IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-54

Trifluridine/tipiracil (colorectal cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Trifluridin/Tipiracil (Kolorektalkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 November 2016). 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Trifluridine/tipiracil (colorectal cancer) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

15 August 2016

Internal Commission No.:

A16-54

Address of publisher:

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:

- Henning Schulze-Bergkamen, Clinic of Internal Medicine II, Marien-Hospital gGmbH, Wesel, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Stefan Kobza
- Christiane Balg
- Charlotte Guddat
- Michaela Florina Kerekes
- Daniela Preukschat
- Cornelia Rüdig
- Dorothea Sow
- Corinna ten Thoren
- Beate Wieseler

Keywords: trifluridine, tipiracil, colorectal neoplasms, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

Page

[3] 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
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
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
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
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 of 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 15 August 2016.

Research question

The aim of this report was to assess the added benefit of trifluridine/tipiracil in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in adult patients with metastatic colorectal cancer (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) therapies, and anti-epidermal growth factor receptor (EGFR) therapies.

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	**Appropriate comparator therapy**[a]
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.	Best supportive care[b]
a: Presentation of the appropriate comparator therapy specified by the G-BA. b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor	

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. Only randomized controlled trials (RCTs) of direct comparisons were included in the assessment.

Results

Study pool

The study pool for the benefit assessment of trifluridine/tipiracil consisted of study TPU-TAS-102-301 (RECOURSE). Deviating from this, the company's study pool contained

study J003-10040030 (J003) (172 patients) in addition to the RECOURSE study. The company's assessment regarding the relevance of the J003 study was not followed for the following decisive reasons: There was high uncertainty whether a sufficient proportion of patients were pretreated in compliance with the approval at the start of the study. In addition, the study protocol mandated dose interruptions under certain conditions, which are not in compliance with the approval. This could have affected up to 50% of the patients in the trifluridine/tipiracil + BSC arm.

Study RECOURSE

The RECOURSE study was a multinational, randomized, double-blind, placebo-controlled phase 3 study. Trifluridine/tipiracil + BSC was compared with placebo + BSC. Adult patients with histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum were enrolled. Knowledge of mutation status of the Kirsten rat sarcoma viral oncogene homologue (KRAS) was required. Patients were required to have received at least 2 prior standard therapy regimens. After each prior standard therapy regimen, patients had tumour progression or had discontinued treatment before tumour progression due to un-acceptable toxicity. Adjuvant chemotherapy could be counted as a regimen if patients had relapsed 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). The patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 1 at the start of the study. Since no patients with ECOG PS > 1 were included, no conclusions can be derived from the available data for these patients.

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 between diagnosis of first metastasis (< 18 months versus ≥ 18 months), and geographic region (Asia [Japan] versus the West [USA, Europe, Australia]).

The drug combination of trifluridine/tipiracil was used in compliance with the approval in the RECOURSE study (35 mg/m^2 body surface area twice daily orally on days 1 to 5 and 8 to 12 of each 28-day cycle). Patients in the placebo + BSC arm received tablets of identical appearance at the same time points. All patients additionally received supportive concomitant treatment (BSC). 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 was overall survival. Patient-relevant outcomes on side effects were additionally recorded. Health-related quality of life was not investigated in the RECOURSE study.

In the framework of supportive concomitant treatment, palliative radiotherapy as well as any cancer drug treatments were excluded. After completion of the study treatment, however, 41.6% of the patients in the trifluridine/tipiracil + BSC arm and 42.5% of the patients in the placebo + BSC arm received further systemic anti-tumour treatments in the follow-up phase. It therefore remains unclear whether the cancer drug treatments excluded in the framework of BSC could have been part of BSC already during the study to alleviate symptoms. For this reason, the informative value of the study is limited.

Of the outcomes included, only overall survival was recorded beyond the end of treatment until the end of the study. The end of the study was planned for the time point when 571 deaths had occurred, which was the case on 24 January 2014. The primary data cut-off for overall survival was conducted on this date. For overall survival, additional results of a later data cut-off (8 October 2014), which, according to the company, were sent to the regulatory authorities in the framework of the approval process, were available. For outcomes of the category "side effects", observation was planned until 30 days after the end of the study treatment or initiation of a new cancer treatment. The data cut-off date for these outcomes was 31 January 2014.

Risk of bias

The risk of bias at study level for the RECOURSE study was rated as low. The risk of bias at outcome level was rated as high for all outcomes except overall survival.

Certainty of conclusions

Several reasons limited the informative value of the results for the RECOURSE study. The main reason for this limitation was that it remained unclear whether the cancer drug treatments excluded from BSC could have been used for symptom relief and thus could have been part of BSC. Overall, no more than hints of an added benefit can therefore be derived.

Results

Mortality

Overall survival

In both data cut-offs, treatment with trifluridine/tipiracil + BSC produced a statistically significant prolongation in overall survival compared with placebo + BSC.

For the decisive second data cut-off on 8 October 2014, the subgroup analyses additionally showed indications of effect modifications by the characteristics "age" and "KRAS mutation status". The effect modification by the KRAS mutation status was regarded to be more robust. Hence only the characteristic "KRAS mutation status" was considered further for the derivation of the extent and probability of the added benefit. As for the total population, there was a statistically significant result for each of the subgroups with KRAS wild type and KRAS mutation. For each of both patient groups, this resulted in a hint of an added benefit of

trifluridine/tipiracil + BSC in comparison with placebo + BSC with separate derivation of the extent of the added benefit for these patient groups.

Morbidity

No patient-relevant outcomes of the category "morbidity" (symptoms) were recorded in the RECOURSE study. This resulted in no hint of an added benefit of trifluridine/tipiracil + BSC in comparison with placebo + BSC for morbidity; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was not investigated in the RECOURSE study. This resulted in no hint of an added benefit of trifluridine/tipiracil + BSC in comparison with placebo + BSC for health-related quality of life; an added benefit is therefore not proven.

Side effects

For all relevant outcomes on side effects – except for discontinuations due to adverse events (AEs) – the company only presented analyses that also included events that, in the opinion of the investigators, were due to clinical progression of the underlying disease. Hence at outcome level, it was estimated on the basis of the underlying individual events in how far these effects could be interpreted as side effects.

