IQWiG Reports – Commission No. A20-35

Trifluridine/tipiracil (colorectal cancer) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Trifluridin/Tipiracil (Kolorektalkarzinom) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 29 June 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

Due to the corona pandemic, no external experts were involved.

IQWiG employees involved in the dossier assessment

- Helmut Hörn
- Nadia Abu Rajab
- Gertrud Egger
- Klaus Gossens
- Tatjana Hermanns
- Stefan Kobza
- Christoph Schürmann
- Volker Vervölgyi

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
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)
KRAS	Kirsten rat sarcoma viral oncogene homologue
MCRC	metastatic colorectal cancer
MID	minimally important difference
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale
VEGF	vascular endothelial growth factor

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination trifluridine/tipiracil. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 31 March 2020.

The G-BA limited the decision on the added benefit of trifluridine/tipiracil for metastatic colorectal cancer (MCRC) in the first assessment in 2016, as there were no data to assess health-related quality of life, no valid data on symptoms of the disease (morbidity) and no sufficiently informative data on side effects regarding severe and serious adverse events (AEs), and it was therefore not possible to establish with the necessary certainty that trifluridine/tipiracil has an added benefit that is sufficiently scientifically proven.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of this report is the assessment of the added benefit of trifluridine/tipiracil in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in 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-vascular endothelial growth factor (VEGF) agents, and anti-epidermal growth factor receptor (EGFR) agents.

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of trifluridine/tipiracil

Therapeutic indication	**ACT**[a]
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]
a. Presentation of the 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. ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor	

In the specification of the ACT, the G-BA assumed an advanced treatment setting, in which the standard therapies that are currently recommended and approved for treatment in the metastatic stage have already been exhausted and for which further antineoplastic treatments are no regular option. An exclusively palliative goal of the treatment was assumed with the determination of BSC as ACT.

The company used the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Results

Study pool and study characteristics

The study pool for the benefit assessment of trifluridine/tipiracil consisted of the RCTs TPU-TAS-102-301 (RECOURSE) and 10040090 (TERRA).

The company additionally included the IC4-95005-183-DEU (TALLISUR) study, which it conducted to fulfil the G-BA's condition of the limitation from the first assessment in 2016. The TALISSUR study is a non-randomized study on the comparison of trifluridine/tipiracil + BSC with BSC conducted in Germany. This study was not included for the following reasons. The non-randomized allocation led to a large imbalance in patient numbers between the study arms. Thus, 185 patients were treated in the trifluridine/tipiracil + BSC arm and 9 patients in the BSC arm. In addition, there were large differences in patient characteristics, e.g. mean age (67 years in the trifluridine/tipiracil + BSC arm versus 78 years in the BSC arm), median duration of the disease (34 versus 50 months) and Eastern Cooperative Oncology Group Performance Status (ECOG PS); e.g. 40 versus 0% of the patients had an ECOG PS of 0. Because of these differences, an added benefit could only be derived on the basis of the results of morbidity and health-related quality of life if the observed effects were so large that they could not be caused by systematic bias alone; however, this is not the case. Finally, the response rates to the instruments used to measure morbidity/symptoms and health-related quality of life were so low that they could not be interpreted even if the biasing factors described above were not present.

Description of the studies RECOURSE and TERRA

The RECOURSE study is a multinational, double-blind RCT on the comparison of trifluridine/tipiracil + BSC with placebo + BSC. The TERRA study is a double-blind RCT on the comparison of trifluridine/tipiracil + BSC with placebo + BSC conducted in Asia. Both studies included patients with pretreated MCRC and an ECOG PS of ≤ 1. The patients had to have received at least 2 standard therapy regimens for the metastatic stage. The standard regimens had to include the drugs fluoropyrimidine, oxaliplatin and irinotecan, an anti-VEGF monoclonal antibody (bevacizumab). In the RECOURSE study, treatment with at least one anti-EGFR monoclonal antibody (cetuximab or panitumumab) was required for Kirsten rat sarcoma

viral oncogene homologue (KRAS) wild type patients. In the TERRA study, this pretreatment was neither inclusion nor exclusion criterion.

In the RECOURSE study, 800 patients were randomly allocated in a 2:1 ratio to treatment with trifluridine/tipiracil + BSC (N = 534) or to placebo + BSC (N = 266). Stratification factors were KRAS mutation status (wild type versus mutation), the time since diagnosis of first metastasis (< 18 months versus ≥ 18 months), and geographical region (Asia [Japan] versus the West [USA, Europe and Australia]). In the TERRA study, 406 patients were randomly allocated in a 2:1 ratio to treatment with trifluridine/tipiracil + BSC (N = 271) or to placebo + BSC (N = 135). Stratification factors were KRAS mutation status (wild type versus mutation) and country (China, Korea, and Thailand). Some of the patients included in the TERRA study were pretreated with a regimen that, according to the company, is not approved in Europe. The company excluded these patients from the population under consideration and only included the results of the 94 patients (n = 61 versus 33) whose pretreatment was in compliance with the approval in Europe.

Trifluridine/tipiracil was used in compliance with the approval in the RECOURSE study and in the relevant subpopulation of the TERRA study. The patients in the placebo + BSC arm received tablets of identical appearance at the same time points. All patients additionally received supportive concomitant treatment (BSC), which could include haematological supportive therapies and antiemetics, among others. Any anticancer drug therapies were excluded. Palliative radiotherapy was completely excluded in the RECOURSE study and permitted in the TERRA study for pain relief for bone metastases. The study treatment was continued until at least one of the following criteria for discontinuation occurred: disease progression, unacceptable toxicity, initiation of a different anti-tumour treatment, or withdrawal of consent.

The primary outcome in each case was overall survival. Patient-relevant outcomes on side effects were additionally recorded. Both studies recorded neither patient-relevant outcomes on morbidity nor health-related quality of life.

Results on 2 data cut-offs are available in both studies. In the RECOURSE study, the first data cut-off was planned for the time point of the 571st death. The second data cut-off was conducted on 8 October 2014 to transmit results on overall survival to the regulatory authorities. In the TERRA study, the first data cut-off was planned for the time point of the 288th death, which occurred on 22 December 2015. After this date, the recording of data on side effects was discontinued; data recording for overall survival ended on 16 February 2016 (second data cut-off); it is unclear according to which criteria the second data cut-off was conducted. For the RECOURSE study, the results of the second data cut-off were used for all outcomes. For the TERRA study, the results of the first data cut-off were used for the side effect outcomes, and the results of the second data cut-off for the results of overall survival.

Both studies are completed.

Due to their similarity, both studies can be pooled in a meta-analysis.

Implementation of the appropriate comparator therapy

BSC is the ACT for the present benefit assessment. According to the specifications of the G-BA, BSC comprises those therapies that provide the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

As mentioned above, any anticancer drug therapies were excluded during the randomized study phase of the studies RECOURSE and TERRA. Palliative radiotherapy was completely excluded in the RECOURSE study and excluded in the TERRA study except for pain relief for bone metastases. This exclusion contradicts the guideline on palliative care, which emphasizes that the management and the alleviation of distressing symptoms are a key part of palliative care when treating patients with incurable cancer. Symptom-oriented measures can be implemented on their own or parallel to tumour-related or causal therapies. According to the guideline, an either-or is not appropriate, which is why tumour-specific measures (e.g. radiotherapy, surgical procedures, antitumour drug treatments) should be weighed up against the primary or sole therapeutic goal of symptom relief.

From this information, it can be deduced for the present therapeutic indication that the prohibition of chemo- and radiotherapy means a restriction of palliative care. Thus, BSC was not adequately implemented in the studies RECOURSE and TERRA, and there was potential undertreatment.

Subsequent therapies

After the end of the randomized study treatment, the patients in both studies received subsequent therapies that was not allowed to be given as concomitant treatment. The proportion of patients with subsequent therapies was about 40% in the RECOURSE study and is unknown for the relevant subpopulation of the TERRA study. It can be inferred from this that there was a need for further treatment after the end of the randomized study medication and that the administration of additional treatment options might have been indicated already during the randomized study treatment.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes was rated as low for both studies.

The risk of bias for overall survival was rated as low for the RECOURSE study and as high for the TERRA study.

The risk of bias for the side effect outcomes, with the exception of the outcome “discontinuation due to AEs”, was rated as high in both studies. The reason for the high risk of bias were incomplete observations for potentially informative reasons.

In both studies, the certainty of results for the outcome "discontinuation due to AEs" was limited despite a low risk of bias.

Despite the high risk of bias in both studies, the certainty of results for the outcome "myelosuppression" and its manifestation "neutropenia" was not limited because the observed effect was very large and it is very unlikely for the control arm that a relevant number of events remained unobserved due to censoring.

Despite the high risk of bias, the certainty of results for the outcome "gastrointestinal toxicity" (System Organ Class [SOC], AEs) was not limited in the RECOURSE study due to the high number of early events and the clear difference between the treatment arms.

For overall survival, the certainty of conclusions was limited because the decisive subgroup analysis (number of prior regimens 2 versus ≥ 3) was only available for the RECOURSE study. Thus, there is no confirmation (replication) by a further study for the subgroup of interest that is necessary for a high certainty of conclusions.

In addition, the limitations in the implementation of the ACT resulted in a reduced certainty of conclusions for all outcomes.

An additional uncertainty factor for the TERRA study was that the formation of the subpopulation considered by the company was not sufficiently described.

Hence, at most indications, e.g. of an added benefit, can be derived on the basis of the available data.

Mortality

The meta-analysis showed a statistically significant difference between the treatment arms in favour of trifluridine/tipiracil + BSC in comparison with placebo + BSC for the outcome "overall survival". In addition, an effect modification by the number of prior regimens (2 versus ≥ 3) was shown on the basis of the RECOURSE study. No added benefit of trifluridine/tipiracil + BSC in comparison with BSC resulted from the subgroup analysis for patients with 2 prior regimens. There was a hint of an added benefit of trifluridine/tipiracil + BSC in comparison with BSC for the subgroup of patients with ≥ 3 prior regimens.

Morbidity

The studies RECOURSE and TERRA did not record any patient-relevant outcomes on morbidity. The data from the TALLISUR study are not interpretable. This resulted in no hint of an added benefit of trifluridine/tipiracil + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was not recorded in the studies RECOURSE and TERRA. The data from the TALLISUR study are not interpretable. This resulted in no hint of an added

benefit of trifluridine/tipiracil + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

The present benefit assessment was based on analyses that also included events attributable to progression and symptoms of the underlying disease. An assessment of the extent to which the respective effects of the individual outcomes were based on events of progression/symptoms is not possible based on the available data. This was taken into account in the assessment of the results insofar as the side effect outcomes were interpreted as a mixture of progression/ symptoms and side effect.

SAEs

The meta-analysis showed a statistically significant difference in favour of trifluridine/ tipiracil + BSC for the outcome "SAEs". As a result, there was a hint of lesser harm of trifluridine/tipiracil + BSC in comparison with BSC.

Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

The meta-analysis showed a statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC for the outcome "severe AEs (CTCAE grade ≥ 3)". As a result, there was a hint of greater harm of trifluridine/tipiracil + BSC in comparison with BSC.

Discontinuation due to AEs

The meta-analysis showed a statistically significant difference in favour of trifluridine/tipiracil + BSC for the outcome "discontinuation due to AEs". However, there was an effect modification by age on study entry (< 65 years versus ≥ 65 years). The results from the subgroup analysis were used for the derivation of the added benefit. This resulted in no hint of greater or lesser harm from trifluridine/tipiracil + BSC in comparison with BSC for patients aged < 65 years. Greater or lesser harm is therefore not proven. For patients ≥ 65 years of age, there was a hint of lesser harm from trifluridine/tipiracil + BSC in comparison with BSC.

