroup analysis on the characteristic “number of prior regimens” for overall survival from the studies RECOURSE and TERRA
- descriptive analysis of the data on quality of life from the TALLISUR study

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

In Module 4 of its dossier, the company did not present any subgroup analysis on the characteristic "number of prior regimens" for overall survival on the TERRA study. Hence, only the subgroup analyses from the RECOURSE study were available for the dossier assessment. Section 2.1 contains the assessment of the subgroup results of the TERRA study subsequently submitted by the company [5] and the meta-analytical summary with the results on the RECOURSE study already presented in the company's dossier.

In its dossier, the company based its conclusion on outcomes on morbidity, health status and health-related quality of life on results of the TALLISUR study, as the studies RECOURSE and TERRA did not record any outcomes from these outcome categories. However, the company considered a comparative analysis of the results as not meaningful due to the uneven distribution of patients in the treatment arms of the TALLISUR study. The company therefore used the curves of the change from baseline in the intervention arm. In its comments, the company presented further descriptive results on morbidity (health status) and health-related quality of life, recorded using the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) and the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) regarding the intervention arm of the TALLISUR study [5]. The interpretability of the TALLISUR study and of the data subsequently submitted is discussed in Section 2.2.

The derivation of the overall conclusion on the added benefit under consideration of dossier assessment A20-35 and the present addendum is conducted in Section 2.3.

2.1 Subgroup analysis on the characteristic "number of prior regimens" on overall survival of the studies TERRA and RECOURSE

In its comments, the company presented subgroup analyses on the characteristic "number of prior regimens" for the outcome "overall survival" for the TERRA study. Regarding further patient-relevant outcomes, the company did not present any analyses from the TERRA study on this subgroup characteristic. This had no consequences for the present addendum, as a statistically significant interaction on this subgroup characteristic in the RECOURSE study was shown only for overall survival. Even if an effect modification for another outcome was detectable in the TERRA study, this would probably not lead to the effect modification being detectable also across studies in the joint meta-analytical consideration with the RECOURSE study.

A description of the respective study and patient characteristics of the studies RECOURSE and TERRA can be found in the dossier assessment [1]. Based on the risk of bias described in the dossier assessment, no more than an indication, e.g. of an added benefit, can be determined for the results on overall survival on the basis of the meta-analysis of both studies.

Results on overall survival

The results of the subgroup analysis of the characteristic "number of prior regimens" for the outcome "overall survival" are presented in Table 1 and Figure 1.

Table 1: Subgroups (overall survival, time to event) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Outcome Characteristic	Trifluridine/tipiracil + BSC		Placebo + BSC		Trifluridine/tipiracil + BSC vs. placebo + BSC	
Study Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]	p-value
Overall survival						
Number of prior regimens[a]						
RECOURSE						
2	95	6.2 [4.7; 7.3] 88 (92.6)	45	4.8 [3.7; 7.2] 39 (86.7)	1.03 [0.69; 1.53]	0.892
≥ 3	439	NC 375 (85.4)[b]	221	NC 210 (95.0)[b]	0.63 [0.53; 0.75][c]	< 0.001[c]
3	*119*	*6.7 [5.9; 7.5]* *107 (89.9)*	*54*	*5.1 [3.5; 6.7]* *51 (94.4)*	*0.73 [0.52; 1.03]*	*0.073*
≥ 4	*320*	*7.8 [6.9; 9.2]* *268 (83.8)*	*167*	*5.5 [4.5; 6.2]* *159 (95.2)*	*0.60 [0.49; 0.73]*	*< 0.001*
TERRA						
2	8	4.7 [3.1; 6.3] 8 (100.0)	5	2.3 [1.0; 7.6] 5 (100.0)	0.48 [0.15; 1.58]	0.228
≥ 3	53	NC 45 (84.9)[b]	28	NC 24 (85.7)[b]	0.78 [0.47; 1.30][c]	0.342[c]
3	17	7.9 [4.1; 10.8] 15 (88.2)	5	4.9 [2.4; 19.4] 4 (80.0)	1.01 [0.33; 3.10]	0.989
≥ 4	36	8.7 [6.5; 9.9] 30 (83.3)	23	5.8 [3.4; 7.7] 20 (87.0)	0.73 [0.41; 1.29]	0.276
Total					Interaction	0.063[b]
2	103[b]	96 (93.2)[b]	50[b]	44 (88.0)[b]		
≥ 3	492[b]	420 (85.4)[b]	249[b]	234 (94.0)[b]		

a. Adjuvant, neoadjuvant and for the metastatic disease.
b. Institute's calculation.
c. Institute's calculation (meta-analysis) on the basis of the data on the subgroups with 3 and ≥ 4 prior regimens.