Serious adverse events (clinical progression and side effects)

The data presented by the company for the outcome "serious adverse events (SAEs)" were not exclusively interpretable as side effects because events for which a relation with clinical progression was reported by the investigator were also recorded. The outcome was therefore interpreted as a combination of clinical progression and side effects.

A statistically significant difference in favour of trifluridine/tipiracil + BSC was shown for the outcome "SAEs" (clinical progression and side effects). As a result, there was a hint of an added benefit of trifluridine/tipiracil + BSC in comparison with placebo + BSC.

Severe adverse events (CTCAE grade ≥ 3; including clinical progression)

Although events for which a relation with clinical progression was reported by the investigator were also included in the analysis of severe AEs, the interpretability of the results as side effects for the outcome "severe AEs" (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3; including clinical progression) was not called into question due to the specific data situation. There was a statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC for the outcome "severe AEs" (CTCAE grade ≥ 3; including clinical progression). As a result, there was a hint of greater harm of trifluridine/ tipiracil + BSC in comparison with placebo + BSC.

Discontinuation due to adverse events

The company presented no usable data for the outcome "discontinuation due to AEs". For this outcome, there was no hint of greater or lesser harm from trifluridine/tipiracil + BSC in comparison with placebo + BSC; greater or lesser harm is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug combination of trifluridine/tipiracil compared with the ACT is assessed as follows:

In the overall assessment, there are positive and negative effects of equal certainty of results ("hint"). Since the results for the outcome "overall survival" showed a relevant effect modification by KRAS mutation status, the overall conclusion on the added benefit was derived separately for patients with KRAS wild type and patients with KRAS mutation.

In the balancing it was also taken into account that health-related quality of life was not investigated in the study included. Inclusion of health-related quality of life is decisive particularly in the palliative treatment situation when reduced health-related quality of life cannot be excluded under consideration of the side effect profile. A noticeable side effect profile was shown for trifluridine/tipiracil + BSC. Severe AEs and SAEs in the System Organ Class (SOC) "blood and lymphatic system disorders" (mainly caused by anaemia and [febrile] neutropenia) occurred more frequently under trifluridine/tipiracil + BSC than in the comparator arm, for instance.

Patients with KRAS wild type

For patients with KRAS wild type, on the positive side, there is an added benefit in the category "mortality" with the extent "major". Furthermore, there is an added benefit with the extent "minor" in the category "serious/severe symptoms and side effects" (SAEs [clinical progression and side effects]). On the negative side in the category "serious/severe side effects", this is accompanied by greater harm (severe AEs with CTCAE grade ≥ 3) with the extent "non-quantifiable", at least "considerable".

Overall, the mortality advantage and the advantage in SAEs (clinical progression and side effects) are limited by the greater harm in severe AEs with CTCAE grade ≥ 3. In addition, negative effects on health-related quality of life cannot be excluded.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

In summary, there is a hint of a minor added benefit of trifluridine/tipiracil in comparison with the ACT for patients with KRAS wild type.

Patients with KRAS mutation

For patients with KRAS mutation, on the positive side, there is an added benefit in the category "mortality" with the extent "minor". As in patients with KRAS wild type, there is additionally an added benefit with the extent "minor" in the category "serious/severe symptoms and side effects" (SAEs [clinical progression and side effects]). On the negative side in the category "serious/severe side effects", this is accompanied by greater harm (severe AEs with CTCAE grade ≥ 3) with the extent "non-quantifiable", at least "considerable".

Overall, in patients with KRAS mutation, the minor mortality advantage and the also minor advantage in SAEs (clinical progression and side effects) is called into question by the greater harm, which is at least "considerable", in severe AEs with CTCAE grade ≥ 3. In addition, negative effects on health-related quality of life cannot be excluded.

In summary, the added benefit of trifluridine/tipiracil in comparison with the ACT for patients with KRAS mutation is not proven.

The result of the assessment of the added benefit of trifluridine/tipiracil in comparison with the ACT is summarized in Table 3.

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

Therapeutic indication	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
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.	Best supportive care[b]	KRAS wild type	Hint of minor added benefit
		KRAS mutation	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: Best supportive care 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; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor

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

2.2 Research question

The aim of this report was to assess 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 therapies, and anti-EGFR therapies.

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	**Appropriate comparator therapy**[a]
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.	Best supportive care[b]
a: Presentation of the appropriate comparator therapy specified by the G-BA. b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. 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. Only RCTs of direct comparisons were included in the assessment.

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: 6 June 2016)
- bibliographical literature search on trifluridine/tipiracil (last search on 6 June 2016)
- search in trial registries for studies on trifluridine/tipiracil (last search on 6 June 2016)

To check the completeness of the study pool:

- search in trial registries for studies on trifluridine/tipiracil (last search on 18 August 2016)

The check identified a registry entry on a further study [3], the relevance of which could not be finally clarified (see Section 2.7.2.3.1 of the full dossier assessment).

2.3.1 Studies included

The study listed in Table 5 was included in the benefit assessment.

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
TPU-TAS-102-301 (RECOURSE[b])	Yes	No	Yes[c]

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with this abbreviated form.
c: 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.
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of trifluridine/tipiracil consisted of study TPU-TAS-102-301 (RECOURSE). Deviating from this, the company's study pool contained study J003-10040030 (J003) (172 patients) in addition to the RECOURSE study. The company's assessment regarding the relevance of the J003 study was not followed for the following decisive reasons: There was high uncertainty whether a sufficient proportion of patients were pretreated in compliance with the approval at the start of the study. In addition, the study protocol mandated dose interruptions depending on the neutrophil count. The Summary of Product Characteristics (SPC) recommends dose interruptions only with lower neutrophil counts. Dose interruptions could have affected up to 50% of the patients in the

trifluridine/tipiracil + BSC arm of the study. A detailed justification on the evaluation of the relevance of the J003 study can be found in Section 2.7.2.3.2 of the full dossier assessment.