Myelosuppression

In the present data situation, the side effect "myelosuppression" was operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC "blood and lymphatic system disorders", considering the Preferred Terms (PTs) "anaemia", "febrile neutropenia", "leukopenia", and "neutropenia" as common manifestations of myelosuppression.

A statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC was shown at the level of the SOC "blood and lymphatic system disorders". This resulted in an indication of greater harm of trifluridine/tipiracil + BSC in comparison with BSC. Greater harm was also shown in the 4 manifestations of myelosuppression, but partly only with lower certainty of conclusions.

An effect modification by age (< 65 years versus ≥ 65 years) was shown for the PT "anaemia". In each case, the results from the subgroup analysis were used for the derivation of the added benefit. This resulted in a hint of greater harm for patients aged ≥ 65 years. For patients aged < 65 years, however, there was no hint of greater or lesser harm from trifluridine/tipiracil + BSC in comparison with BSC. Thus, greater or lesser harm for patients < 65 years of age is not proven for the PT "anaemia".

Gastrointestinal toxicity

In the present data situation, the side effect "gastrointestinal toxicity" was operationalized as AEs of the SOC "gastrointestinal disorders", considering the PTs "diarrhoea", "nausea" and "vomiting" as common manifestations of gastrointestinal toxicity.

A statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC was shown for the SOC "gastrointestinal disorders". This resulted in an indication of greater harm of trifluridine/tipiracil + BSC in comparison with BSC. Greater harm was also shown in the 3 manifestations of gastrointestinal toxicity.

Further specific AEs

Psychiatric disorders (SOC, AEs)

Results for the outcome "psychiatric disorders" (SOC, AEs) were available in the RECOURSE study, but not in the TERRA study. The added benefit was therefore derived solely on the basis of the RECOURSE study.

The RECOURSE study showed a statistically significant difference in favour of trifluridine/tipiracil + BSC for the outcome "psychiatric disorders" (SOC, AEs). As a result, there was a hint of lesser harm of trifluridine/tipiracil + BSC in comparison with BSC.

Hypertension (PT, severe AEs [CTCAE grade ≥ 3])

Results for the outcome "hypertension" (PT, severe AEs [CTCAE grade ≥ 3]) were available in the RECOURSE study, but not in the TERRA study. The added benefit was therefore derived solely on the basis of the RECOURSE study.

The RECOURSE study showed a statistically significant difference in favour of trifluridine/tipiracil + BSC for the outcome "hypertension" (PT, severe AEs [CTCAE grade ≥ 3]). As a result, there was a hint of lesser harm of trifluridine/tipiracil + BSC in comparison with BSC.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug trifluridine/tipiracil in comparison with the ACT are assessed as follows:

For the present benefit assessment, usable data were 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 consideration, there are both positive and negative effects of trifluridine/tipiracil + BSC in comparison with BSC, which had the probability of a hint, except for the outcomes "myelosuppression" and its manifestation "neutropenia" as well as "gastrointestinal toxicity" (each indication).

Since the results for the only benefit outcome on the positive side showed a relevant effect modification by the number of prior regimens, separate conclusions are drawn for patients with 2 prior regimens and for patients with at least 3 prior regimens.

Patients with 2 prior regimens

For patients with 2 prior regimens, there is no added benefit for overall survival. The positive and negative effects are therefore limited to side effects.

In the outcomes of the category of serious/severe side effects, there is, on the positive side, in each case a hint of lesser harm from SAEs and the specific AE "hypertension", each of considerable extent. In addition, 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 of considerable extent for the outcome "severe AEs (CTCAE grade ≥ 3)". This includes the symptom "myelosuppression" with an indication of greater harm of major extent. In addition, in the outcome category of non-

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

serious/non-severe side effects, there is an indication of greater harm of considerable extent for the outcome “gastrointestinal toxicity”.

Overall, the negative effects predominate not only qualitatively due to the type of events that occurred (e.g. vomiting and diarrhoea compared with sleep disorders), but also quantitatively due to the clearly higher number of patients affected.

In summary, a hint of lesser benefit of trifluridine/tipiracil + BSC in comparison with the ACT BSC is derived for patients with MCRC who have been treated with 2 prior regimens.

Patients with at least 3 prior regimens

On the positive side, there was a hint of an added benefit of major extent for overall survival for patients with at least 3 prior regimens. In addition, there were the same positive and negative effects from the side effect outcomes as for patients with 2 prior regimens.

In the overall consideration of the added benefit for overall survival and greater harm for the side effect outcomes, there is an added benefit of trifluridine/tipiracil + BSC in comparison with BSC. 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, a hint of a minor added benefit of trifluridine/tipiracil + BSC in comparison with the ACT BSC is derived for patients with MCRC who have been treated with at least 3 prior regimens.

Summary

In summary, there is a hint of a lesser benefit of trifluridine/tipiracil + BSC versus the ACT BSC for patients with MCRC with 2 prior regimens, and a hint of a minor added benefit for patients with MCRC with at least 3 prior regimens.

Table 3 shows a summary of probability and extent of the added benefit of trifluridine/tipiracil.

Table 3: Trifluridine/tipiracil – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Subgroup**	**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]	2 prior regimens	Hint of lesser benefit[c]
		≥ 3 prior regimens	Hint 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 approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is the assessment of the added benefit of trifluridine/tipiracil in comparison with BSC as ACT in 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.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of trifluridine/tipiracil

Therapeutic indication	**ACT[a]**
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]
a. Presentation of the 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. ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor	

In the specification of the ACT, the G-BA assumed an advanced treatment setting, in which the standard therapies that are currently recommended and approved for treatment in the metastatic stage have already been exhausted and for which further antineoplastic treatments are no regular option. An exclusively palliative goal of the treatment was assumed with the determination of BSC as ACT.

The company used the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on trifluridine/tipiracil (status: 10 February 2020)
- bibliographical literature search on trifluridine/tipiracil (last search on 10 February 2020)
- search in trial registries/trial results databases for studies on trifluridine/tipiracil (last search on 10 February 2020)
- search on the G-BA website for trifluridine/tipiracil (last search on 10 February 2020)

To check the completeness of the study pool:

- search in trial registries for studies on trifluridine/tipiracil (last search on 8 April 2020)

No additional relevant study was identified from the check.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study	Study category			Available sources		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
TPU-TAS-102-301 (RECOURSE[d])	Yes	No[e]	Yes	Yes [3][f]	Yes [4-7]	Yes [8-14]
10040090 (TERRA[d])	Yes	No[e]	Yes	No[g]	Yes [15]	Yes [16]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website.
d. In the following tables, the study is referred to with this abbreviated form.
e. The study was sponsored by Taiho. On 19 October 2015, the application for approval in the European Union, including the marketing rights for trifluridine/tipiracil (Lonsurf) in Europe, was transferred to Les Laboratoires Servier.
f. The study report was identified on the EMA website in the check of completeness (https://www.ema.europa.eu/en/medicines/human/EPAR/lonsurf).
g. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

BSC: best supportive care; CSR: clinical study report; EMA: European Medicines Agency; G-BA: Federal Joint Committee; RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of trifluridine/tipiracil consisted of the RCTs TPU-TAS-102-301 (RECOURSE) and 10040090 (TERRA). This study pool deviates from the study pool of the company, which additionally included the non-randomized comparative study IC4-95005-183-DEU (TALLISUR).

The reasons why the TALLISUR study was not included for the derivation of the added benefit are explained below. The RCTs RECOURSE and TERRA are presented in Sections 2.3.2 and 2.4 and used for the derivation of the added benefit in Section 2.5.

Description of the TALLISUR study

The tables on the characteristics of the study, the interventions and the patient characteristics of the TALLISUR study are presented in Appendix D of the full dossier assessment.

The TALISSUR study [17-19] is a non-randomized study on the comparison of trifluridine/tipiracil + BSC with BSC conducted in Germany. The company conducted this study to fulfil the G-BA's condition of the limitation from the first assessment in 2016 [12]. In the condition of the limitation, the G-BA requested data that, in contrast to the evidence provided in 2016, also allowed conclusions on disease-specific morbidity, health-related quality of life and side effects (see Section 2.5.2).

The company justified the choice of the non-randomized design with ethical concerns. According to the company, conducting an RCT with placebo as a comparison would have resulted in a part of the patients being deprived of a proven effective therapy so that the "equivalence" between the 2 alternative medical interventions as the central ethical requirement for an RCT (equipoise principle) would not have been fulfilled.

The study included patients at the age of ≥ 18 years with MCRC who needed treatment due to the progression of the MCRC, with no restrictions regarding the EOCG PS. The patients had to have been previously treated with, or not be considered candidates for, available therapies. These therapies include fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

According to the company, the patients were allocated to the respective treatment arm in accordance with standard oncological practice after detailed consultation and in accordance with the patient's wishes in the sense of participatory decision-making by the physician and the patient. As a result of this allocation, 185 patients were treated in the trifluridine/tipiracil + BSC arm and 9 patients in the BSC arm. Besides the large imbalance in patient numbers, there were also large differences in patient characteristics, e.g. mean age (67 years in the trifluridine/tipiracil + BSC arm versus 78 years in the BSC arm), median duration of the disease (34 versus 50 months) and ECOG PS; e.g. 40 versus 0% of the patients had an ECOG PS of 0 (see Table 35 in Appendix D of the full dossier assessment).

The data on morbidity and health-related quality of life were recorded with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS).

Assessment of the TALLISUR study

Since there were results from the RCTs RECOURSE and TERRA available for the outcomes of overall survival and side effects, there was no need to refer to the results of the non-randomized TALLISUR study. The following explanations are therefore limited to the interpretability of the results on morbidity and health-related quality of life.

Because of the non-randomized allocation of patients and the resulting large differences regarding patient characteristics between the treatment arms, an added benefit could only be derived on the basis of the results of morbidity and health-related quality of life if the observed effects were so large that they could not be caused by systematic bias alone; however, this is not the case. In Module 4 A (Section 4.3.2.2.2), the company also considered the interpretability of the data to be severely limited, as the "patients in the treatment arm differ notably from the patients in the comparator arm regarding health status, so that a comparison of the 2 treatment groups is not meaningful." Therefore, the company conducted only a descriptive interpretation of the results of the TALLISUR study and presented the results of the

statistical tests for the comparison of the 2 study arms only as supplementary information in the Appendix of Module 4 A.

In addition, the response rates for the used instruments were low. At the start of the study treatment, only 126 of the 185 patients in the trifluridine/tipiracil + BSC arm and 6 of the 9 patients in the BSC arm completed the questionnaires. This corresponds to a response rate of less than 70% already at this early time point. In the next examination (start of cycle 2), the response rate in relation to the 126 versus 6 patients with a questionnaire at the start of treatment dropped to 59% versus 67%, and, in relation to the 185 versus 9 patients included, to 39% versus 44%. With such a low response rate, the results would not be interpretable even if the biasing factors described above had not been present, e.g. if the data had been recorded in a double-blind RCT.