BSC: best supportive care; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least) one event; NC: not calculable; RCT: randomized controlled trial; vs.: versus

The meta-analysis of the studies RECOURSE and TERRA showed no statistically significant interaction by the characteristic "number of prior regimens" for the outcome "overall survival". Based on the new data, the results of the respective total populations already presented in dossier assessment A20-35 [1] were used for the assessment of the added benefit for the outcome "overall survival". On the basis of the total populations, the meta-analysis showed a statistically significant difference between the treatment arms in favour of trifluridine/tipiracil + best supportive care (BSC) in comparison with placebo + BSC for the outcome "overall survival" (hazard ratio [95% confidence interval]: 0.70 [0.60; 0.81]). This resulted in an indication of an added benefit of trifluridine/tipiracil + BSC in comparison with BSC.

2.2 Results on morbidity (health status) and health-related quality of life of the TALLISUR study

Results of TALLISUR unsuitable for descriptive analysis

In the TALLISUR study, morbidity (health status) and health-related quality of life were recorded using the instruments EQ-5D VAS and EORTC QLQ-C30. For the reasons described in the dossier assessment, the TALLISUR study was not used for a benefit assessment [1]. The company's comments could also not refute the points of criticism regarding the TALLISUR study. The results of the TALLISUR study are therefore still unusable for the assessment of an added benefit of trifluridine/tipiracil + BSC in comparison with BSC.

For the same reasons, conclusions on effects from a purely descriptive analysis are also not possible. This concurs with the assessment of the company, which did not consider a comparison of the treatment groups as meaningful and only provided a descriptive presentation of the results of the intervention arm on the EORTC QLQ-C30 and the EQ-5D VAS. However, a before-after comparison or a descriptive analysis of the results of the intervention arm on the basis of the available data are also associated with high uncertainty and low informative value and thus inadequate. This is justified below.

Table 2 and Table 3 show the proportions of patients with evaluable questionnaires on the EORTC QLQ-C30 and the EQ-5D VAS per 28-day treatment cycle. According to the information provided by the company in Module 4 of the dossier, the documentation time, i.e. the period in which the patients could complete the questionnaires and send them back, was to comprise the last 2 days of each 28-day cycle until the first day of the following cycle. This period was subsequently extended to the total treatment-free time of a cycle – from day 12 of a cycle to day 1 of the following cycle. The information provided in Table 2 and Table 3 refers to the extended period. Furthermore, data are only available for patients who submitted an evaluable questionnaire at the start of the study and ≥ 1 further evaluable questionnaire in a following cycle (referred to as "FAS-C30 population" in the company's dossier). However, about 1 third of the patients allocated to the treatment are not considered in this analysis population. There is no information on why such a large proportion of the treated patients is not included in the analysis population chosen by the company. The percentages in Table 2 and

Table 3 were therefore calculated based on the total number of the patients allocated to the respective treatment.

The tables show that a large proportion of treated patients in both treatment arms were not included in the analysis in the beginning of the recording, and that the proportions of patients with evaluable questionnaires were already below 70% at this early time point (see Table 2 and Table 3). In the further course of the study, these proportions continue to decrease sharply and are < 10% for both instruments in cycle 6. The company did not provide any information on the reasons for the low proportions of patients with evaluable questionnaires. It remains unclear what caused them. Hence, the descriptive results of the intervention arm are not usable due to the high uncertainty and the associated low informative value. The graphic display of the mean change from baseline by cycles for the EORTC QLQ-C30 and the EQ-5D VAS are presented as supplementary information in Appendix A. Since from cycle 6, the proportions of patients with evaluable questionnaires are < 10%, the results of the later cycles are not presented due to the additionally reduced informative value.