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

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 metastatic colorectal cancer (ECOG PS ≤ 1) with at least 2 prior regimens of standard treatment and ▪ 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: at most 28 days prior to the start of treatment Treatment duration[b]: until at least one of the following criteria for discontinuation occurred: disease progression, unacceptable toxicity, initiation of a different anti-tumour treatment, withdrawal of consent Duration of follow-up: outcome-specific, at most until death or end of study[c]	101 study centres in Australia, Austria, Belgium, Czech Republic, France, Germany, Great Britain, Ireland, Italy, Japan, Spain, Sweden, USA 6/2012–ND[d] 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

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Following the positive primary analysis and unblinding, patients in the control group had the option to switch to treatment with trifluridine/tipiracil.
c: Planned end of study: after reaching the number of deaths planned for the sample size or 12 months after inclusion of the last patient (the event that occurred last).
d: Designated as completed by the company without the date of completion being mentioned. April 2016 is the estimated study completion date provided in the registry entry [4].

AE: adverse event; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study	Intervention	Comparison
RECOURSE	▪ Trifluridine/tipiracil 35 mg/m^2 BSA orally (twice daily) on days 1–5 and 8–12 of each 28-day cycle ▪ BSC	▪ Placebo 35 mg/m^2 BSA orally (twice daily) on days 1–5 and 8–12 of each 28-day cycle ▪ BSC
	Dose reduction/interruption according to the SPC of trifluridine/tipiracil [5]	
	Pretreatment: ▪ standard therapy regimens had to include all of the following drugs: fluoropyrimidine, oxaliplatin, irinotecan, an anti-VEGF monoclonal antibody (bevacizumab); for patients with KRAS wild type: at least one anti-EGFR monoclonal antibody (cetuximab or panitumumab) **Concomitant treatment (BSC):** ▪ haematological supportive therapies (blood transfusion, blood cell stimulating drugs) ▪ antidiarrhoeal drugs (e.g. loperamide) ▪ prophylactic medication for diarrhoea ▪ antiemetics ▪ Antiviral thymidine kinase substrates (e.g. stavudine, zidovudine, telbivudine), which may influence the efficacy of the intervention, should be used with care. Switching to a different antiviral drug should be considered. **Concomitant treatment prohibited:** ▪ palliative radiotherapy as well as all cancer drug treatments except the allowed concomitant medication/BSC	

BSA: body surface area; BSC: best supportive care; EGFR: epidermal growth factor receptor, KRAS: Kirsten rat sarcoma viral oncogene homologue; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; VEGF: vascular endothelial growth factor; vs.: versus

The RECOURSE study was a multinational, randomized, double-blind, placebo-controlled phase 3 study. Trifluridine/tipiracil + BSC was compared with placebo + BSC. Adult patients with histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum were enrolled. Knowledge of the KRAS mutation status was required. Patients were required to have received at least 2 prior standard therapy regimens. After each prior standard therapy regimen, patients had tumour progression or had discontinued treatment before tumour progression due to unacceptable toxicity. Adjuvant chemotherapy could be counted as a regimen if patients had relapsed 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 28 and Table 29 in Appendix C of the full dossier assessment). The patients had to have an ECOG PS of ≤ 1 at the start of the study. Since no patients with ECOG PS > 1 were included, no conclusions can be derived from the available data for these patients.

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 between diagnosis of first metastasis (< 18 months versus ≥ 18 months), and geographic region (Asia [Japan] versus the West [USA, Europe and Australia]).

The drug combination of trifluridine/tipiracil was used in compliance with the approval in the RECOURSE study (35 mg/m^2 body surface area twice daily orally on days 1 to 5 and 8 to 12 of each 28-day cycle). Patients in the placebo + BSC arm received tablets of identical appearance at the same time points. All patients additionally received supportive concomitant treatment (BSC). 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 was overall survival. Patient-relevant outcomes on side effects were additionally recorded. Health-related quality of life was not investigated in the RECOURSE study.

In the framework of supportive concomitant treatment, palliative radiotherapy as well as any cancer drug treatments were excluded. After completion of the study treatment, however, 41.6% of the patients in the trifluridine/tipiracil + BSC arm and 42.5% of the patients in the placebo + BSC arm received further systemic anti-tumour treatments in the follow-up phase (see Table 29 in Appendix C of the full dossier assessment). It therefore remains unclear whether the cancer drug treatments excluded in the framework of BSC could have been part of BSC already during the study to alleviate symptoms. For this reason, the informative value of the study is limited (see end of this section).

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

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

Study **Outcome category** **Outcome**	**Planned follow-up**
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 investigated in the study
Side effects	Until 30 days after the end of study treatment

a: Planned end of study: after reaching the number of deaths planned for the sample size or 12 months after start of the study treatment of the last randomized patient (the event that occurred last).
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus

Of the outcomes included, only overall survival was recorded until death or end of study. The end of the study was planned for the time point when 571 deaths had occurred, which was the case on 24 January 2014. The primary data cut-off for overall survival was conducted on this date. For overall survival, additional results of a later data cut-off (8 October 2014), which, according to the company, were sent to the regulatory authorities in the framework of the approval process, were available. Before this second data cut-off, 2 patients had switched from the placebo + BSC arm to the trifluridine/tipiracil + BSC arm after unblinding in May 2014. For outcomes of the category “side effects”, observation was planned until 30 days after the end of the study treatment or initiation of a new cancer treatment. The data cut-off date for these outcomes was 31 January 2014.

Table 9 and Table 10 show the characteristics of the patients in the study included.

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

Study Group	N[a]	Age [years] mean (SD)	Sex [F/M] %	Region Japan/Australia/ Europe/ North America %	Ethnicity Caucasian/Black, African American/Asian, Oriental/ not reported %	Treatment discontinuation n (%)	Study discontinuation n (%)
RECOURSE							
Trifluridine/tipiracil + BSC	534	62 (10)	39/61	33/4/51/12	57/1/35/8	496[b] (93.1)	371 (69.6)[c]
Placebo + BSC	266	62 (11)	38/62	33/4/50/13	58/2/35/5	263[b] (99.2)	214 (80.8)[c]

a: Number of randomized patients; values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b: The main reason for discontinuation was radiological disease progression (trifluridine/tipiracil + BSC: n = 416; placebo + BSC: n = 222).
c: Includes deaths (trifluridine/tipiracil + BSC: n = 367; placebo + BSC: n = 211).