Finally, the descriptive analyses of the company were unsuitable for the present benefit assessment. The company's approach used in the qualitative consideration of the mean change from baseline regarding the EORTC QLQ-C30 and the EQ-5D VAS in the trifluridine/tipiracil + BSC arm was not appropriate. In this approach, the company plotted the mean changes from baseline in curves in comparison with the minimal important difference (MID) of 10 points, concluding that this consideration showed that quality of life was maintained under therapy with trifluridine/tipiracil. This approach was not appropriate because, in the responder analyses of the time to deterioration by ≥ 10 points presented by the company, an event, i.e. a relevant deterioration of symptoms or health-related quality of life, occurred in 40 to 70% of the patients, depending on the domain, and thus the maintenance of symptoms or health-related quality of life cannot be concluded. Furthermore, MIDs that – like the MID of ≥ 10 points used by the company – were determined at an individual level are not suitable as relevance criteria for the interpretation of mean changes at group level (see de Vet 2010 [20], for example).

In summary, the results on symptoms and health-related quality of life from the TALLISUR study are not usable. The 2 included studies RECOURSE and TERRA did not record any patient-relevant outcomes on morbidity and health-related quality of life (see Section 2.4.1). Hence, the assessment of health-related quality of life and symptoms of the disease (morbidity) of trifluridine/tipiracil + BSC in comparison with the ACT BSC is not possible also after expiry of the limitation of the decision.

2.3.2 Study characteristics

2.3.2.1 Characteristics of the studies and of the interventions of the studies RECOURSE and TERRA

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
RECOURSE	RCT, double-blind, parallel	Adult patients with MCRC (ECOG PS ≤ 1) with ≥ 2 prior standard therapy regimens: ▪ tumour progression after each prior standard therapy regimen or ▪ its discontinuation before tumour progression due to unacceptable toxicity	Trifluridine/tipiracil + BSC (N = 534) placebo + BSC (N = 266)	Screening: ≤ 28 days Treatment[b]: until disease progression, unacceptable toxicity, initiation of a different anti-tumour treatment, or treatment discontinuation following the physician's decision, or withdrawal of consent Observation[c]: outcome-specific, at most until death or end of study[d]	101 centres in Australia, Austria, Belgium, Czech Republic, France, Germany, Great Britain, Ireland, Italy, Japan, Spain, Sweden, USA 6/2012–5/2016[f] First data cut-off: ▪ overall survival: 24 January 2014 ▪ further outcomes: 31 January 2014 Second data cut-off: ▪ overall survival: 8 October 2014	Primary: overall survival Secondary: AEs
TERRA	RCT, double-blind, parallel	Adult patients with MCRC (ECOG PS ≤ 1) with ≥ 2 prior standard therapy regimens: ▪ tumour progression after each prior standard therapy regimen or ▪ unacceptable toxicity	Trifluridine/tipiracil + BSC (N = 271) placebo + BSC (N = 135) Relevant subpopulation thereof[e]: trifluridine/tipiracil + BSC (n = 61) placebo + BSC (n = 33)	Screening: 28 days Treatment: until disease progression, unacceptable toxicity, or treatment discontinuation following the physician's decision, or withdrawal of consent Observation[c]: outcome-specific, at most until death or end of study[d]	30 centres in China, Korea, Thailand 10/2013–6/2016 First data cut-off: ▪ time to treatment failure and AEs: 22 December 2015 Second data cut-off: ▪ overall survival: 16 February 2016	Primary: overall survival Secondary: AEs

Table 6: Characteristics of the studies included – RCT, trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Patients in the control arm had the option to switch to open-label trifluridine/tipiracil after the positive primary analysis.
c. Outcome-specific information is provided in Table 8.
d. Planned end of study: after reaching the number of deaths planned for the sample size (571 deaths in the RECOURSE study and 288 deaths in the TERRA study) or 12 months after inclusion of the last patient (the event that occurred last).
e. According to the company, patients who were pretreated in compliance with the European approval (see Section 2.3.2.1).
f. Contradictory data between the registry entry at https://clinicaltrials.gov/ct2/show/NCT01607957 and Module 4 A; Module 4 A describes that the study lasted until 1/2014.

AE: adverse event; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; MCRC: metastatic colorectal cancer; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Study	Intervention	Comparison
RECOURSE	Oral 35 mg trifluridine/14.33 mg per m^2 BSA, twice daily, on days 1–5 and 8–12 of each 28-day cycle + BSC	Oral placebo, twice daily, on days 1-5 and 8-12 of each 28-day cycle + BSC
	Dose reduction/interruption according to the SPC	
	Pretreatment ▪ ≥ 2 standard therapy regimens with all of the following drugs under consideration of the country-specific approval: ▫ fluoropyrimidine, oxaliplatin, irinotecan ▫ bevacizumab ▫ cetuximab or panitumumab for KRAS wild type patients ▪ adjuvant chemotherapy could be counted as a regimen if patients had relapsed during or within 6 months of completion **Non-permitted pretreatment:** ▪ major surgery within 4 weeks before baseline ▪ anticancer therapy within 3 weeks before baseline, bevacizumab within 4 weeks before baseline ▪ extended field radiation within 4 weeks before baseline or limited field radiation within 2 weeks before baseline **Permitted concomitant treatment** ▪ haematological supportive therapies (blood transfusion, blood cell stimulating drugs) ▪ antidiarrhoeal drugs (e.g. loperamide) ▪ oral antibiotics for infection prophylaxis in patients with persistent diarrhoea for 24 hours ▪ antiemetics ▪ antiviral thymidine kinase substrates (e.g. stavudine, zidovudine, telbivudine) to be used with care **Concomitant treatment prohibited:** ▪ palliative radiotherapy ▪ anticancer drug therapies, including chemotherapy, immunotherapy, BRMs, herbal drugs or endocrine therapy	

Table 7: Characteristics of the intervention – RCT, trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Study	Intervention	Comparison
TERRA	Oral 35 mg trifluridine/14.33 mg per m^2 BSA, twice daily, on days 1–5 and 8–12 of each 28-day cycle + BSC	Oral placebo, twice daily, on days 1–5 and 8–12 of each 28-day cycle + BSC
	Dose reduction/interruption according to the SPC	
	Pretreatment ▪ ≥ 2 standard chemotherapy regimens with all of the following drugs under consideration of the country-specific approval: fluoropyrimidine, oxaliplatin and irinotecan ▪ adjuvant chemotherapy could be counted as a regimen if patients had relapsed during or within 6 months of completion **Non-permitted pretreatment:** ▪ major surgery within 4 weeks before baseline ▪ anticancer therapy within 3 weeks before baseline, bevacizumab within 4 weeks or mitomycin C within 6 weeks before baseline ▪ extended field radiation within 4 weeks before baseline or limited field radiation within 2 weeks before baseline **Permitted concomitant treatment** ▪ haematological supportive therapies (blood transfusion, blood cell stimulating drugs) ▪ antidiarrhoeal drugs (e.g. loperamide) ▪ oral antibiotics for infection prophylaxis in patients with persistent diarrhoea for 24 hours ▪ antiemetics ▪ antiviral thymidine kinase substrates (e.g. stavudine, zidovudine, telbivudine) to be used with care **Concomitant treatment prohibited:** ▪ palliative radiotherapy, except for pain relief for bone metastases ▪ anticancer drug therapies, including chemotherapy, immunotherapy, BRMs, herbal drugs or endocrine therapy	

BRM: biological response modifier; BSA: body surface area; BSC: best supportive care; KRAS: Kirsten rat sarcoma viral oncogene homologue; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

Study RECOURSE

The RECOURSE study is a multinational, double-blind RCT on the comparison of trifluridine/tipiracil + BSC with placebo + BSC. According to the inclusion criteria, the patients had to be at least 18 years of age on study entry and had to have histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum with known KRAS mutation status. The patients had to have received at least 2 standard therapy regimens for the metastatic stage. After each prior standard therapy regimen, patients had to have tumour progression or have discontinued treatment before tumour progression due to unacceptable toxicity. Adjuvant chemotherapy could be counted as a regimen if patients had relapsed during or within 6 months after the adjuvant chemotherapy. The standard therapy regimens had to include the drugs fluoropyrimidine, oxaliplatin and irinotecan, an anti-VEGF monoclonal antibody

(bevacizumab), and – for patients with KRAS wild type – at least one anti-EGFR monoclonal antibody (cetuximab or panitumumab); a detailed presentation of the pretreatment of the study population can be found in Table 22 in Appendix A of the full dossier assessment. The patients had to have an ECOG PS of ≤ 1 on study entry so that no conclusions can be derived from the RECOURSE study for patients with an ECOG PS of ≥ 2.

A total of 800 patients were randomly assigned in a ratio of 2:1, either to treatment with trifluridine/tipiracil + BSC (534 patients) or to treatment with placebo + BSC (266 patients). Stratification factors were KRAS mutation status (wild type versus mutation), the time since diagnosis of first metastasis (< 18 months versus ≥ 18 months), and geographical region (Asia [Japan] versus the West [USA, Europe and Australia]).

Trifluridine/tipiracil was used in compliance with the approval in the RECOURSE study [21]. The patients in the placebo + BSC arm received tablets of identical appearance at the same time points. All patients additionally received supportive concomitant treatment (BSC), which could include haematological supportive therapies and antiemetics, among others. Palliative (and implicitly also curative) radiotherapy as well as any anticancer drug therapies were excluded (see Table 7). The study treatment was continued until at least one of the following criteria for discontinuation occurred: disease progression, unacceptable toxicity, initiation of a different anti-tumour treatment, or withdrawal of consent. About 40% of the patients received subsequent therapy after completion of the randomized study treatment (see Section 2.3.2.5).

The primary outcome was overall survival. Patient-relevant outcomes on side effects were additionally recorded. The RECOURSE study recorded neither patient-relevant outcomes on morbidity nor health-related quality of life.

Results on 2 data cut-offs are available for the RECOURSE study. The first data cut-off was planned for the time point of the 571th death, which occurred on 24 January 2014. The primary data cut-off for overall survival was conducted on this date. The second data cut-off was conducted on 8 October 2014, according to the company, to transmit results on overall survival to the regulatory authorities. After the first data cut-off and unblinding of the study in May 2014, treatment switching from the placebo + BSC arm to the trifluridine/tipiracil + BSC arm was allowed, but was only used in 2 cases (see first assessment [14]). For the present benefit assessment, the results of the second data cut-off were used for the derivation of the added benefit.

The RECOURSE study is completed.

Study TERRA

The TERRA study is a double-blind RCT on the comparison of trifluridine/tipiracil + BSC with placebo + BSC conducted in Asia (China, Korea and Thailand).

The inclusion and exclusion criteria of the TERRA study largely concur with the inclusion and exclusion criteria of the RECOURSE study (see above). An important difference is that pretreatment with an anti-VEGF monoclonal antibody (bevacizumab) and – for patients with KRAS wild type – at least one anti-EGFR monoclonal antibody (cetuximab or panitumumab) was allowed but not required as an inclusion criterion.

A total of 406 patients were randomly assigned in a ratio of 2:1, either to treatment with trifluridine/tipiracil + BSC (271 patients) or to treatment with placebo + BSC (135 patients). Stratification factors were KRAS mutation status (wild type versus mutation) and country (China, Korea, and Thailand). According to the company, only the part of the study population who were pretreated in compliance with the approval in Europe is relevant for the early benefit assessment. According to the company, these are patients with KRAS wild type who had been treated with cetuximab or panitumumab and with aflibercept or bevacizumab or ramucirumab before study inclusion, as well as patients with mutant KRAS who had been treated with aflibercept or bevacizumab or ramucirumab before study inclusion. Thus, the company considered the results of 94 patients. These were 61 patients in the trifluridine/tipiracil + BSC arm and 33 patients in the placebo + BSC arm.