Table 2: Proportions of patients with evaluable questionnaires on the EORTC QLQ-C30, treatment-free period −16 to +1 days of a cycle (of 28 days) – non-RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (study TALLISUR) (multipage table)

Study / **Documentation time**	**Trifluridine/tipiracil + BSC** **N = 185**		**Placebo + BSC** **N = 9**	
TALLISUR	**Number of patients in the company's analysis population[a, b]**	**Proportion of patients with evaluable questionnaires n (%)[c]**	**Number of patients in the company's analysis population[a, b]**	**Proportion of patients with evaluable questionnaires n (%)[c]**
Questionnaire before cycle 1 (baseline)	126	126 (68.1)	6	6 (66.7)
Questionnaire 2 before cycle 2	126	113 (61.1)	6	5 (55.6)
Questionnaire 3 before cycle 3	82	69 (37.3)	4	3 (33.3)
Questionnaire 4 before cycle 4	51	45 (24.3)	3	2 (22.2)
Questionnaire 5 before cycle 5	35	25 (13.5)	1	0 (0.0)
Questionnaire 6 before cycle 6	21	16 (8.6)	0	0 (0.0)
Questionnaire 7 before cycle 7	14	12 (6.4)	0	0 (0.0)
Questionnaire 8 before cycle 8	12	11 (5.9)	0	0 (0.0)
Questionnaire 9 before cycle 9	12	10 (5.4)	0	0 (0.0)
Questionnaire 10 before cycle 10	9	8 (4.3)	0	0 (0.0)
Questionnaire 11 before cycle 11	7	6 (3.2)	0	0 (0.0)
Questionnaire 12 before cycle 12	4	3 (1.6)	0	0 (0.0)
Questionnaire 13 before cycle 13	4	4 (2.2)	0	0 (0.0)
Questionnaire 14 before cycle 14	1	1 (0.5)	0	0 (0.0)
Questionnaire 18 before cycle 18	1	1 (0.5)	0	0 (0.0)
End of treatment	97	97 (52.4)	4	4 (44.4)
Follow-up 2	1	1 (0.5)	1	0 (0.0)
Follow-up 3	28	28 (15.1)	2	1 (11.1)
Follow-up 4	37	37 (20.0)	2	1 (11.1)

Table 2: Proportions of patients with evaluable questionnaires on the EORTC QLQ-C30, treatment-free period −16 to +1 days of a cycle (of 28 days) – non-RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (study TALLISUR) (multipage table)

Study / **Documentation time**	**Trifluridine/tipiracil + BSC** **N = 185**		**Placebo + BSC** **N = 9**	
TALLISUR	**Number of patients in the company's analysis population[a, b]**	**Proportion of patients with evaluable questionnaires n (%)[c]**	**Number of patients in the company's analysis population[a, b]**	**Proportion of patients with evaluable questionnaires n (%)[c]**
Follow-up 5	47	47 (25.4)	2	1 (11.1)
Follow-up 6	47	47 (25.4)	2	1 (11.1)
Follow-up 7	44	44 (23.8)	2	1 (11.1)
Follow-up 8	39	39 (21.1)	2	2 (22.2)
Follow-up 9	30	30 (16.2)	2	1 (11.1)
Follow-up 10	30	30 (16.2)	2	0 (0.0)
Follow-up 11	25	25 (13.5)	1	0 (0.0)
Follow-up 12	20	20 (10.8)	1	0 (0.0)

a. Patients who had completed one evaluable questionnaire at baseline and ≥ 1 further evaluable questionnaire (referred to as "FAS-C30 population" in the company's dossier).
b. The company did not provide any information explaining the difference in the number of patients analysed by the company (FAS-C30) and the number of patients allocated to the respective treatment.
c. Institute's calculation based on the number of patients in the respective treatment group.

BSC: best supportive care; FAS-C30: full analysis set for the EORTC QLQ-C30; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; N: number of patient in the treatment group; RCT: randomized controlled trial; vs.: versus

Table 3: Proportions of patients with evaluable questionnaires on the EQ-5D VAS, treatment-free period −16 to +1 days of a cycle (of 28 days) – non-RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (study TALLISUR) (multipage table)