BSC: best supportive care; F: female; M: male; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 10: Characteristics of the study population (disease characteristics) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study Group	N[a]	Time between diagnosis of first metastasis and randomization [weeks] mean (SD)	ECOG PS 0/1/2 n (%)	Location of primary tumour [colon/rectum] n (%)	Number of organs with metastases 1–2/≥ 3 n (%)	KRAS mutation status [mutation/wild type/ unknown] n (%)
RECOURSE						
Trifluridine/tipiracil + BSC	534	44.1 (29.3)	301 (56.4)/233 (43.6)/0 (0)	338 (63.3)/196 (36.7)	324 (60.7)/210 (39.3)	274 (51.3)/260 (48.7)/0 (0)[b]
Placebo + BSC	266	45.5 (28.3)	147 (55.3)/119 (44.7)/0 (0)	161 (60.5)/105 (39.5)	153 (57.5)/113 (42.5)	132 (49.6)/134 (50.4)/0 (0)[c]

a: Number of randomized patients; values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b: Data based on the eCRF; deviations in the IWRS for KRAS mutation status mutation/wild type/unknown n (%): 272 (50.9)/262 (49.1)/0 (0).
c: Data based on the eCRF; deviations in the IWRS for KRAS mutation status mutation/wild type/unknown n (%): 135 (50.8)/131 (49.2)/0 (0).

BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; IWRS: interactive voice/web response system; KRAS: Kirsten rat sarcoma viral oncogene homologue; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The characteristics between the treatment arms of the RECOURSE study were balanced. The mean age of the patients was 62 years at the time point of randomization. More than half of the patients were Caucasians. About 39% of the patients were women.

At the time point of randomization, the metastatic disease had been diagnosed for about 45 weeks on average, and was localized in the colon in more than half of the patients. At the start of the study, about the same number of patients with KRAS wild type and with KRAS mutation were included in both arms. At this time point, more than half of the patients had an ECOG PS of 0, the remaining patients had an ECOG PS of 1. About 60% of the patients in both treatment arms had metastases in 1 to 2 organs; the remaining patients had metastases in 3 or more organs.

The most common reason (> 80% in both groups) for treatment discontinuation was disease progression diagnosed with imaging techniques, both in the trifluridine/tipiracil + BSC arm and in the placebo + BSC arm. Death was recorded as the reason of study discontinuation in nearly all cases; an additional 3 patients were lost to follow-up in each of both study arms. One additional patient withdrew consent in the trifluridine/tipiracil + BSC arm.

Although according to the approval, treatment with trifluridine/tipiracil, in principle, is an option for all tumour types of colorectal cancer [5], the RECOURSE study only included patients with adenocarcinoma. With more than 95%, this tumour type constitutes the majority of colorectal cancers, however [6,7].

Table 11 shows the median and mean treatment duration of the patients and the observation period for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study **Data cut-off** **Duration of the study phase** **Outcome category**	**Trifluridine/tipiracil + BSC**	**Placebo + BSC**
RECOURSE		
Data cut-off 24 January 2014/31 January 2014[a]		
Treatment duration [weeks]		
	N = 533	N = 265
Median [min; max]	6.7 [0.1; 78]	5.7 [0.1; 63.7]
Mean (SD)	12.7 (12.0)	6.8 (6.1)
Observation period [weeks[b]]		
	N = 534	N = 266
Mortality: overall survival		
Median [min; max]	28.0 [1.3; 82.2]	22.1 [1.7; 82.6]
Mean (SD)	30.4 (ND)	25.3 (ND)
Morbidity	No patient-relevant outcomes of this category recorded	
Health-related quality of life	Not investigated in the study	
Side effects	ND	
Data cut-off 8 October 2014[c]	ND	

a: The first data cut-off date for overall survival was 24 January 2014. The data cut-off date for all further patient-relevant outcomes was 31 January 2014.
b: Institutes calculation from months.
c: From the patient-relevant outcomes, only overall survival was analysed at this data cut-off.
BSC: best supportive care; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Information on the data cut-off from 24 January 2014 (overall survival) and from 31 January 2014 (all further patient-relevant outcomes) was available on treatment and observation period.

Whereas the median treatment duration only differed marginally between the study arms (6.7 weeks in the trifluridine/tipiracil + BSC arm versus 5.7 weeks in the placebo + BSC arm), the mean treatment duration differed notably (12.7 weeks versus 6.8 weeks). This pattern of results can be explained by the fact that in most cases the study treatment was discontinued due to disease progression; and a difference between the study arms in the time to progression only became apparent from month 2, after disease progression had already occurred in about 50% of the patients (see Figure 8 in Appendix A.3 of the full dossier assessment).

For the outcome “overall survival”, both the median (28.0 weeks versus 22.1 weeks) and the mean observation period (30.4 weeks versus 25.3 weeks) differed between the study arms. No

corresponding information was available for outcomes of the category of side effects. Assuming the planned follow-up period of 30 days for adverse events (AEs), the median observation period for the outcomes on side effects was about 11 weeks versus about 10 weeks with a mean observation period of about 17 weeks versus about 11 weeks.

Table 12 shows the risk of bias at study level.

Table 12: Risk of bias at 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
			Patient	Treating staff			
RECOURSE	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the RECOURSE study was rated as low. This concurs with the company's assessment.

Overall assessment of the informative value

Several reasons limited the informative value of the results for the RECOURSE study (see also Section 2.7.2.8.1 of the full dossier assessment). The main reason for this limitation was that it remained unclear whether the cancer drug treatments excluded from BSC could have been used for symptom relief and thus could have been part of BSC. Overall, no more than hints of an added benefit can therefore be derived. This deviates from the assessment of the company, which derived proof on the basis of 2 studies.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - no patient-relevant outcomes of this category recorded
- Health-related quality of life
  - not investigated in the study included
- Side effects
  - serious adverse events (SAEs)
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to 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) (see Section 2.7.2.4.3 of the full dossier assessment).

The outcomes on side effects presented by the company also included events caused by clinical progression of the underlying disease. According to the study protocol, disease progression itself was not to be reported as an AE term. However, if signs, symptoms and complications of disease progression occurred, these were to be reported as AE or SAE together with a statement whether they were associated with disease progression.