In Module 4 A of the dossier, the company did not provide any information that would make the formation of the relevant subpopulation of the TERRA study comprehensible. The information provided in the publication of the TERRA study (Xu 2018 [16]) also make the approach only partially comprehensible. Thus, an uncertainty remains, which is considered in the derivation of the added benefit.

The randomized study treatment and the restrictions in concomitant treatment were similar to those in the RECOURSE study (see Table 7); however, palliative radiotherapy was – unlike in the RECOURSE study – not completely excluded, but was allowed for pain relief for bone metastases. The same outcomes were recorded as in the RECOURSE study. An unknown proportion of the patients received subsequent therapy after completion of the randomized study treatment (see Section 2.3.2.5).

Results on 2 data cut-offs are available for the TERRA study. The first data cut-off was planned for the time point of the 288th death, which occurred on 22 December 2015. The recording of data on side effects was discontinued after this date. The data recording for overall survival ended on 16 February 2016 (second data cut-off), when 316 deaths had occurred. Module 4 A, the study protocol and the Xu 2018 publication include no information according to which criteria the second data cut-off was conducted. The company presented the results on side effects for the first data cut-off and the results on overall survival for the second data cut-off. Both data cut-offs were considered correspondingly in the dossier assessment. In the present situation, the results for overall survival were used because of the temporal proximity to the first data cut-off , since it is unlikely that the unplanned implementation of the second data cut-off had a relevant influence on the result for this outcome. However, in order to take into

account the uncertainty regarding the conduct of the second data cut-off, a high risk of bias was assumed for overall survival in the TERRA study.

The TERRA study is completed.

2.3.2.2 Planned follow-up observation in the studies RECOURSE and TERRA

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow up observation – RCT, trifluridine/tipiracil + BSC vs. placebo + BSC

Study **Outcome category** **Outcome**	**Planned follow-up observation**
RECOURSE	
Mortality:	
Overall survival	Until death or end of study[a]
Morbidity	No patient-relevant outcomes of this category recorded
Health-related quality of life	Not recorded
Side effects	
All outcomes in the category of side effects	Until 30 days after the end of the study medication
TERRA	
Mortality	
Overall survival	Until death or end of study[a]
Morbidity	No patient-relevant outcomes of this category recorded
Health-related quality of life	Not recorded
Side effects	
All outcomes in the category of side effects	Until 30 days after the end of the study medication
a. Planned end of study: after reaching the number of deaths planned for the sample size (571 deaths in the RECOURSE study and 288 deaths in the TERRA study) or 12 months after inclusion of the last patient (the event that occurred last).	
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus	

The observation periods for the outcomes on side effects were systematically shortened in both studies because they were only recorded for the time period of treatment with the study medication (plus 30 days). To be able to draw reliable conclusions on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

2.3.2.3 Characteristics of the populations in the studies RECOURSE and TERRA

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study populations – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Study	RECOURSE		TERRA[a]	
Characteristics Category	Trifluridine/ tipiracil + BSC	Placebo + BSC	Trifluridine/ tipiracil + BSC	Placebo + BSC
	N[b] = 534	N[b] = 266	N[b] = 61	N[b] = 33
Age [years], median [min; max]	63 [27; 82]	63 [27; 82]	55 [32; 80]	56 [33; 75]
Sex [F/M], %	39/61	38/62	43/57	39/61
Family origin, n (%)				
Caucasian	306 (57.3)	155 (58.3)	0 (0.0)	0 (0.0)
Asian or oriental	184 (34.5)	94 (35.3)	61 (100)	33 (100)
Black or African American	4 (0.7)	5 (1.9)	0 (0.0)	0 (0.0)
Not recorded	40 (7.5)	12 (4.5)	0 (0.0)	0 (0.0)
Region, n (%)				
Europe	271 (50.7)	132 (49.6)	0 (0.0)	0 (0.0)
Australia	21 (3.9)	11 (4.1)	0 (0.0)	0 (0.0)
North America	64 (12.0)	35 (13.2)	0 (0.0)	0 (0.0)
Asia	178 (33.3)[c]	88 (33.1)[c]	61 (100)[d]	33 (100)
ECOG PS, n (%)				
0	301 (56.4)	147 (55.3)	12 (19.7)	6 (18.2)
1	233 (43.6)	119 (44.7)	49 (80.3)	27 (81.8)
≥ 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disease duration: time from diagnosis of cancer to randomization [months], median [min; max]	31 [5; 172]	32 [8; 154]	26.2 [5.2; 100.4]	33 [5.3; 77.3]
KRAS mutation status (eCRF), n (%)				
Wild type	260 (48.7)	134 (50.4)	25 (41.0)	19 (57.6)
Mutant	274 (51.3)	132 (49.6)	36 (59.0)	14 (42.4)
KRAS mutation status (IWRS), n (%)				
Wild type	262 (49.1)	131 (49.2)	25 (41.0)	19 (57.6)
Mutant	272 (50.9)	135 (50.8)	36 (59.0)	14 (42.4)
Location of primary tumour, n (%)				
Colon	338 (63.3)	161 (60.5)	36 (59.0)	23 (69.7)
Rectum	196 (36.7)	105 (39.5)	25 (41.0)	10 (30.3)
Number of organs with metastases, n (%)				
1–2	324 (60.7)	153 (57.5)	34 (55.7)	15 (45.5)
≥ 3	210 (39.3)	113 (42.5)	27 (44.3)	18 (54.5)
Number of prior systemic therapies, n (%)				
2	95 (17.8)	45 (16.9)	8 (13.1)	5 (15.2)
3	119 (22.3)	54 (20.3)	17 (27.9)	5 (15.2)
≥ 4	320 (59.9)	167 (62.8)	36 (59.0)	23 (69.7)
Treatment discontinuation, n (%)	528 (98.9)	266 (100)	61 (100)	33 (100)
Study discontinuation, n (%)	495 (92.7)	255 (95.9)	51 (83.6)	25 (75.8)

Table 9: Characteristics of the study populations – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Study	RECOURSE		TERRA[a]	
Characteristics Category	Trifluridine/ tipiracil + BSC	Placebo + BSC	Trifluridine/ tipiracil + BSC	Placebo + BSC
	N[b] = 534	N[b] = 266	N[b] = 61	N[b] = 33

a. Approval-compliant subpopulation.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Patients from Japan.
d. patients from China, Korea and Thailand.

BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; F: female; IWRS: interactive voice/web response system; KRAS: Kirsten rat sarcoma viral oncogene homologue; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; vs.: versus

The patient characteristics are largely comparable between the studies and between the treatment arms in both studies.

The median age was 63 years in the RECOURSE study and 56 years in the TERRA study; the median disease duration in both studies was about 33 months on study entry.

The proportion of women was about 40% (see also Section 2.3.2.7). About half of the patients had KRAS wild type. More than 96% of the patients in the RECOURSE study had been pretreated with at least 2 systemic therapies in the metastatic stage (see Table 22 in Appendix A of the full dossier assessment). In the TERRA study, all patients had received at least 2 prior systemic therapies; it is unclear, however, whether all patients had received at least 2 prior systemic therapies for the metastatic stage, as required in the inclusion criteria. Information on the distribution of the drugs used in the patients' prior therapy was not available in Module 4 A.

The largest differences between the studies concerned family origin and ECOG PS on study entry. The difference in family origin was due to the fact that the TERRA study was conducted in Asia, and the RECOURSE study was conducted also in other parts of the world. Besides, the proportion of patients with an ECOG PS of 0 was notably larger in the RECOURSE study (about 55%) than in the TERRA study, where slightly less than 20% had an ECOG PS of 0. These differences were not considered important enough to stand in the way of a meta-analysis of the 2 studies.

Although, according to the approval, treatment with trifluridine/tipiracil is an option for all tumour types of MCRC [21], both studies only included patients with adenocarcinoma. With more than 95%, this tumour type constitutes the majority of colorectal cancers, however [22,23]. Furthermore, both studies included only pretreated patients, although, according to the Summary of Product Characteristics (SPC), trifluridine/tipiracil can also be given to patients who are not considered candidates for available therapies.

Despite these limitations, it is assumed that the studies RECOURSE and TERRA sufficiently represent the therapeutic indication.

2.3.2.4 Treatment durations and observation periods in the studies RECOURSE and TERRA

Table 10 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study **Duration of the study phase** **Outcome category**	**Trifluridine/tipiracil + BSC**	**Placebo + BSC**
RECOURSE	N = 533	N = 265
Treatment duration [weeks]		
Median [min; max]	9.0 [ND]	8.0 [ND]
Observation period [months]		
Overall survival		
Median [min; max]	5.1 [0.3; 17.3][a]	4.2 [0.7; 15.1][a]
Side effects		
Median [min; max]	2.5 [0.3; 24.5]	1.9 [0.1; 19.4]
TERRA	N = 61	N = 33
Treatment duration [weeks]		
Median [min; max]	8.3 [ND]	8.0 [ND]
Observation period [months]		
Overall survival		
Median [min; max]	7.1 [1.6; 21.8]	3.8 [1.0; 19.4]
Side effects		
Median [min; max]	2.3 [0.3; 14.1]	1.8 [0.7; 5.3]

a. ITT population (N = 800).

BSC: best supportive care; ITT: intention to treat; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

The median treatment duration and the median observation period for side effects were comparable between the 2 studies. The median observation period for overall survival was somewhat shorter in the trifluridine/tipiracil + BSC arm of the RECOURSE study than in the trifluridine/tipiracil + BSC arm of the TERRA study, whereas it was only slightly longer in the placebo + BSC arm of the RECOURSE study than in the placebo + BSC arm of the TERRA study.

The median treatment duration and the median observation period were slightly longer in the trifluridine/tipiracil + BSC arms than in the placebo + BSC arms.

2.3.2.5 Implementation of the appropriate comparator therapy and administration of subsequent therapies

Implementation of the appropriate comparator therapy

As mentioned in Section 2.3.2.1, any anticancer drug therapies were excluded during the randomized study phase of the studies RECOURSE and TERRA. Palliative radiotherapy was completely excluded in the RECOURSE study and excluded in the TERRA study except for pain relief for bone metastases. This exclusion contradicts the guideline on palliative care [24], which emphasizes that the management and the alleviation of distressing symptoms are a key part of palliative care when treating patients with incurable cancer. Symptom-oriented measures can be implemented on their own or parallel to tumour-related or causal therapies. According to the guideline, an either-or is not appropriate, which is why tumour-specific measures (e.g. radiotherapy, surgical procedures, antitumour drug treatments) should be weighed up against the primary or sole therapeutic goal of symptom relief. The S3 guideline on colorectal cancer [25] and the American Society of Clinical Oncology guideline [26] include little information on the treatment in the present therapeutic indication, but the latter points out that chemoradiation or short-course radiation of the primary tumour with palliative intent may be necessary in certain cases to alleviate pain, bleeding, or obstruction.

It was also stated in the oral hearings on the first assessment [27] and on the extension of approval to pretreated metastatic gastric cancer [28] that these therapies play an important role in the alleviation of symptoms. In the oral hearing on gastric cancer, it was postulated that these therapies had no effect on overall survival, so the protocol-related limitations in BSC were negligible. However, it was not denied that the palliative use of radiotherapy or systemic anticancer therapy could have improved the patients' morbidity or health-related quality of life.

An exploratory search for sources on the influence of BSC on overall survival did not yield clear evidence, neither in one direction nor the other (see [29-32], for example). Thus, it cannot be excluded that the protocol-related limitations of BSC had an influence on overall survival.