Study / **Documentation time**	**Trifluridine/tipiracil + BSC** N = 185		**Placebo + BSC** N = 9	
TALLISUR	**Number of patients in the company's analysis population[a, b]**	**Proportion of patients with evaluable questionnaires n (%)[c]**	**Number of patients in the company's analysis population[a, b]**	**Proportion of patients with evaluable questionnaires n (%)[c]**
Questionnaire before cycle 1 (baseline)	126	126 (68.1)	6	6 (66.7)
Questionnaire 2 before cycle 2	126	113 (61.1)	6	5 (55.6)
Questionnaire 3 before cycle 3	82	68 (36.8)	4	3 (33.3)
Questionnaire 4 before cycle 4	53	47 (25.4)	3	2 (22.2)
Questionnaire 5 before cycle 5	36	26 (14.1)	1	1 (11.1)
Questionnaire 6 before cycle 6	22	16 (8.6)	0	0 (0.0)
Questionnaire 7 before cycle 7	15	12 (6.5)	0	0 (0.0)
Questionnaire 8 before cycle 8	13	11 (5.9)	0	0 (0.0)
Questionnaire 9 before cycle 9	13	10 (5.4)	0	0 (0.0)
Questionnaire 10 before cycle 10	9	8 (4.3)	0	0 (0.0)
Questionnaire 11 before cycle 11	7	6 (3.2)	0	0 (0.0)
Questionnaire 12 before cycle 12	4	3 (1.6)	0	0 (0.0)
Questionnaire 13 before cycle 13	4	3 (1.6)	0	0 (0.0)
Questionnaire 14 before cycle 14	1	1 (0.5)	0	0 (0.0)
Questionnaire 18 before cycle 18	1	1 (0.5)	0	0 (0.0)
End of treatment	98	50 (27.0)	4	4 (44.4)
Follow-up 2	1	0 (0.0)	1	0 (0.0)
Follow-up 3	29	9 (4.9)	2	1 (11.1)
Follow-up 4	38	13 (7.0)	2	1 (11.1)

Table 3: Proportions of patients with evaluable questionnaires on the EQ-5D VAS, treatment-free period −16 to +1 days of a cycle (of 28 days) – non-RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (study TALLISUR) (multipage table)

Study / **Documentation time**	**Trifluridine/tipiracil + BSC** **N = 185**		**Placebo + BSC** **N = 9**	
TALLISUR	**Number of patients in the company's analysis population[a, b]**	**Proportion of patients with evaluable questionnaires n (%)[c]**	**Number of patients in the company's analysis population[a, b]**	**Proportion of patients with evaluable questionnaires n (%)[c]**
Follow-up 5	48	14 (7.6)	2	1 (11.1)
Follow-up 6	48	15 (8.1)	2	1 (11.1)
Follow-up 7	46	14 (7.6)	2	1 (11.1)
Follow-up 8	40	19 (10.3)	2	2 (22.2)
Follow-up 9	31	9 (4.9)	2	1 (11.1)
Follow-up 10	32	9 (4.9)	2	0 (0.0)
Follow-up 11	27	2 (1.1)	1	0 (0.0)
Follow-up 12	20	0 (0.0)	1	0 (0.0)

a. Patients who had completed one evaluable questionnaire at baseline and ≥ 1 further evaluable questionnaire (referred to as "FAS-C30 population" in the company's dossier).
b. The company did not provide any information explaining the difference in the number of patients analysed by the company (FAS-C30) and the number of patients allocated to the respective treatment.
c. Institute's calculation based on the number of patients in the respective treatment group.

BSC: best supportive care; FAS-C30: full analysis set for the EORTC QLQ-C30; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; N: number of patient in the treatment group; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

2.3 Overall conclusion on added benefit

Table 4 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 4: Positive and negative effects from the assessment of trifluridine/tipiracil + BSC in comparison with BSC

Positive effects	**Negative effects**
Mortality ▪ Overall survival: indication of added benefit – extent: "major"	–
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: "considerable" ▪ Hypertension: hint of lesser harm – extent: "considerable"	Serious/severe side effects ▪ Severe AEs (CTCAE grade ≥ 3): hint of greater harm – extent: "considerable", including ▫ myelosuppression indication of greater harm – extent: "major" as manifestation of myelosuppression: - anaemia age (≥ 65 years) hint of greater harm – extent: "major" - febrile neutropenia: hint of greater harm – extent: "considerable" - leukopenia: hint of greater harm – extent: "minor" - neutropenia: indication of greater harm – extent: "major"
Non-serious/non-severe side effects ▪ Discontinuation due to AEs: ▫ age (≥ 65 years) hint of lesser harm – extent: "considerable" ▪ Psychiatric disorders: hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ Gastrointestinal toxicity: indication of greater harm – extent: "considerable", including: ▫ diarrhoea ▫ nausea ▫ vomiting in each case hint of greater harm – extent: "considerable"
Patient-relevant outcomes of morbidity and health-related quality of life: not recorded in the studies RECOURSE and TERRA	
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