Table 13 shows for which outcomes data were available in the studies included.

Table 13: Matrix of outcomes – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study	Outcomes					
	Overall survival	Morbidity	Health-related quality of life	SAEs (clinical progression and side effects)	Severe AEs (CTCAE grade ≥ 3) (including clinical progression)	Discontinuation due to AEs
RECOURSE	Yes	No[a]	No[b]	Yes	Yes	Yes

a: No patient-relevant outcomes of this category recorded.
b: Not investigated in the study.
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.4.2 Risk of bias

Table 14 shows the risk of bias for the relevant outcomes.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study		Outcomes					
	Study level	Overall survival	Morbidity	Health-related quality of life	SAEs (clinical progression and side effects)	Severe AEs (CTCAE grade ≥ 3) (including clinical progression)	Discontinuation due to AEs
RECOURSE	L	L	–[a]	–[b]	H[c]	H[c]	–[d]

a: No patient-relevant outcomes of this category recorded.
b: Not investigated in the study.
c: Due to potentially informative censoring; see Section 2.7.2.4.2 of the full dossier assessment.
d: No usable data available due to the high proportion of not necessarily patient-relevant events or due to a lack of survival time analysis; see Section 2.7.2.4.3 of the full dossier assessment.
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias for the outcome “overall survival” was rated as low. This concurs with the company’s assessment.

The risk of bias for the outcomes “SAEs” (clinical progression and side effects) and “severe AEs” (including clinical progression) was rated as high due to potentially informative censoring. The data available for the outcome “discontinuation due to AEs” (including progression) were not usable because of the high proportion of events based on a combination of clinical and not necessarily symptomatic radiological progression, which as a whole are therefore not necessarily patient-relevant. There was no survival time analysis for the analysis without progression (see Section 2.4.3). The risk of bias was therefore not assessed for the outcome “discontinuation due to AEs”. These assessments deviate from those of the company, which rated the risk of bias as low for all outcomes on side effects.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.7.2.4.2 of the full dossier assessment.

2.4.3 Results

Table 15 summarizes the results on the comparison of trifluridine/tipiracil + BSC with placebo + BSC in MCRC patients. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations. The available Kaplan-Meier curves on the outcomes included are presented in Appendix A.1 and Appendix A.2 of the full dossier assessment.

Table 15: Results (overall survival, side effects) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study **Outcome category**	**Trifluridine/tipiracil + BSC**		**Placebo + BSC**		**Trifluridine/tipiracil + BSC vs. placebo + BSC**
Outcome **Data cut-off**[a]	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value**[b]
RECOURSE					
Mortality					
Overall survival					
24 January 2014	534	7.1 [6.5; 7.8] 364 (68.2)	266	5.3 [4.6; 6.0] 210 (78.9)	0.68 [0.58; 0.81]; < 0.001
8 October 2014	534	7.2 [6.6; 7.8] 463 (86.7)	266	5.5 [4.6; 5.9] 249 (93.6)	0.69 [0.59; 0.81]; < 0.001
Morbidity	No patient-relevant outcomes of this category recorded				
Health-related quality of life	Not investigated in the study				
Side effects					
AEs (presented as additional information, including clinical progression)	533	0.2 [0.2; 0.3] 524 (98.3)	265	0.4 [0.3; 0.4] 247 (93.2)	–
SAEs (clinical progression and side effects)	533	NA [8.7; NA] 158 (29.6)	265	5.4 [3.7; NA] 89 (33.6)	0.70 [0.53; 0.91]; 0.008
Severe AEs (CTCAE grade ≥ 3)[c]	533	1.6 [1.3; 1.8] 370 (69.4)	265	2.5 [2.0; 3.3] 137 (51.7)	1.44 [1.18; 1.77]; < 0.001
Discontinuation due to AEs (including progression)	No interpretable data[d]				
Discontinuation due to AEs (without progression)	533	ND 19 (3.6[e])	265	ND 4 (1.5[e])	ND

(continued)

Table 15: Results (overall survival, side effects) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC (continued)

a: For overall survival, the company presented results on the data cut-offs from 24 January 2014 and 8 October 2014; for all other patient-relevant outcomes, only results for the data cut-off from 31 January 2014 were available.
b: HR and 95% CI from Cox model; p-value from log-rank test; each adjusted for KRAS mutation status (wild type vs. mutation), time since diagnosis of first metastasis (< 18 months vs. ≥ 18 months) and geographical region (Asia vs. West) from IWRS/IVRS.
c: Including clinical progression; nonetheless interpretable as side effects (see Section 2.7.2.4.3 of the full dossier assessment).
d: Due to the majority of discontinuations in this operationalization that are not based on AEs, but on a combination of clinical and not necessarily symptomatic radiological progression.
e: Institute's calculation.
AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; IWRS/IVRS: interactive voice/web response system; KRAS: Kirsten rat sarcoma viral oncogene homologue; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

One relevant study was available for the assessment of trifluridine/tipiracil in the treatment MCRC. Due to the reduced informative value (see also Section 2.3.2 and Section 2.7.2.8.1 of the full dossier assessment), at most hints of an added benefit can be derived.

Mortality

Overall survival

In both data cut-offs, treatment with trifluridine/tipiracil + BSC produced a statistically significant prolongation in overall survival compared with placebo + BSC. For the decisive second data cut-off on 8 October 2014, the subgroup analyses additionally showed indications of effect modifications by the characteristics "age" and "KRAS mutation status" (see Section 2.4.4). The results were therefore interpreted separately by subgroups. For the outcome "overall survival" for patients with KRAS wild type and KRAS mutation, this resulted in a hint of an added benefit of trifluridine/tipiracil + BSC in comparison with placebo + BSC with separate derivation of the extent of the added benefit for both patient groups (see Section 2.5.1).

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

Morbidity

No patient-relevant outcomes of the category "morbidity" (symptoms) were recorded in the RECOURSE study. This resulted in no hint of an added benefit of trifluridine/tipiracil + BSC in comparison with placebo + BSC for morbidity; an added benefit is therefore not proven.