From the information provided above, it can be deduced overall for the present therapeutic indication that the prohibition of chemo- and radiotherapy means a restriction of palliative care. Thus, BSC was not adequately implemented in the studies RECOURSE and TERRA, and there was potential undertreatment.

Subsequent therapies

The company did not provide any information on subsequent therapies in Module 4 A. The information from the first assessment of the RECOURSE study [13,14] shows that more than 40% of the patients in the total population received further treatments after the end of the study medication (see Table 23 in Appendix A of the full dossier assessment). There is no information regarding which drugs were used after the end of the study treatment, however.

It can be inferred from the publication of the TERRA study [16] that part of the patients of the TERRA study received anticancer drug therapies as subsequent therapy that were not allowed to be administered as concomitant treatment. There is no information on the proportion in the subpopulation considered by the company, however. In addition, there is no information on whether palliative radiotherapy was used after the end of the randomized study treatment and, if so, what the proportion of patients was.

The large proportion of patients with subsequent therapy shows that there was a need for further treatment after the end of the randomized study medication and that the administration of additional treatment options might have been indicated already during the randomized study treatment.

Summary

BSC was not implemented adequately in the 2 studies. This led to a reduced certainty of conclusions in the derivation of the added benefit (see Sections 2.4.2 and 2.5.2).

2.3.2.6 Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
RECOURSE	Yes	Yes	Yes	Yes	Yes	Yes	Low
TERRA	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for both studies. This concurs with the company's assessment.

2.3.2.7 Transferability of the study results to the German health care context

In Module 4 A (Section 4.3.1.2.1) and in the individual outcomes, the company discussed the transferability of the results of the studies RECOURSE and TERRA to the German health care context as follows.

According to the company, the RECOURSE study was the study relevant for the European approval, which is why the patients concurred with the approval. From the TERRA study, only the patients with approval-compliant pretreatment were considered.

The mean age of the patients in both studies was below the median age at disease onset. But the median age of patients with MCRC who start third-line treatment is lower than the median age at disease onset of all patients with MCRC. Thus, the median age of the study patients was relatively close to the median age of the patients in the health care context. In addition, 191 patients aged ≥ 70 years were included, and subgroup analyses did not show effect modifications by age relevant for the conclusion.

The subgroup analyses showed no effect modification by family origin or region so that it could be assumed that there was no difference between Caucasians and Asians in the efficacy of trifluridine/tipiracil in the present therapeutic indication.

Furthermore, the company discussed that the studies RECOURSE and TERRA included only patients with an ECOG PS of 0 or 1. Referring to the characteristics in the trifluridine/tipiracil compassionate-use programme [33], the company stated that the proportion of patients with an ECOG PS ≥ 2 for whom treatment with trifluridine/tipiracil is indicated is only just under 10% in Germany. According to the company, this proportion was confirmed by the characteristics of the TALLISUR study, which had no limitations regarding ECOG PS.

Finally, the outcomes were determined according to internationally valid, objective criteria which are applied in the same way in everyday health care in Germany.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
- Health-related quality of life
- Side effects
  - serious AEs (SAEs)
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs

- myelosuppression, operationalized as blood and lymphatic system disorders (SOC, severe AEs CTCAE grade ≥ 3), including as common manifestations: anaemia, febrile neutropenia, leukopenia, neutropenia (in each case PT, severe AEs CTCAE grade ≥ 3)
- gastrointestinal toxicity, operationalized as gastrointestinal disorders (SOC, AEs), including as common manifestations: diarrhoea, nausea, vomiting (in each case PT, AEs)
- if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 12 shows for which outcomes data were available in the studies included.

Table 12: Matrix of outcomes – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study	Outcomes								
	Overall survival	**Morbidity**	**Health-related quality of life**	**SAEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Discontinuation due to AEs**	**Gastrointestinal toxicity[a]**	**Myelosuppression[b]**	**Further specific AEs[c]**
RECOURSE	Yes	No[d]	No[e]	Yes	Yes	Yes	Yes	Yes	Yes
TERRA	Yes	No[d]	No[e]	Yes	Yes	Yes	Yes	Yes	Yes

a. Operationalized as gastrointestinal disorders (SOC, AEs), including as common manifestations: diarrhoea, nausea, vomiting (in each case PT, AEs).
b. Operationalized as blood and lymphatic system disorders (SOC, severe AEs CTCAE grade ≥ 3), including as common manifestations: anaemia, febrile neutropenia, leukopenia, neutropenia (in each case PT, severe AEs CTCAE grade ≥ 3).
c. The following events are considered (MedDRA coding): psychiatric disorders (SOC, AEs) and hypertension (PT, severe AEs CTCAE grade ≥ 3).
d. No patient-relevant outcomes of this category recorded.
e. Outcome not recorded.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study	Study level	Outcomes								
		Overall survival	Morbidity	Health-related quality of life	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Gastrointestinal toxicity[a]	Myelosuppression[b]	Further specific AEs[c]
RECOURSE	L	L	–[d]	–[e]	H[f]	H[f]	L[g]	H[f]	H[f]	H[f]
TERRA	L	H[h]	–[d]	–[e]	H[f]	H[f]	L[g]	H[f]	H[f]	H[f]

a. Operationalized as gastrointestinal disorders (SOC, AEs), including as common manifestations: diarrhoea, nausea, vomiting (in each case PT, AEs).
b. Operationalized as blood and lymphatic system disorders (SOC, severe AEs CTCAE grade ≥ 3), including as common manifestations: anaemia, febrile neutropenia, leukopenia, neutropenia (in each case PT, severe AEs CTCAE grade ≥ 3).
c. The following events are considered (MedDRA coding): psychiatric disorders (SOC, AEs) and hypertension (PT, severe AEs CTCAE grade ≥ 3).
d. No patient-relevant outcomes of this category recorded.
e. Outcome not recorded.
f. Incomplete observations for potentially informative reasons.
g. Despite the low risk of bias, limited certainty of results is assumed for the outcome "discontinuation due to AEs".
h. Missing information according to which criteria the second data cut-off was conducted. Results on the planned (first) data cut-off are not available.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The risk of bias for overall survival was rated as low in the RECOURSE study. This concurs with the company's assessment. In the TERRA study, in contrast, the risk of bias for overall survival was rated as high, contrary to the company's assessment, as no results on the planned (first) data cut-off were available and it was unclear according to which criteria the second data cut-off was conducted.

The risk of bias for the side effect outcomes, with the exception of the outcome "discontinuation due to AEs", was rated as high in both studies. The reason for the high risk of bias were incomplete observations for potentially informative reasons due to the follow-up observation of only 30 days after the end of the study treatment. The company considered the overall risk of bias for the results on side effects and rated it as low.

Despite a low risk of bias, the certainty of results for the outcome "discontinuation due to AEs" was limited in both studies, as treatment discontinuation for other reasons (e.g. progression

according to the Response Evaluation Criteria in Solid Tumours [RECIST]) represents a competing event. After discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs this concerns.

Overall assessment of the certainty of conclusions

In summary, the certainty of results on all outcomes is to be rated as limited based on the respective high risk of bias – except for the outcomes "overall survival" in the RECOURSE study and "discontinuation due to AEs". The certainty of results was reduced in the outcome "discontinuation due to AEs", however, since it is unknown how many events could not be observed due to the occurrence of competing events (e.g. progression). For the outcomes "gastrointestinal toxicity" and "myelosuppression" and its common manifestation "neutropenia", however, the certainty of results was not limited despite the high risk of bias (see Section 2.4.3).

Besides the limitations due to the risk of bias, it is uncertain for all outcomes whether the ACT was implemented adequately (see Section 2.3.2.5). This resulted in a limited certainty of conclusions for all outcomes in both studies.

An additional uncertainty factor for the TERRA study was that the formation of the subpopulation considered by the company was not sufficiently described.

Hence, at most indications, e.g. of an added benefit, can be derived on the basis of the available data.

2.4.3 Results

Table 14 summarizes the results on the comparison of trifluridine/tipiracil + BSC versus placebo + BSC in patients with MCRC. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on the presented event time analyses can be found in Appendix C of the full dossier assessment. The tables with the events on common AEs, SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuations due to AEs can be found in Appendix B of the full dossier assessment. Forest plots of the meta-analyses calculated by the Institute can be found in Appendix C.2 of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Outcome category **Outcome** **With/without progression or manifestations of specific AEs** **Study**	**Trifluridine/tipiracil + BSC** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Placebo + BSC** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Trifluridine/tipiracil + BSC vs. placebo + BSC** **HR [95% CI]; p-value**
Mortality					
Overall survival					
RECOURSE[a]	534	7.2 [6.6; 7.8] 463 (86.7)	266	5.2 [4.6; 5.9] 249 (93.6)	0.69 [0.59; 0.81]; < 0.001[b]
TERRA[c]	61	8.0 [6.3; 9.2] 53 (86.9)	33	4.4 [3.2; 7.2] 29 (87.9)	0.69 [0.43; 1.10]; 0.118[d]
Total					0.70 [0.60; 0.81]; < 0.001[e]
Morbidity	No patient-relevant outcomes of this category recorded				
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)					
With progression of the underlying disease					
RECOURSE[a]	533	0.2 [0.2; 0.3] 524 (98.3)	265	0.4 [0.3; 0.4] 249 (94.0)	–
TERRA[f]	61	0.4 [0.3; 0.4] 61 (100)	33	0.4 [0.2; 0.9] 29 (87.9)	–
Without progression of the underlying disease[g]					
RECOURSE[a]	*533*	*0.3 [0.2; 0.3]* *520 (97.6)*	*265*	*0.4 [0.4; 0.4]* *244 (92.1)*	–
SAEs					
With progression of the underlying disease					
RECOURSE[a]	533	11.6 [8.7; NA] 162 (30.4)	265	5.4 [5.1; NA] 89 (33.6)	0.72 [0.55; 0.94]; 0.014[b]
TERRA[f]	61	NA [NA; NA] 15 (24.6)	33	NA [NA; NA] 12 (36.4)	0.53 [0.25; 1.14]; 0.098[d]
Total					0.69 [0.54; 0.89]; 0.004[e]
Without progression of the underlying disease[g]					
RECOURSE[a]	*533*	*NA [NA; NA]* *118 (22.1)*	*265*	*NA [NA; NA]* *45 (17.0)*	*1.02 [0.72; 1.45]; 0.904[b]*

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Outcome category **Outcome**	**Trifluridine/tipiracil + BSC**		**Placebo + BSC**		**Trifluridine/tipiracil + BSC vs. placebo + BSC**
With/without progression or manifestations of specific AEs **Study**	**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**
Severe AEs (CTCAE grade ≥ 3)					
With progression of the underlying disease					
RECOURSE[a]	533	1.5 [1.3; 1.8] 372 (69.8)	265	2.5 [2.0; 3.3] 138 (52.1)	1.44 [1.18; 1.77]; < 0.001[b]
TERRA[f]	61	2.3 [1.9; 6.1] 34 (55.7)	33	1.4 [0.5; NA] 18 (54.5)	0.75 [0.42; 1.35]; 0.342[d]
Total					1.36 [1.12; 1.64]; 0.002[e]
Without progression of the underlying disease[g]					
RECOURSE[a]	*533*	*1.8 [1.6; 2.0]* *343 (64.4)*	*265*	*3.8 [2.8; 18.6]* *110 (41.5)*	*1.74 [1.40; 2.17]; < 0.001[b]*
Discontinuation due to AEs					
With progression of the underlying disease					
RECOURSE[a]	533	NA [NA; NA] 57 (10.7)	265	NA [NA; NA] 36 (13.6)	0.63 [0.41; 0.96]; 0.030[b]
TERRA[f]	61	NA [NA; NA] 5 (8.2)	33	NA [NA; NA] 7 (21.2)	0.36 [0.12; 1.15]; 0.072[d]
Total					0.59 [0.39; 0.87]; 0.009[e]
Without progression of the underlying disease[g]					
RECOURSE[a]	*533*	*NA [NA; NA]* *16 (3.0)*	*265*	*NA [NA; NA]* *4 (1.5)*	*1.64 [0.54; 4.98]; 0.376[b]*
Gastrointestinal toxicity, operationalized as gastrointestinal disorders (SOC, AE)[h]					
RECOURSE[a]	533	0.5 [0.4; 0.5] 414[k] (77.7)	265	1.5 [1.1; 1.9] 162[k] (61.1)	1.62 [1.34; 1.95][i]; < 0.001[j]
TERRA[f]	61	1.0 [0.4; 1.3] 43 (70.5)	33	1.8 [1.5; 5.1] 20 (60.6)	1.49 [0.85; 2.59][i]; 0.159[j]
Total					1.56 [1.31; 1.86]; < 0.001[e]