For the present benefit assessment, usable data were still only available for the outcome categories of mortality and side effects. The analyses on side effects also included events that were attributable to progression and symptoms of the underlying disease, however. The outcomes were therefore interpreted as a mixture of progression/symptoms and side effect. Since no usable data were available for the outcome categories of morbidity and health-related quality of life, there was therefore no multiple assessment of symptoms.

In the overall assessment, there are positive and negative effects, which, with the exception of the outcomes "gastrointestinal toxicity" and "myelosuppression" and its common manifestation "neutropenia" (each indication) have the probability of a hint.

On the positive side, there is an indication of an added benefit of major extent for the outcome "overall survival".

In addition, in the outcomes of the category of serious/severe side effects, there is in each case a hint of lesser harm from serious adverse events (SAEs) and the specific adverse event (AE) "hypertension", each of considerable extent. Furthermore, in the outcomes of the category of non-serious/non-severe side effects, there is a hint of lesser harm of considerable extent in the outcome "psychiatric disorders" and, for patients aged ≥ 65 years, in the outcome "discontinuation due to AEs".

On the negative side, this is accompanied by a hint of greater harm for the outcome "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" of considerable extent. This includes the symptom "myelosuppression" with an indication of greater harm of major extent. In addition, in the outcome category of non-serious/non-severe side effects, there is an indication of greater harm of considerable extent for the outcome "gastrointestinal toxicity".

In the overall consideration, the positive effects of trifluridine/tipiracil + BSC in comparison with BSC outweigh the negative effects. However, since there are still no results on patient-relevant outcomes of morbidity or health-related quality of life available, it remains unclear whether and, if applicable, to what extent the advantage from overall survival is limited by disadvantages in these outcomes in the present palliative treatment goal.

Overall, an indication of a minor added benefit of trifluridine/tipiracil + BSC in comparison with the appropriate comparator therapy BSC is derived for patients with MCRC who have been previously treated with, or are not considered candidates for, available therapies.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of trifluridine/tipiracil from dossier assessment A20-35: There is an indication of a minor added benefit also for patients with MCRC who have been previously treated with, or are not considered candidates for, available therapies, and have received 2 prior regimens.

The following Table 5 shows the result of the benefit assessment of trifluridine/tipiracil + BSC under consideration of dossier assessment A20-35 and the present addendum.

Table 5: Trifluridine/tipiracil – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Monotherapy for the treatment of adult patients with MCRC who have been previously treated with, or are not considered candidates for, available therapies. These therapies include fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.	BSC[b]	Indication of minor added benefit[c]

a. Presentation of the respective ACT specified by the G-BA.
b. BSC means the best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life.
c. The studies RECOURSE and TERRA included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor

The G-BA decides on the added benefit.

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Appendix A – Forest plots on the meta-analysis on overall survival calculated by the Institute