This deviates from the assessment of the company, which claimed proof of an added benefit for the total population in the category of serious or severe symptoms for the outcomes

"progression-free survival (PFS)", tumour assessment (disease control rate), time to treatment failure and time to reaching an ECOG PS ≥ 2.

Health-related quality of life

Health-related quality of life was not investigated in the RECOURSE study. This resulted in no hint of an added benefit of trifluridine/tipiracil + BSC in comparison with placebo + BSC for health-related quality of life; an added benefit is therefore not proven. The company did not mention health-related quality of life in the derivation of an added benefit in the dossier.

Side effects

For all relevant outcomes on side effects – except for discontinuations due to AEs (see below) – the company only presented analyses that also included events that, in the opinion of the investigators, were due to clinical progression of the underlying disease. Hence at outcome level, it was estimated on the basis of the underlying individual events in how far these effects could be interpreted as side effects or were caused by clinical progression of the underlying disease.

Serious adverse events (clinical progression and side effects)

The data presented by the company for the outcome "SAEs" were not exclusively interpretable as side effects because events for which a relation with clinical progression was reported by the investigator were also recorded (see also Section 2.7.2.4.3 of the full dossier assessment). The outcome was therefore interpreted as a combination of clinical progression and side effects.

A statistically significant difference in favour of trifluridine/tipiracil + BSC was shown for the outcome "SAEs" (clinical progression and side effects). As a result, there was a hint of an added benefit of trifluridine/tipiracil + BSC in comparison with placebo + BSC.

This deviates from the assessment of the company, which claimed an indication of lesser harm.

Severe adverse events (CTCAE grade ≥ 3; including clinical progression)

There was a statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC for the outcome "severe AEs" (CTCAE grade ≥ 3; including clinical progression). As a result, there was a hint of greater harm of trifluridine/tipiracil + BSC in comparison with placebo + BSC.

This deviates from the assessment of the company, which derived an indication of greater harm.

Although events for which a relation with clinical progression was reported by the investigator were also included in the analysis of severe AEs, the interpretability of the results as side effects for the outcome "severe AEs" (CTCAE grade ≥ 3; including clinical

progression) was not called into question. The reason for this is that the difference in the overall rates of severe AEs between the study arms (trifluridine/tipiracil + BSC: 69.4%; placebo + BSC: 51.7%) was notably larger than the different rates of events for which the investigator determined a relation with clinical progression (trifluridine/tipiracil + BSC: 6.7%; placebo + BSC: 11.7%) and also pointed in different directions. Hence the difference between the study arms for the outcome "severe AEs" (CTCAE grade ≥ 3; including clinical progression) was mainly caused by side effects (see also Section 2.7.2.4.3 of the full dossier assessment).

Discontinuation due to adverse events

The company presented no usable data for the outcome "discontinuation due to AEs". For this outcome, there was no hint of greater or lesser harm from trifluridine/tipiracil + BSC in comparison with placebo + BSC; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which derived proof of lesser harm.

The data presented by the company for the outcome "discontinuation due to AEs" were not usable for the reasons described below.

In Module 4 A, the company reported events from a survival time analysis, in which the majority of discontinuations were not due to side effects, but to a combination of clinical and not necessarily symptomatic radiological progression (see Table 27 in Appendix B of the full dossier assessment). Due to the large proportion of these reasons for discontinuation, the results of this analysis were not usable.

The clinical study report (CSR) provides the number of patients with discontinuation due to AEs without progression for each of both study arms. Analyses based on these data were not adequate due to the different observation periods between the study arms. The survival time analysis required for the interpretation of the discontinuations due to AEs without progression was not presented by the company.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment (see also Section 2.7.2.4.3 of the full dossier assessment):

- sex (men/women)
- age ($< 65/\geq 65$ years)
- KRAS mutation status (wild type/mutation)
- region (Asia/West)
- location of primary tumour (colon/rectum)
- number of organs with metastases ($1\text{-}2/\geq 3$)

- number of prior therapy regimens (2/3/≥ 4)

Data in the CSR on the pretreatment of patients with KRAS wild type and with KRAS mutation showed that the subgroup characteristics "KRAS mutation status" and "number of prior regimens" were not independent from each other: Compared with the presence of KRAS mutation, the presence of KRAS wild type resulted in a higher number of prior regimens. Hence at outcome level it cannot be excluded in effect modifications by both subgroup characteristics that the effect modification by the KRAS mutation status caused the effect modification by the number of prior regimens. Only the effect modification by KRAS mutation status was therefore considered and presented in this case.

For the outcome "overall survival", subgroup analyses on all characteristics mentioned above were available at the first data cut-off (24 January 2014). At the second data cut-off (8 October 2014), only subgroup analyses for the characteristics "sex", "age", "KRAS mutation status", and "region" were available. Since at the second data cut-off, no subgroup analyses were available for the characteristics "location of primary tumour", "number of organs with metastases" and "number of prior regimens", it is unknown whether there were effect modifications by these characteristics at this data cut-off.

Suitable subgroup analyses at the data cut-off 31 January 2014 for the outcomes in the category of side effects with interpretable data (SAEs, severe AEs with CTCAE grade ≥ 3) were only available on the characteristics "sex", "age", "KRAS mutation status" and "region". It was therefore unknown for the remaining characteristics whether there were effect modifications for these outcomes.

For the outcome "overall survival", only the results are presented hereinafter, for which there was at least an indication of an interaction between treatment and subgroup characteristic. For outcomes on side effects, only results for which there was proof of an effect modification are presented due to the increased uncertainty caused by potentially informative censoring (see Section 2.7.2.2 of the full dossier assessment).

The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 summarizes the subgroup analyses on the comparison of trifluridine/tipiracil + BSC with placebo + BSC in MCRC patients. Where necessary, the data from the dossier were supplemented by the Institute's calculations.