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Outcome category Outcome	Trifluridine/tipiracil + BSC		Placebo + BSC		Trifluridine/tipiracil + BSC vs. placebo + BSC
With/without progression or manifestations of specific AEs Study	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
Diarrhoea (PT, AE)[h, l]					
RECOURSE[a]	533	10.3 [7.7; 18.2] 173 (32.5)	265	NA [NA; NA] 33 (12.5)	2.58 [1.78; 3.76][i]; < 0.001[j]
TERRA[f]	61	NA [NA; NA] 9 (14.8)	33	5.1 [5.1; NA] 3 (9.1)	1.42 [0.38; 5.31][i]; 0.598[j]
Total					2.50 [1.75; 3.59]; < 0.001[e]
Nausea (PT, AE)[h, l]					
RECOURSE[a]	533	3.4 [2.2; 13.5] 261 (49.0)	265	17.7 [NA; NA] 64 (24.2)	2.38 [1.81; 3.14][i]; < 0.001[j]
TERRA[f]	61	5.3 [1.3; NA] 28 (45.9)	33	NA [NA; NA] 5 (15.2)	3.47 [1.34; 9.00][i]; 0.006[j]
Total					2.41 [1.85; 3.14]; < 0.001[e]
Vomiting (PT, AE)[h]					
RECOURSE[a]	533	NA [NA; NA] 151 (28.3)	265	17.7 [NA; NA] 39 (14.7)	1.93 [1.35; 2.77][i]; < 0.001[j]
TERRA[f]	61	NA [NA; NA] 15 (24.6)	33	NA [NA; NA] 6 (18.2)	1.26 [0.48; 3.29][i]; 0.633[j]
Total					1.78 [1.28; 2.49]; < 0.001[e]
Myelosuppression, operationalized as blood and lymphatic system disorders (SOC, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	6.9 [4.7; 9.7] 193 (36.2)	265	NA [NA; NA] 11 (4.2)	8.77 [4.77; 16.13][i]; < 0.001[j]
TERRA[f]	61	NA [NA; NA] 17 (27.9)	33	NA [NA; NA] 5 (15.2)	1.57 [0.57; 4.30][i]; 0.377[j]
Total					5.57 [3.30; 9.38]; < 0.001[e]
Anaemia (PT, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	17.9 [15.8; NA] 92 (17.3)	265	NA [NA; NA] 7 (2.6)	5.49 [2.53; 11.89][i]; < 0.001[j]
TERRA[f]	61	NA [NA; NA] 7 (11.5)	33	NA [NA; NA] 5 (15.2)	0.70 [0.22; 2.22][i]; 0.546[j]
Total					2.97 [1.56; 5.65]; 0.004[e]

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Outcome category Outcome	Trifluridine/tipiracil + BSC		Placebo + BSC		Trifluridine/tipiracil + BSC vs. placebo + BSC
With/without progression or manifestations of specific AEs Study	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
Febrile neutropenia (PT, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	NA [NA; NA] 21 (3.9)	265	NA [NA; NA] 0 (0.0)	RR: 21.42 [1.30; 352.23]; 0.001[m]
TERRA[f]	61	ND	33	ND	ND
Leukopenia (PT, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	NA [NA; NA] 15 (2.8)	265	NA [NA; NA] 0 (0.0)	RR: 15.44 [0.93; 257.08]; 0.006[m]
TERRA[f]	61	ND	33	ND	ND
Neutropenia (PT, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	NA [NA; NA] 110 (20.6)	265	NA [NA; NA] 0 (0.0)	RR: 110.09 [6.87; 1764]; < 0.001
TERRA[f]	61	NA [NA; NA] 10 (16.4)	33	NA [NA; NA] 0 (0.0)	RR: 11.52 [0.70; 190.52]; 0.0878
Total					RR: 61.61 [8.53; 445]; < 0.001[n]
Psychiatric disorders (SOC, AE)[h]					
RECOURSE[a]	533	NA [NA; NA] 51 (9.6)	265	NA [NA; NA] 42 (15.8)	0.48 [0.32; 0.73][i]; < 0.001[j]
TERRA[f]	61	ND	33	ND	ND
Hypertension (PT, CTCAE grade ≥ 3)[h]					
RECOURSE[a]	533	NA [NA; NA] 8 (1.5)	265	NA [NA; NA] 10 (3.8)	0.33 [0.13; 0.86][i]; 0.017[j]
TERRA[f]	61	ND	33	ND	ND

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Outcome category Outcome	Trifluridine/tipiracil + BSC		Placebo + BSC		Trifluridine/tipiracil + BSC vs. placebo + BSC
With/without progression or manifestations of specific AEs Study	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

a. Data cut-off 8 October 2014.
b. Log-rank test, stratified by KRAS status, time since diagnosis of first metastasis, and region.
c. Data cut-off 16 February 2016.
d. Log-rank test, stratified by KRAS status and country.
e. Fixed-effect model based on individual patient data, stratified by KRAS status.
f. Data cut-off 23 December 2015.
g. AEs considered by the investigator to be related to progression of the underlying disease were not considered in the analyses of the overall rates shown here.
h. With progression of the underlying disease.
i. Effect and CI: Cox proportional hazards model, adjusted by region, baseline ECOG PS, and prior ramucirumab treatment.
j. Log-rank test, adjusted by region, baseline ECOG PS, and prior ramucirumab treatment.
k. Contradictory data on frequencies. Different frequencies are cited in another section of Module 4 A (trifluridine/tipiracil + BSC: n = 413 vs. placebo + BSC: n = 161).
l. Designations of SOC and PT from MedDRA without adaptation.
m. Institute's calculation, unconditional exact test (CSZ method according to [34]).
n: Institute's calculation, fixed-effect model (Mantel-Haenszel method). In the calculation, the correction factor of 0.5 was added to each cell frequency of the 2x2 table in both studies.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; KRAS: Kirsten rat sarcoma viral oncogene homologue; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SOC: System Organ Class; vs: versus

On the basis of the 2 available RCTs, at most an indication, e.g. of an added benefit, can be determined for the outcome "overall survival".

Despite the high risk of bias, indications, e.g. of greater harm, can partly be determined for the outcomes of the outcome category of side effects because the certainty of results was partly not limited due to the large number of early events and the clear differences between the treatment arms. Further information can be found in Section 2.4.2 and in the description of the results below.

Mortality

Overall survival

The meta-analysis showed a statistically significant difference between the treatment arms in favour of trifluridine/tipiracil + BSC in comparison with placebo + BSC for the outcome "overall survival".

For the outcome "overall survival", an effect modification by the number of prior regimens (2 versus ≥ 3) on the basis of the RECOURSE study was shown in the addendum to the first assessment [13]. The results from the subgroup analysis of the RECOURSE study were used for the derivation of the added benefit (see Section 2.4.4). There are no corresponding analyses on the TERRA study. Thus, there is no confirmation (replication) by a further study for the subgroup of interest that is necessary for a high certainty of conclusions. The maximum certainty of conclusions for overall survival was therefore reduced to a hint.

No added benefit of trifluridine/tipiracil + BSC in comparison with BSC resulted from the subgroup analyses for patients with 2 prior regimens; an added benefit for these patients is not proven. There was a hint of an added benefit of trifluridine/tipiracil + BSC in comparison with BSC for the subgroup of patients with ≥ 3 prior regimens.

This deviates from the assessment of the company, which did not use any subgroup results for this subgroup characteristic for the derivation of the added benefit and derived proof of an added benefit on the basis of the meta-analyses of the total populations of both studies.

Morbidity

The studies RECOURSE and TERRA did not record patient-relevant morbidity outcomes. The data from the TALLISUR study are not interpretable (see Section 2.3.1). This resulted in no hint of an added benefit of trifluridine/tipiracil + BSC in comparison with BSC; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived proof of an added benefit on the basis of outcomes that are not patient-relevant.

Health-related quality of life

Health-related quality of life was not recorded in the studies RECOURSE and TERRA. The data from the TALLISUR study are not interpretable. This resulted in no hint of an added benefit of trifluridine/tipiracil + BSC in comparison with BSC; an added benefit is therefore not proven.

This assessment concurs with that of the company insofar as the company did not conduct a formal derivation of the added benefit. In the company's opinion, the results of the TALLISUR study showed maintained health-related quality of life under treatment with trifluridine/tipiracil, which supported the relevance of the positive effects in overall survival. An assessment of the company's interpretation can be found in Section 2.3.1.

Side effects

The outcomes on the overall rates of side effects – i.e. AEs, SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs – include not only treatment-related AEs, but also AEs attributable to progression of the underlying disease. For these outcomes, the company presented analyses with and without AEs attributable to progression of the underlying disease,

and thus followed the comments in the dossier assessment of trifluridine/tipiracil for the treatment of gastric cancer [35]. In the RECOURSE study, the assessment of whether an AE was due to progression of the underlying disease was carried out by the investigator and documented in the electronic case report form. According to the study protocol, the same approach was planned for the TERRA study; however, for the analyses presented, the classification was made on the basis of a list included in Module 4 A (Appendix G6.7). The company did not specify in Module 4 A who compiled this list, when, and according to which criteria. Since selective reporting cannot be ruled out by this procedure, the analyses of the TERRA study without AEs attributable to progression of the underlying disease were not taken into account.

Hereinafter, the results on the overall rates of side effects that include AEs attributable to progression of the underlying disease are interpreted as a mixture of progression/symptoms and side effects. On the basis of the results without AEs attributable to progression of the underlying disease, a descriptive examination is carried out to determine which of the 2 aspects, if any, is responsible for the effect. This concurs with the company's approach in Module 4 A.

SAEs

The meta-analysis showed a statistically significant difference in favour of trifluridine/tipiracil + BSC for the outcome "SAEs". As a result, there was a hint of lesser harm of trifluridine/tipiracil + BSC in comparison with BSC.

This deviates from the assessment of the company, which derived proof of an added benefit.

The analysis of SAEs without events attributable to progression of the underlying disease showed no statistically significant difference between the treatment arms on the basis of the results in the RECOURSE study. This suggests that the advantage of tipiracil/trifluridine + BSC in comparison with BSC for the outcome "SAEs" in the RECOURSE study was mostly caused by progression events and not by treatment-related AEs.

Severe AEs (CTCAE grade ≥ 3)

The meta-analysis showed a statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC for the outcome "severe AEs (CTCAE grade ≥ 3)". As a result, there was a hint of greater harm of trifluridine/tipiracil + BSC in comparison with BSC.