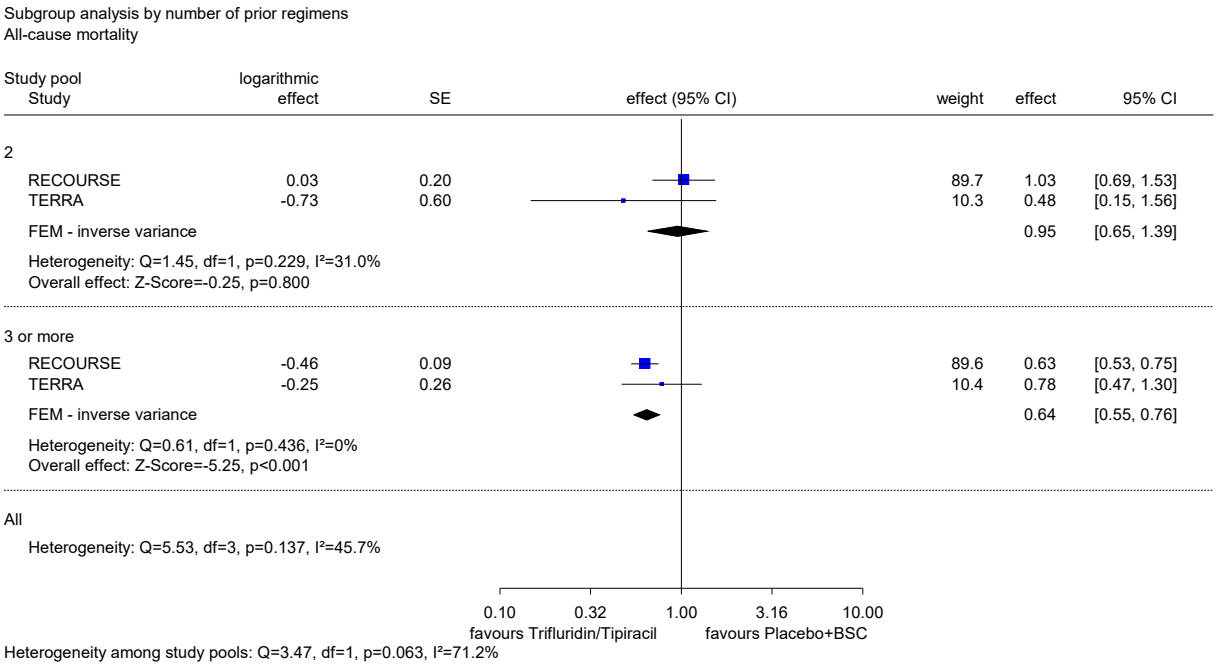
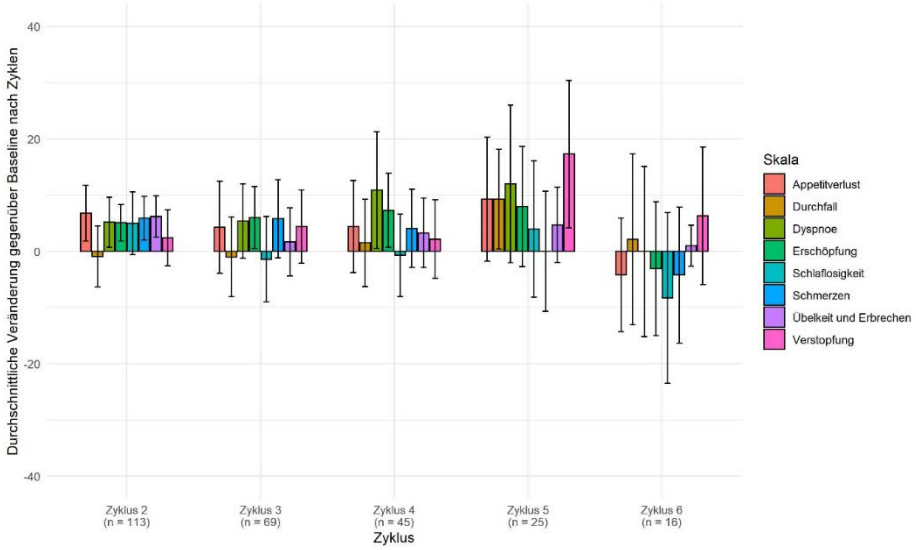


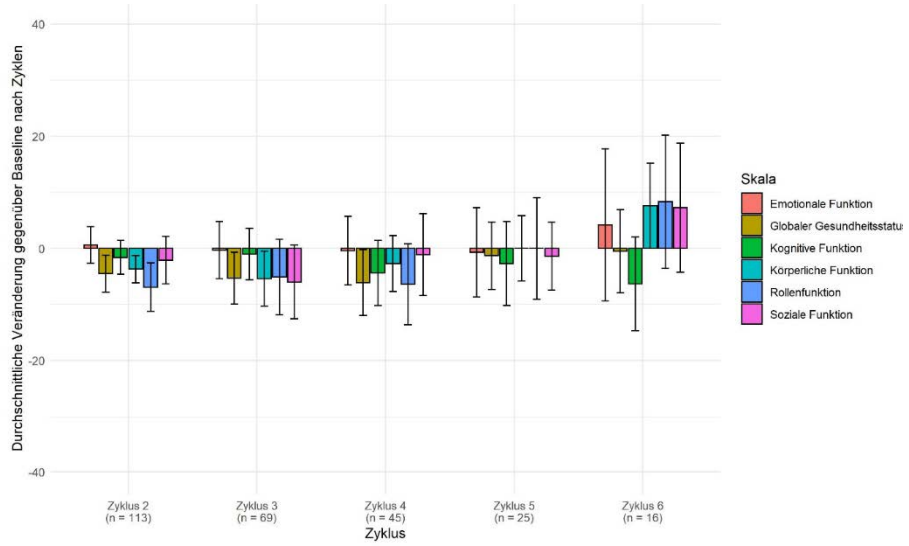
Figure 1: Subgroup analysis on the outcome "overall survival" by the number of prior regimens (2 vs. ≥ 3) (studies RECOURSE and TERRA)