Table 16: Subgroups (overall survival; data cut-off: 24 January 2014) – RCT, direct comparison: trifluridine/tipiracil + BSC vs. placebo + BSC

Study **Outcome**	**Trifluridine/tipiracil + BSC**		**Placebo + BSC**		**Trifluridine/tipiracil + BSC vs. placebo + BSC**	
Data cut-off **Characteristic** **Subgroup**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]**	**p-value[a]**
RECOURSE						
Overall survival						
Data cut-off 24 January 2014						
KRAS mutation status						
Wild type	262	8.0 [6.9; 9.2] 173 (66.0)	131	5.7 [4.5; 6.6] 107 (81.7)	0.58 [0.45; 0.74]	< 0.001
Mutation	272	6.5 [5.6; 7.1] 191 (70.2)	135	4.9 [4.2; 6.1] 103 (76.3)	0.80 [0.63; 1.02]	0.071
					Interaction:	0.069[b]
Data cut-off 8 October 2014						
Age						
< 65 years	300	7.2 [6.5; 8.0] ND	148	5.6 [4.9; 6.5] ND	0.76 [0.62; 0.94]	0.012
≥ 65 years	234	7.1 [6.3; 8.0] ND	118	4.5 [3.9; 6.0] ND	0.60 [0.48; 0.77]	< 0.001
					Interaction:	0.141[b]
KRAS mutation status						
Wild type	262	8.0 [7.2; 9.3] ND	131	5.6 [4.5; 6.5] ND	0.60 [0.48; 0.75]	< 0.001
Mutation	272	6.5 [5.6; 7.1] ND	135	4.9 [4.2; 6.1] ND	0.78 [0.63; 0.98]	0.029
					Interaction:	0.101[b]

a: HR and 95% CI from Cox model; p-value from log-rank test; at the data cut-off on 24 January 2014, each adjusted for KRAS mutation status (wild type vs. mutant), time since diagnosis of first metastasis (< 18 months vs. ≥ 18 months) and geographical region (Asia vs. West) from IWRS/IVRS; adjustment was presumably also conducted at the data cut-off on 8 October 2014.

b: Institute's calculation, Q test.

BSC: best supportive care; CI: confidence interval; HR: hazard ratio; IWRS/IVRS: interactive voice/web response system; KRAS: Kirsten rat sarcoma viral oncogene homologue; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

There were indications of effect modifications by the subgroup characteristics “age” and “KRAS mutation status” for the outcome “overall survival”. There was an indication of effect modification by KRAS mutation status for both data cut-offs; additionally, the KRAS mutation status was a stratification factor at randomization. The effect modification by the characteristic “age” was only shown at the second data cut-off (8 October 2014), additionally, age was no stratification factor. Overall, the effect modification by KRAS mutation status was assessed to be more robust; hence only the characteristic “KRAS mutation status” was considered further for the derivation of extent and probability of the added benefit. The results of the second data cut-off (8 October 2014) were used for this because they were assessed to be more informative.

Since there was only an indication of an effect modification for the characteristic “KRAS mutation status”, besides the result in the respective subgroup, the result of the total population was also used in the interpretation.

As for the total population, there was a statistically significant result for each of the subgroups with KRAS wild type and KRAS mutation. For these patient groups, this resulted in a hint of an added benefit of trifluridine/tipiracil + BSC in comparison with placebo + BSC with separate derivation of the extent of the added benefit for these patient groups (see Section 2.5.1).

This deviates from the assessment of the company, which for overall survival only considered the subgroup analyses at the first data cut-off (24 January 2014) in Module 4 A and identified no indication of an effect modification by the subgroup characteristic “age” on this basis. Regarding the indication of an effect modification by the subgroup characteristic “KRAS mutation status”, the company explained that the estimated effects of both subgroups pointed in the same direction, which suggests an advantage in overall survival under trifluridine/ tipiracil + BSC treatment compared with placebo + BSC for both subgroups. The company therefore did not consider this interaction further in the derivation of the added benefit and used the total population instead. These arguments and the resulting approach of the company were not followed. With the same direction of effect in the subgroups, a different extent of added benefit between the subgroups is possible. It is therefore necessary to interpret the results separately by subgroups.

In addition, an indication of effect modification by the number of prior regimens was shown for the outcome “overall survival” at the first data cut-off (24 January 2014). As described above, this indication of effect modification could be caused by the indication of effect modification for the characteristic “KRAS mutation status”. Hence the indication of effect modification for the characteristic “number of prior regimens” was not considered further and not presented.

Side effects

There was no proof of an effect modification by the subgroup characteristics considered for the outcomes on side effects.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, 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 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 added benefit at outcome level

The data presented in Section 2.4 resulted in the following assessment of trifluridine/ tipiracil + BSC in comparison with placebo + BSC:

- a hint of an added benefit for overall survival
- a hint of an added benefit for SAEs (clinical progression and side effects)
- a hint of greater harm for severe AEs (CTCAE grade ≥ 3; including clinical progression)

The extent of the respective added benefit at outcome level was estimated from these results (see Table 17).

Table 17: Extent of added benefit at outcome level: trifluridine/tipiracil + BSC vs. placebo + BSC

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trifluridine/tipiracil + BSC vs. placebo + BSC** **Median time to event** **HR [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival KRAS mutation status	7.2 vs. 5.5 months 0.69 [0.59; 0.81] p < 0.001	
Wild type	8.0 vs. 5.6 months 0.60 [0.48; 0.75] p < 0.001 probability: "hint"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Mutation	6.5 vs. 4.9 months 0.78 [0.63; 0.98] p = 0.029 probability: "hint"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"
Morbidity		
No patient-relevant outcomes of this category recorded		
Health-related quality of life		
Not investigated in the study included		
Side effects		
SAEs (clinical progression and side effects)	NA vs. 5.4 months 0.70 [0.53; 0.91] p = 0.008 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Severe AEs (CTCAE grade ≥ 3)[c]	1.6 vs. 2.5 months 1.44 [1.18; 1.77] 0.69 [0.56; 0.85][d] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "non-quantifiable", at least "considerable"[e]
Discontinuation due to AEs	No usable data	Greater/lesser harm not proven

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Only analyses that also included events caused by clinical progression are available.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: The extent is potentially underestimated due to events caused by progression (see Section 2.7.2.4.3 of the full dossier assessment).