This deviates from the assessment of the company, which derived an indication of lesser benefit.

In the RECOURSE study, the effect estimation to the disadvantage of trifluridine/tipiracil + BSC is even higher in the analysis of severe AEs (CTCAE grade ≥ 3) without events attributable to deterioration of the underlying disease. This suggests that the disadvantage of tipiracil/trifluridine + BSC in comparison with BSC for the outcome "severe AEs (CTCAE grade ≥ 3)" in the RECOURSE study was probably caused by treatment-related AEs and not by prevention of progression events.

Discontinuation due to AEs

The meta-analysis showed a statistically significant difference in favour of trifluridine/tipiracil + BSC for the outcome "discontinuation due to AEs".

For the outcome "discontinuation due to AEs", there was an effect modification by age on study entry (< 65 years versus ≥ 65 years). The results from the subgroup analysis were used for the derivation of the added benefit (see Section 2.4.4). This resulted in no hint of greater or lesser harm from trifluridine/tipiracil + BSC in comparison with BSC for patients aged < 65 years. Greater or lesser harm is therefore not proven. For patients ≥ 65 years of age, there was a hint of lesser harm from trifluridine/tipiracil + BSC in comparison with BSC.

This deviates from the assessment of the company, which derived proof of an added benefit on the basis of the total population.

The analysis of the outcome "discontinuation due to AEs" without events attributable to deterioration of the underlying disease showed no statistically significant difference between the treatment arms on the basis of the RECOURSE study. This suggests that the advantage of tipiracil/trifluridine + BSC in comparison with BSC for the outcome "discontinuation due to AEs" in the RECOURSE study was mostly caused by progression events and not by treatment-related AEs. There was no effect modification by age on study entry (< 65 years versus ≥ 65 years).

Myelosuppression

In the present data situation, the outcome "myelosuppression" was operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC "blood and lymphatic system disorders", considering the PTs "anaemia", "febrile neutropenia", "leukopenia", and "neutropenia" as common manifestations of myelosuppression.

A statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC was shown at the level of the SOC "blood and lymphatic system disorders". This resulted in greater harm of trifluridine/tipiracil + BSC in comparison with BSC. Greater harm was also shown in the 4 manifestations of myelosuppression. The observed effect was very large, and it is very unlikely for the control arm that a relevant number of events remained unobserved due to censoring. This resulted in an indication of greater harm at SOC level and for the common manifestation "neutropenia"; there was a hint of greater harm for each of the common manifestations "febrile neutropenia" and "leukopenia".

An effect modification by age (< 65 years versus ≥ 65 years) was shown for the PT "anaemia" (see Section 2.4.4). In each case, the results from the subgroup analysis were used for the derivation of the added benefit. This resulted in a hint of greater harm for patients aged ≥ 65 years. For patients aged < 65 years, however, there was no hint of greater or lesser harm from trifluridine/tipiracil + BSC in comparison with BSC. Thus, greater or lesser harm for these patients is not proven for the outcome "anaemia".

This assessment deviates from that of the company, which analysed the data on this outcome in the chosen operationalization, but did not consider the results in the derivation of the added benefit.

Gastrointestinal toxicity

In the present data situation, the outcome "gastrointestinal toxicity" was operationalized as AEs of the SOC "gastrointestinal disorders", considering the PTs "diarrhoea", "nausea" and "vomiting" as common manifestations of gastrointestinal toxicity.

Despite the high risk of bias, the certainty of results for the outcome "gastrointestinal toxicity" (SOC, AEs) in the RECOURSE study was not limited: Due to the high number of early events and the marked difference between the treatment arms, it is not assumed that incomplete follow-up observation led to such a significant number of events being unconsidered that the observed effect was called into question (see Figure 11 of the full dossier assessment). Hence, an indication, e.g. of greater harm, can be derived for this outcome.

A statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC was shown for the SOC "gastrointestinal disorders". This resulted in an indication of greater harm of trifluridine/tipiracil + BSC in comparison with BSC. Greater harm was also shown in the 3 manifestations of gastrointestinal toxicity; the certainty of conclusions was a hint, however.

This assessment deviates from that of the company, which derived proof of greater harm and did not consider PTs further.

Further specific AEs

Psychiatric disorders (SOC, AEs)

For the outcome "psychiatric disorders" (SOC, AEs), the frequency criterion was exceeded in the RECOURSE study but not in the TERRA study (see Appendix B of the full dossier assessment), which is why no results were available for the TERRA study in Module 4 A. The added benefit was therefore derived solely on the basis of the RECOURSE study.

The RECOURSE study showed a statistically significant difference in favour of trifluridine/tipiracil + BSC for the outcome "psychiatric disorders" (SOC, AEs). As a result, there was a hint of lesser harm of trifluridine/tipiracil + BSC in comparison with BSC.

Hypertension (PT, severe AEs [CTCAE grade ≥ 3])

For the outcome "hypertension" (PT, severe AEs [CTCAE grade ≥ 3]), the frequency criterion was exceeded in the RECOURSE study but not in the TERRA study (see Appendix B of the full dossier assessment), which is why no results were available for the TERRA study in Module 4 A. The added benefit was therefore derived solely on the basis of the RECOURSE study.

The RECOURSE study showed a statistically significant difference in favour of trifluridine/tipiracil + BSC for the outcome "hypertension" (PT, severe AEs [CTCAE grade ≥ 3]). As a result, there was a hint of lesser harm of trifluridine/tipiracil + BSC in comparison with BSC.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- age (< 65 years, ≥ 65 years)
- sex (male, female)

The number of prior regimens (2 versus ≥ 3) was additionally considered as subgroup characteristic, 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 [13].

The p-values of the interaction tests presented in the company's subgroup analyses are not in all cases comprehensible. Thus, the Institute conducted its own calculations of all interaction tests on the basis of the aggregate data (effect estimations and confidence intervals) of the subgroups of the respective studies for the outcomes relevant for the report and used these results.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup. Available Kaplan-Meier curves on the subgroup results can be found in Appendix C.3 of the full dossier assessment.

Table 15 summarizes the subgroup results of the meta-analysis of the studies RECOURSE and TERRA.

Table 15: Subgroups (overall survival, side effects, time to event) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Outcome Characteristic Study Subgroup	Trifluridine/tipiracil + BSC N	Trifluridine/tipiracil + BSC Median time to event in months [95% CI] Patients with event n (%)	Placebo + BSC N	Placebo + BSC Median time to event in months [95% CI] Patients with event n (%)	Trifluridine/tipiracil + BSC vs. placebo + BSC 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*
					Interaction:	0.027[b, d]
TERRA						
2				ND		
3				ND		
≥ 4				ND		
Treatment discontinuation due to AEs						
Age						
RECOURSE						
< 65 years	299	NA 36 (12.0)	147	NA 14 (9.5)	1.05 [0.56; 1.97]	0.876
≥ 65 years	234	NA 21 (9.0)	118	NA 22 (18.6)	0.36 [0.19; 0.67]	0.001
TERRA						
< 65 years	49	NA 5 (10.2)	28	NA 7 (25.0)	0.38 [0.12; 1.21][e]	0.090
≥ 65 years	12	NA 0 (0.0)	5	NA 0 (0.0)	NC	
Total					Interaction:	0.050[f, g]
< 65 years	348	41 (11.8)[b]	175	21 (12.0)[b]	0.85 [0.49; 1.48]	ND
≥ 65 years	246	21 (8.5)[b]	123	22 (17.9)[b]	NC	ND

Table 15: Subgroups (overall survival, side effects, time to event) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Outcome Characteristic Study Subgroup	Trifluridine/tipiracil + BSC N	Trifluridine/tipiracil + BSC Median time to event in months [95% CI] Patients with event n (%)	Placebo + BSC N	Placebo + BSC Median time to event in months [95% CI] Patients with event n (%)	Trifluridine/tipiracil + BSC vs. placebo + BSC HR [95% CI]	 p-value
Myelosuppression[h]						
Age						
RECOURSE						
< 65 years	299	10.2 [6.1; NA] 85 (28.4)	147	NA 8 (5.4)	4.93 [2.38; 10.20][e]	< 0.001
≥ 65 years	234	4.0 [2.8; 7.4] 108 (46.2)	118	NA 3 (2.5)	19.52 [6.19; 61.61][e]	< 0.001
TERRA						
< 65 years	49	NA 12 (24.5)	28	NA 5 (17.9)	1.13 [0.39; 3.29][e]	0.822
≥ 65 years	12	NA 5 (41.7)	5	NA 0 (0.0)	NC	0.193
Total					Interaction:	0.005[f]
< 65 years	348	97 (27.9)[b]	175	13 (7.4)[b]	3.15 [1.73; 5.73]	ND
≥ 65 years	246	113 (45.9)[b]	123	3 (2.4)[b]	NC	ND
Anaemia (PT, severe AE [CTCAE grade ≥ 3])[i]						
Age						
RECOURSE						
< 65 years	299	ND 33 (11.0)	147	ND 5 (3.4)	2.84 [1.10; 7.35][e]	0.024
≥ 65 years	234	11.8 [9.7; 17.9] 59 (25.2)	118	ND 2 (1.7)	12.86 [3.12; 52.95][e]	< 0.001
TERRA						
< 65 years	49	ND 4 (8.2)	28	ND 5 (17.9)	0.44 [0.12; 1.62][e]	0.203
≥ 65 years	12	ND 3 (25.0)	5	ND 0 (0.0)	NC	0.320
Total					Interaction:	0.009[f]
< 65 years	348	37 (10.6)[b]	175	10 (5.7)[b]	1.51 [0.70; 3.26]	ND
≥ 65 years	246	62 (25.2)[b]	123	2 (1.6)[b]	NC	ND

Table 15: Subgroups (overall survival, side effects, time to event) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (multipage table)

Outcome Characteristic Study Subgroup	Trifluridine/tipiracil + BSC		Placebo + BSC		Trifluridine/tipiracil + BSC vs. placebo + BSC	
	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

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.
d. 2 versus ≥ 3 prior regimens.
e. Wald confidence limits.
f. Institute's calculation using the effect estimations from the respective studies.
g. p-value = 0.049955.
h. Operationalized as blood and lymphatic system disorders (SOC, CTCAE grade ≥ 3).
i. Manifestation of myelosuppression.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least) one event; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Overall survival

For the outcome "overall survival", the RECOURSE study showed a statistically significant interaction for the characteristic "number of prior regimens" (2 versus ≥ 3). This subgroup analysis was not available for the TERRA study. The added benefit was therefore derived solely on the basis of the RECOURSE study. The missing subgroup analyses for the TERRA study increased the uncertainty, however, which is why at most hints, e.g. of an added benefit, can be derived for the subgroup results.

No statistically significant difference between the treatment arms was shown for patients with 2 prior regimens on the basis of the RECOURSE study. This resulted in no hint of an added benefit of trifluridine/tipiracil + BSC in comparison with BSC for the subgroup of patients with 2 prior regimens. An added benefit for these patients is therefore not proven.

A statistically significant difference between the treatment arms in favour of trifluridine/tipiracil + BSC was shown for patients with ≥ 3 prior regimens on the basis of the RECOURSE study. This resulted in a hint of an added benefit for patients with ≥ 3 prior regimens.

This deviates from the assessment of the company, which presented subgroup analyses according to the number of prior regimens for the RECOURSE study, but not for the TERRA study, in the Appendix to Module 4 A and derived proof of an added benefit on the basis of the meta-analyses of the total population of both studies.