Appendix B – Graphic displays of the mean change of the scales of the EORTC QLQ-C30 and the EQ-5D VAS in comparison with baseline of the TALLISUR study



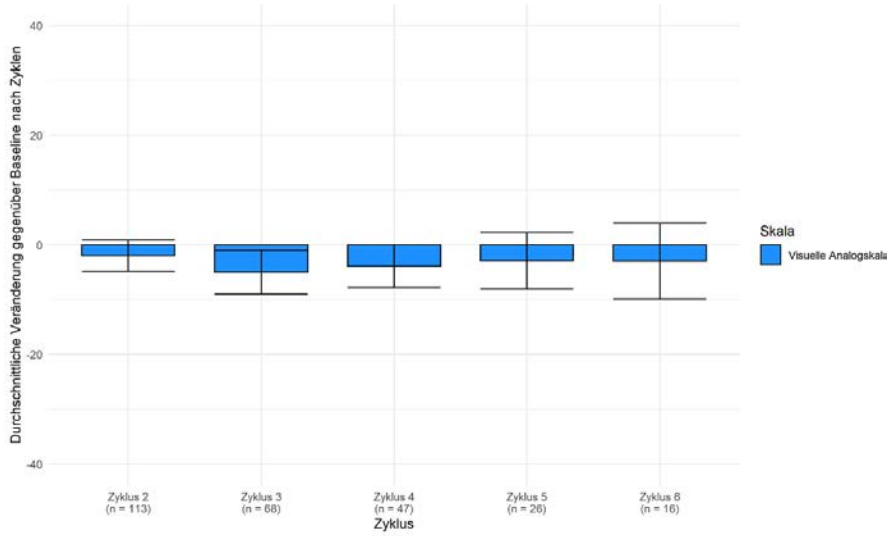
Translation of the terms used in the figure:
Durchschnittliche Veränderung gegenüber Baseline nach Zyklen = mean change from baseline by cycles; Zyklus = cycle; Skala = scale; Appetitverlust = appetite loss; Durchfall = diarrhoea; Dyspnoe = dyspnoea; Erschöpfung = fatigue; Schlaflosigkeit = insomnia; Schmerzen = pain; Übelkeit und Erbrechen = nausea and vomiting; Verstopfung = constipation

Figure 2: Mean change in disease-related symptoms measured with the symptom scales of the EORTC QLQ-C30 in comparison with baseline under treatment with trifluridine/tipiracil + BSC for the first 6 cycles (higher values indicate more severe symptoms; information on variance probably standard deviation)



Translation of the terms used in the figure:
Durchschnittliche Veränderung gegenüber Baseline nach Zyklen = mean change from baseline by cycles; Zyklus = cycle; Skala = scale; Emotionale Funktion = emotional functioning; Globaler Gesundheitsstatus = global health status; Kognitive Funktion = cognitive functioning; Rollenfunktion = role functioning; Soziale Funktion = social functioning

Figure 3: Mean change in health-related quality of life measured with the global health status and the functional scales of the EORTC QLQ-C30 in comparison with baseline under trifluridine/tipiracil + BSC for the first 6 cycles (higher values indicate better status or better functioning; information on variance probably standard deviation)



Translation of the terms used in the figure:
Durchschnittliche Veränderung gegenüber Baseline nach Zyklen = mean change from baseline by cycles; Zyklus = cycle; Skala = scale; Visuelle Analogskala = visual analogue scale

Figure 4: Mean change in health status measured with the EQ-5D VAS in comparison with baseline under treatment with trifluridine/tipiracil + BSC for the first 6 cycles (higher values indicate better health status; information on variance probably standard deviation)