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; KRAS: Kirsten rat sarcoma viral oncogene homologue; NA: not achieved; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of trifluridine/tipiracil + BSC compared with placebo + BSC

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ KRAS mutation status: wild type Hint of an added benefit - extent: “major” ▫ KRAS mutation status: mutation Hint of an added benefit - extent: “minor” Serious/severe symptoms and side effects ▪ SAEs (clinical progression and side effects): hint of an added benefit – extent: “minor”	Serious/severe side effects ▪ Severe AEs CTCAE grade ≥ 3: hint of greater harm – extent: “non-quantifiable”, at least “considerable“[a]
Health-related quality of life was not investigated in the study included	
a: The extent is potentially underestimated due to events caused by progression that were included in the analysis. AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; KRAS: Kirsten rat sarcoma viral oncogene homologue; SAE: serious adverse event; vs.: versus	

In the overall assessment, there are positive and negative effects of equal certainty of results (“hint”). Since the results for the outcome “overall survival” showed a relevant effect modification by KRAS mutation status, the overall conclusion on the added benefit was derived separately for patients with KRAS wild type and patients with KRAS mutation.

In the balancing it was also taken into account that health-related quality of life was not investigated in the study included. Inclusion of health-related quality of life is decisive particularly in the palliative treatment situation when reduced health-related quality of life cannot be excluded under consideration of the side effect profile. A noticeable side effect profile was shown for trifluridine/tipiracil + BSC (see Table 23, Table 24 and Table 25 in Appendix B of the full dossier assessment). Severe AEs and SAEs in the SOC “blood and lymphatic system disorders” (mainly caused by anaemia and [febrile] neutropenia) occurred more frequently under trifluridine/tipiracil + BSC than in the comparator arm, for instance.

Patients with KRAS wild type

For patients with KRAS wild type, on the positive side, there is an added benefit in the category “mortality” with the extent “major”. Furthermore, there is an added benefit with the extent “minor” in the category “serious/severe symptoms and side effects” (SAEs [clinical progression and side effects]). On the negative side in the category “serious/severe side

effects", this is accompanied by greater harm (severe AEs with CTCAE grade ≥ 3) with the extent "non-quantifiable", at least "considerable".

Overall, the mortality advantage and the advantage in SAEs (clinical progression and side effects) are limited by the greater harm in severe AEs with CTCAE grade ≥ 3. In addition, negative effects on health-related quality of life cannot be excluded.

In summary, there is a hint of a minor added benefit of trifluridine/tipiracil in comparison with the ACT for patients with KRAS wild type.

Patients with KRAS mutation

For patients with KRAS mutation, on the positive side, there is an added benefit in the category "mortality" with the extent "minor". As in patients with KRAS wild type, there is additionally an added benefit with the extent "minor" in the category "serious/severe symptoms and side effects" (SAEs [clinical progression and side effects]). On the negative side in the category "serious/severe side effects", this is accompanied by greater harm (severe AEs with CTCAE grade ≥ 3) with the extent "non-quantifiable", at least "considerable".

Overall, in patients with KRAS mutation, the minor mortality advantage and the also minor advantage in SAEs (clinical progression and side effects) is called into question by the greater harm, which is at least "considerable", in severe AEs with CTCAE grade ≥ 3. In addition, negative effects on health-related quality of life cannot be excluded.

In summary, the added benefit of trifluridine/tipiracil in comparison with the ACT for patients with KRAS mutation is not proven.

The result of the assessment of the added benefit of trifluridine/tipiracil in comparison with the ACT is summarized in Table 19.

Table 19: Trifluridine/tipiracil – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
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.	Best supportive care[b]	KRAS wild type	Hint of minor added benefit
		KRAS mutation	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: Best supportive care 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; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor

This deviates from the company's approach, which derived proof of a considerable added benefit.

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

2.6 List of included studies

TPU-TAS-102-301 (RECOURSE)

Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015; 372(20): 1909-1919.

Taiho Oncology. Randomised, double-blind, phase 3 study of TAS-102 plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic colorectal cancer refractory to standard chemotherapies: study TPU-TAS-102-301; addendum to clinical study report [unpublished]. 2016.

Taiho Oncology. Randomised, double-blind, phase 3 study of TAS-102 plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic colorectal cancer refractory to standard chemotherapies: study TPU-TAS-102-301; clinical study report [unpublished]. 2014.

Taiho Oncology. Randomised, double-blind, phase 3 study of TAS-102 plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic colorectal cancer refractory to standard chemotherapies: study TPU-TAS-102-301; Zusatzanalysen [unpublished]. 2016.

Taiho Oncology. Randomized, double-blind, phase 3 study of TAS-102 plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic colorectal cancer refractory to standard chemotherapies [online]. In: EU Clinical Trials Register. [Accessed: 22.08.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-000109-66.

Taiho Oncology. Study of TAS-102 in patients with metastatic colorectal cancer refractory to standard chemotherapies (RECOURSE) [online]. In: ClinicalTrials.gov. 21.12.2015 [Accessed: 22.08.2016]. URL: https://ClinicalTrials.gov/show/NCT01607957.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

3. Taiho Pharmaceutical. A Pharmacogenomics study of TAS-102 [online]. In: Clinical Trials Information/JapicCTI. 13.01.2015 [Accessed: 22.08.2016]. URL: http://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-121918.

4. Taiho Oncology. Study of TAS-102 in patients with metastatic colorectal cancer refractory to standard chemotherapies (RECOURSE) [online]. In: ClinicalTrials.gov. 21.12.2015 [Accessed: 22.08.2016]. URL: https://ClinicalTrials.gov/show/NCT01607957.

5. Servier Deutschland. Lonsurf: Fachinformation [online]. 04.2016. URL: http://www.fachinfo.de/.

6. Hofheinz RD, Arnold D, Borner M, Folprecht G, Graeven U, Hebart H et al. Kolonkarzinom [online]. In: Onkopedia Leitlinien. 01.2016 [Accessed: 19.08.2016]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/kolonkarzinom/@@view/pdf/index.pdf?filename=kolonkarzinom.pdf.

7. Hofheinz RD, Arnold D, Borner M, Folprecht G, Ghadimi BM, Graeven U et al. Rektumkarzinom [online]. In: Onkopedia Leitlinien. 03.2016 [Accessed: 19.08.2016]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/rektumkarzinom.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-54-trifluridine/tipiracil-colorectal-cancer-benefit-assessment-according-to-35a-social-code-book-v.7570.html.