Treatment discontinuation due to AEs

For the outcome "treatment discontinuation due to AEs", there was a statistically significant interaction for the characteristic of age (< 65 years versus ≥ 65 years).

No statistically significant difference between the treatment arms was shown for patients < 65 years of age on the basis of the meta-analysis. This resulted in no hint of greater or lesser harm from trifluridine/tipiracil + BSC in comparison with BSC for the subgroup of patients aged < 65 years. Hence, greater or lesser harm is not proven for these patients.

A statistically significant difference in favour of trifluridine/tipiracil + BSC was shown for patients aged ≥ 65 years on the basis of the results of the RECOURSE study. In the TERRA study, there were no events in this subgroup in any treatment arm. This resulted in a hint of lesser harm from trifluridine/tipiracil + BSC in comparison with BSC for the subgroup of patients aged ≥ 65 years based on the results of the RECOURSE study.

This deviates from the assessment of the company, which derived proof of an added benefit for the total population.

Myelosuppression

A statistically significant interaction for the characteristic "age" (< 65 years versus ≥ 65 years) was shown for the outcome "myelosuppression" (operationalized as blood and lymphatic system disorders [SOC, CTCAE grade ≥ 3]).

A statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC was shown for patients aged < 65 years on the basis of the results of the meta-analysis. This resulted in an indication of greater harm from trifluridine/tipiracil + BSC in comparison with BSC for the subgroup of patients aged < 65 years.

A statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC was shown for patients aged ≥ 65 years on the basis of the results of the RECOURSE study. This resulted in an indication of greater harm from trifluridine/tipiracil + BSC in comparison with BSC for the subgroup of patients aged ≥ 65 years.

Since there is an indication of harm of the same extent in both subgroups, hereinafter the result of the total population is considered in the derivation of the added benefit.

This is in line with the assessment of the company, which derived an indication of lesser benefit on the basis of the results of the total population.

Anaemia (SOC, CTCAE grade ≥ 3) as common manifestation of myelosuppression

For the outcome "anaemia" (SOC, CTCAE grade ≥ 3), a common manifestation of myelosuppression, there was a statistically significant interaction for the characteristic of age (< 65 years versus ≥ 65 years).

No statistically significant difference between the treatment arms was shown for patients < 65 years of age on the basis of the meta-analysis. This resulted in no hint of greater or lesser harm from trifluridine/tipiracil + BSC in comparison with BSC for the subgroup of patients aged < 65 years. Hence, greater or lesser harm is not proven for these patients.

A statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC was shown for patients aged ≥ 65 years on the basis of the results of the RECOURSE study. A large effect was shown for these patients, but this subgroup analysis was based only on the RECOURSE study. This resulted in a hint of greater harm from trifluridine/tipiracil + BSC in comparison with BSC for the subgroup of patients aged ≥ 65 years.

This deviates from the assessment of the company, which rated the effect modification by age as irrelevant due to fewer events in the TERRA study.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

Determination of the outcome category for the outcomes on side effects

The dossier did not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

The outcome “discontinuation due to AEs” was assigned to the category “non-serious/non-severe”, as there was no information about whether the respective events were mostly serious/severe.

The outcome “gastrointestinal toxicity” and the common manifestations “diarrhoea”, “nausea” and “vomiting” as well as the outcome “psychiatric disorders” were assigned to the category “non-serious/non-severe”, as the majority of the respective events were mostly non-serious/non-severe.

The outcome “myelosuppression” and the common manifestations “anaemia”, “febrile neutropenia”, “leukopenia” and “neutropenia” as well as the outcome “hypertension” were assigned to the category “serious/severe”, as only severe AEs (CTCAE grade ≥ 3) were considered in the operationalization.

Table 16: Extent of added benefit at outcome level: trifluridine/tipiracil + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trifluridine/tipiracil + BSC vs. placebo + BSC** **Time to event (months)** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival Number of prior regimens		
2	Median: 6.2 vs. 4.8 months HR: 1.03 [0.69; 1.53] p = 0.892[c]	Added benefit not proven
≥ 3	Median: NR HR: 0.63 [0.53; 0.75] p < 0.001 probability: "hint"[c]	Outcome category: mortality CI_u < 0.85 added benefit, extent: "major"
Patient-relevant outcomes of morbidity		
No usable data		Lesser benefit/added benefit not proven
Health-related quality of life		
No usable data		Lesser benefit/added benefit not proven
Side effects		
SAEs, with progression of the underlying disease	Median: 11.6–NA vs. 5.4–NA months[d] HR: 0.69 [0.54; 0.89] p = 0.004 probability: "hint"	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 lesser harm, extent: "considerable"
Severe AEs (CTCAE grade ≥ 3), with progression of the underlying disease	Median: 1.5–2.3 vs. 1.4–2.5 months[d] HR: 1.36 [1.12; 1.64] HR: 0.74 [0.61; 0.89][e] p = 0.002 probability: "hint"	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 greater harm, extent: "considerable"
Discontinuation due to AEs, with progression of the underlying disease		
Age		
< 65 years	Median: NA vs. NA HR: 0.85 [0.49; 1.48] p = ND	Greater/lesser harm not proven
≥ 65 years	Median: NA vs. NA HR: 0.36 [0.19; 0.67] p = 0.001 probability: "hint"[c]	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"

Table 16: Extent of added benefit at outcome level: trifluridine/tipiracil + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trifluridine/tipiracil + BSC vs. placebo + BSC** **Time to event (months)** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Gastrointestinal toxicity, with progression of the underlying disease	Median: 0.5–1.0 vs. 1.5–1.8 months[d] HR: 1.56 [1.31; 1.86] HR: 0.64 [0.54; 0.76][e] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Diarrhoea	Median: 10.3–NA vs. 5.1–NA months[d] HR: 2.50 [1.75; 3.59] HR: 0.40 [0.28; 0.57][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Nausea	Median: 3.4–5.3 vs. 17.7–NA months[d] HR: 2.41 [1.85; 3.14] HR: 0.42 [0.32; 0.54][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Vomiting	Median: NA vs. 17.7–NA months[d] HR: 1.78 [1.28; 2.49] HR: 0.56 [0.40; 0.78][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Myelosuppression	Median: 6.9–NA vs. NA HR: 5.57 [3.30; 9.38] HR: 0.18 [0.11; 0.30][e] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm, extent: "major"
Anaemia		
Age		
< 65 years	Median: ND vs. ND HR: 1.51 [0.70; 3.26] p = ND	Outcome category: serious/severe side effects greater/lesser harm not proven
≥ 65 years	Median: ND vs. ND HR: 12.86 [3.12; 52.95] HR: 0.08 [0.02; 0.32][e] p < 0.001 probability: "hint"[c]	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm, extent: "major"

Table 16: Extent of added benefit at outcome level: trifluridine/tipiracil + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trifluridine/tipiracil + BSC vs. placebo + BSC** **Time to event (months)** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Febrile neutropenia	Median: NA vs. NA RR: 21.42 [1.30; 352.23] RR: 0.05 [< 0.01; 0.77][e] p = 0.001 probability: "hint"[c]	Outcome category: serious/severe side effects $0.75 < CI_u < 0.90$ greater harm, extent: "considerable"
Leukopenia	Median: NA vs. NA RR: 15.44 [0.93; 257.08] RR: 0.07 [< 0.01; 1.08][e, f] p = 0.006 probability: "hint"[c]	Outcome category: serious/severe side effects greater harm, extent: "minor"
Neutropenia	Median: NA vs. NA RR: 61.61 [8.53; 445] RR: 0.02 [< 0.01; 0.12][e] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"
Psychiatric disorders	Median: NA vs. NA HR: 0.48 [0.32; 0.73] p < 0.001 probability: "hint"[c]	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Hypertension	Median: NA vs. NA 0.33 [0.13; 0.86] p = 0.017 probability: "hint"[e]	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Based on the results of the RECOURSE study.
d: Minimum and maximum medians of the time to event in the studies included.
e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; NA: not achieved; ND: no data; NR: not reported; QLQ-C30: Quality of Life Questionnaire-Core 30; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 17: Positive and negative effects from the assessment of trifluridine/tipiracil + BSC in comparison with BSC

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ number of prior regimens: ≥ 3 hint of an 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 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.

Since the results for overall survival showed a relevant effect modification by the number of prior regimens, separate conclusions are drawn for patients with 2 prior regimens and for patients with at least 3 prior regimens.

Patients with 2 prior regimens

For patients with 2 prior regimens, there is no added benefit for overall survival. The positive and negative effects are therefore limited to side effects.

In the outcomes of the category of serious/severe side effects, there is, on the positive side, in each case a hint of lesser harm from SAEs and the specific AE "hypertension", each of considerable extent. In addition, 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 of considerable extent for the outcome "severe AEs (CTCAE grade ≥ 3)". 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".

Overall, the negative effects predominate not only qualitatively due to the type of events that occurred (e.g. vomiting and diarrhoea compared with sleep disorders), but also quantitatively due to the clearly higher number of patients affected.

In summary, a hint of lesser benefit of trifluridine/tipiracil + BSC in comparison with the ACT BSC is derived for patients with MCRC who have been treated with 2 prior regimens.

Patients with at least 3 prior regimens

On the positive side, there was a hint of an added benefit of major extent for overall survival for patients with at least 3 prior regimens. In addition, there were the same positive and negative effects from the side effect outcomes as for patients with 2 prior regimens.

In the overall consideration of the added benefit for overall survival and greater harm for the side effect outcomes, there is an added benefit of trifluridine/tipiracil + BSC in comparison with BSC. 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, a hint of a minor added benefit of trifluridine/tipiracil + BSC in comparison with the ACT BSC is derived for patients with MCRC who have been treated with at least 3 prior regimens.

The result of the assessment of the added benefit of trifluridine/tipiracil + BSC in comparison with the ACT is summarized in Table 18.

Table 18: Trifluridine/tipiracil – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Subgroup**	**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]	2 prior regimens	Hint of lesser benefit[c]
		≥ 3 prior regimens	Hint 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 assessment described above deviates from that of the company, which derived proof of considerable added benefit for the total population.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary information on the implementation of the conditions of the limitation

The G-BA stated the following in its justification of the decision on trifluridine/tipiracil from 2 February 2017 [12]:

> *"For the renewed benefit assessment after expiry of the decision, data in comparison with the appropriate comparator therapy have to be recorded on the basis of comparative clinical studies. If randomization is not an option, the best possible comparability or similarity of patient characteristics in the treatment groups should be aimed for. Data on all patient-relevant outcomes – mortality, morbidity, health-related quality of life and side effects – are to be presented, which, compared with the evidence presented so far on the added benefit of trifluridine/tipiracil, also allow conclusions on disease-specific morbidity, health-related quality of life and side effects in addition to mortality and overall side effects. In particular, the data on side effects should be more informative with regard to the recording of adverse events without symptoms of progression, the categorization of adverse events according to all severity grades (CTCAE grades) and the presentation of specific adverse events. The study population must sufficiently concur with the actual health care setting in Germany, which particularly requires consideration of patients with an ECOG Performance Status of 2 or higher."*

To meet these requirements, the company conducted the non-randomized controlled study TALLISUR. As described in Section 2.3.1, an added benefit could only be derived on the basis of the results of morbidity and health-related quality of life if the observed effects were so large that they could not be caused by systematic bias alone; however, this is not the case. The results from the meta-analysis of the RCTs RECOURSE and TERRA were used for the derivation of the added benefit on the basis of overall survival and side effects because they have a lower risk of bias in comparison with non-randomized studies and are therefore more informative.

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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